

# A Review On: Exploring Novel Therapeutic Approaches in Beta Thalassemia

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## Abstract:

One of the most prevalent monogenic disorders in the world is hemoglobinopathies. One to five percent of people worldwide carry a hereditary thalassemia mutation. The thalassemias are characterized by inherited autosomal recessive abnormalities in hemoglobin synthesis. The Mediterranean, Middle East, Indian subcontinent, and East and Southeast Asia all have significant populations of them. However, as a result of recent immigration, thalassemias are now increasing in prevalence in Europe and North America, making this condition a global health concern. There are significant difficulties and restrictions with the thalassemia conventional medicines that are now accessible. The lifespan of thalassemia patients has increased due to a better understanding of the pathophysiology of  $\beta$ -thalassemia as well as significant advancements in iron-chelation therapy and transfusion program optimization. This has also opened the door for new therapeutic approaches. Based on their attempts to address various aspects of the underlying pathophysiology of  $\beta$ -thalassemia, they can be divided into three categories: improvement of iron overload, correction of the globin chain imbalance, and treatment of inadequate erythropoiesis. In this review, we give a general overview of the cutting-edge therapy strategies being researched and developed for thalassemia.

**KEYWORDS:** Beta thalassemia, Bone marrow transplantation, Iron chelation.

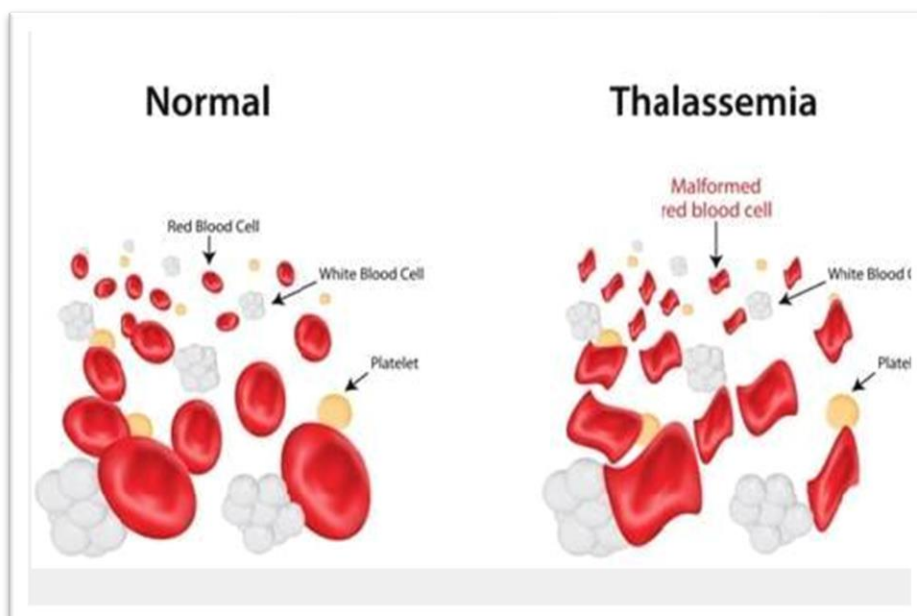
## INTRODUCTION

One to five percent of the world's population are carriers for a hereditary thalassemia mutation, and beta thalassemia is the most prevalent monogenic disease there is <sup>[1]</sup>. The Greek words Thalassa (sea) and haima (blood) are the source of the word thalassemia. Cooley's anaemia is a different name for this condition that is occasionally used in literature. Prof. Cooley Thomas was a pediatrician in the USA who first identified the clinical features of this ailment in individuals of Italian ancestry in 1925. <sup>[2,3]</sup> A genetic blood condition called thalassemia that a person inherits from their parents may cause the improper synthesis of hemoglobin. Alpha and beta thalassemia are the two primary kinds <sup>[4]</sup> The number of missing genes—two for beta globin and four for alpha—determines the severity of alpha and beta thalassemia <sup>[5]</sup>.

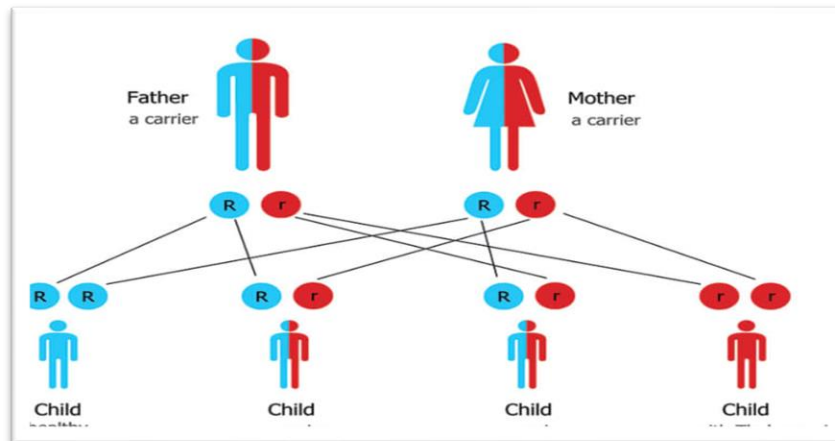
There are two main types of thalassemia Alpha thalassemia Beta thalassemia And the beta thalassemia is again classified into three types Beta thalassemia minor Beta thalassemia intermedia Beta thalassemia major

## ETIOLOGY

Thalassemia is caused by an imbalanced synthesis of hemoglobin, which is caused by a decrease in the production of at least one globin polypeptide chain (beta, alpha, gamma, or delta). Thalassemia is inherited in an autosomal recessive manner. Reduced synthesis of beta-polypeptide chains causes beta thalassemia. Heterozygotes (carriers) have mild to severe microcytic anaemia (thalassemia minor) but no symptoms. Homozygotes (beta-thalassemia major or Cooley's anaemia) experience bone marrow hyperactivity and severe anaemia. Reduced alpha globin production leads to alpha thalassemia. Silent alpha thalassemia is a condition that occurs from heterozygotes for a single gene deficiency. Alpha thalassemia trait is caused by heterozygotes with errors in two of the four genes; these individuals often experience mild to moderate microcytic anaemia without any other symptoms. The creation of tetramers of extra beta chains (HbH) or, in infancy, gamma chains (Bart's Hb) results from defects in three of the four genes that more severely limit alpha-chain production. Without prenatal blood transfusions, all four gene defects are fatal because hemoglobin without alpha chains is unable to carry oxygen. Hemoglobin E (Hb E)-related thalassemia is an additional form. One of the most prevalent hemoglobinopathies, Hb E, is caused by a missense mutation at codon 26, which is part of the beta globin gene's splicing sequence. In addition to changing the structure, this mutation slows the pace at which beta globin is produced. As a result, modest Beta thalassemia phenotype is typically present in Hb E trait and disease. In Southeast Asia, India, and Bangladesh, co-inheritance of Hb E with thalassemia is frequent [6]. The phenotype of this Hb E/Thalassemia compound heterozygote condition varies, ranging from moderate anaemia to transfusion need [7]. The most prominent genotype accounts for 50% of severe beta thalassemia worldwide and is Hb E/Beta thalassemia [8]. A higher risk of pulmonary hypertension or vitamin D deficiency exists in Hb E/Beta thalassemia patients [9,10].



**Fig 1: Thalassemia**



**Fig 2: Inheritance of beta thalassemia**

## **PATHOPHYSIOLOGY**

B-thalassemia patients erythropoiesis reflects the effects of an excess of unpaired  $\alpha$ -globin [11,12]. In actuality, rather than the underproduction of hemoglobin, the main determinant of illness severity is the degree of imbalance in the  $\alpha$ -globin against  $\beta$ -globin biosynthetic ratio [13-15]. There is a two-fold increase in  $\alpha$ -globin production in  $\beta$ -thalassemia trait, which is associated with reasonably normal hematopoiesis with only minor microcytosis and red cell hypochromia. The  $\alpha$  to non- $\alpha$  biosynthetic ratio is normally 3–4/1 in people with thalassemia intermedia because residual  $\beta$ -globin synthesis ability and often modest but variable  $\gamma$ -globin synthesis capacity help to lessen the effects of excess globin production. The severe phenotype of people with  $\beta$ -thalassemia mutations is caused by a substantial chain biosynthesis imbalance. After being synthesized,  $\alpha$ -globin joins forces with  $\alpha$ -hemoglobin stabilizing protein (AHSP), a molecular chaperone, to create a protein complex before being released to join forces with  $\beta$ -globin to form the hemoglobin tetramer [16].  $\alpha$ -globin folding is facilitated by AHSP, which also prevents aggregates from forming improperly folded. Human microcytosis and anaemia are linked to  $\alpha$ -Globin mutations that hinder interaction with AHSP [17]. In a mouse model of  $\beta$  thalassemia, loss of AHSP has also been demonstrated to impair erythropoiesis [18]. There is proof that AHSP levels could affect the  $\beta$ -thalassemia phenotype [19].

## **RECENT ADVANCES IN THE TREATMENT OF BETA THALASSEMIA**

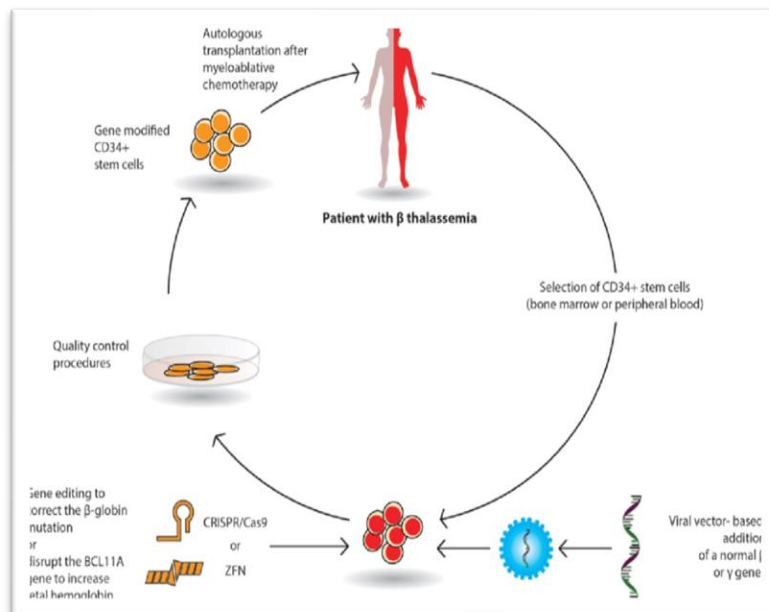
### **1) Bone marrow transplantation**

In a TDT patient, the goal of a bone marrow transplant is to restore the tissue's capacity to produce functional hemoglobin. According to data from the European Bone Marrow Transplant (EBMT) registry, after a median observation period of 2 years, the 2-year overall survival (OS) and event-free survival (EFS) rates were 88.1% and 81.1%, respectively, for 1493 consecutive patients with thalassemia major transplanted between 2000 and 2010. Patients who had received bone marrow, peripheral blood, or cord blood (individually or in combination) had OS and EFS of 90%, 81%, and 93% (P 0.001), respectively [20]. The Pesaro risk assessment [21], which divides transplantation outcomes into three classifications based on hepatomegaly, portal fibrosis, and irregular chelation history [22], is part of the pre-transplant examination. Patients in class 1 have none of the risk factors, patients in class 2 have one or two risk factors, and patients in class 3 have all three risk factors. While the transplant-related mortality (TRM) increased from class 1 to class 3, the thalassemia-free survival (TFS) was, respectively, 85-90% for class

1, 80% for class 2, and 65-70% for class 3 [23]. Therefore, HSCT should be made available to a young TDT patient with a matched sibling donor (MSD) before iron overload and consequent tissue damage emerge. A 2-year OS of 91% for MSD transplants, compared to 88% for matched family donors and 77% for matched unrelated donors, is the safest outcome, according EBMT data. In a recent study, Li et al. examined the usage of unrelated donors and HLA-matched related donors in China, India, and the USA for children and young adults with TDT. After HLA-matched relative, HLA-mismatched relative, HLA-matched unrelated, and HLA-mismatched unrelated donor transplants, the 5-year odds of overall survival (OS) were reported to be 89%, 73%, 87%, and 83%, respectively. After transplants using HLA-matched relatives, HLA-mismatched relatives, HLA-matched unrelated donors, and HLA-mismatched unrelated donors, the 5-year probabilities of EFS were 86%, 70%, 82%, and 78%, respectively [24]. Following transplantation from HLA-matched related and HLA-matched unrelated donors, this research demonstrates equivalent event-free and OS. Notably, the main restrictions on the use of hematopoietic stem cell transplantation (HSCT) are the availability of a suitable donor, the patient's fitness, and procedure-related toxicity. Due to this, it is necessary to research novel conditioning protocols or apply autologous gene therapy to the most extreme cases.

## 2) Gene Therapy

A very promising cure for beta-thalassemia involves the autologous transplantation of hematopoietic stem cells that have undergone genetic modification. Several gene transfer procedures have been thoroughly investigated over the past ten years. Among them, lentivirus vectors have been applied to erythroid stem Biology 2021, 10, 546 5 of 15 cells from thalassemic patients and thalassemic mice models. These studies have concentrated on the addition of or -globin, the upregulation of -globin-activating transcription factors, the silencing of DNA- or RNA-binding proteins that prevent the expression of -globin repressors, such as BCL11A, and the genome editing of -globin mutations or -globin repressors (Figure 4). Several clinical trials that are now being conducted have shown encouraging findings.



**Fig no : Stepwise procedure of gene therapy by gene addition and by gene editing in beta Thalassaemia**

In order to restore fetal Hb (HbF) production, the patient's chosen CD34+ erythroid progenitor cells (bone marrow or peripheral cells) undergo genetic modification either through the viral vector-based addition of a normal globin gene or through gene editing with nucleases (Crisp/Cas9 or ZFN), which corrects the globin mutation or deletes genomic regions of the BCL11A gene. After rigorous quality control processes, the genetically corrected CD34+ stem cells are ready for autologous transplantation. After receiving the appropriate myeloablative treatment, the patient is next given stem cells.

### 3) Allogeneic Hematopoietic Stem Cell Transplantation (ALLO-HSCT)

Allo-HSCT is a potentially effective cure for TDT illness, however its side effects and mortality raise serious questions. According to the Pesaro criteria, having good risk characteristics in TDT patients is associated with a success rate of more than 90%. Three factors related to iron toxicity are included in the Pesaro criteria, which are applicable to patients under the age of 16: the regularity of iron chelation, the existence of hepatomegaly, and the presence of liver fibrosis. The best candidates are typically young children without comorbidities and a sibling donor who shares the same human leukocyte antigen (HLA). Busulfan and cyclophosphamide, two alkylating drugs, are used in the usual myeloablative condition regimens in addition to chemotherapy [25-27]. Due to heightened rates of graft rejection and transplant-related mortality, AlloHSCT in thalassemic patients with high-risk criteria can be challenging. Adults with TDT will always be at high risk, but a number of novel conditioning protocols are being tested in clinical studies in an effort to enhance the outcomes of transplantation. Positive outcomes have been documented with modified or reduced intensity conditioning, as well as nonmyeloablative regimens (such as treosulfan/thiotepa/fludarabine). Age and Pesaro categorization both lose a significant amount of their prognostic power with these contemporary, promising techniques [28,29]. The bone marrow is a better source of stem cells than peripheral blood, probably because there is a lesser danger of developing chronic graft-versus-host disease. In an effort to reduce the likelihood of graft rejection in high-risk thalassemic patients, peripheral blood stem cells have also been employed. Fully matched sibling donors are ideal, however matched unrelated donors and related cord blood transfusions in patients meeting low-risk criteria may also be taken into account. Haploidentical transplants and unrelated umbilical cord blood cell collection should ideally take place in a clinical study setting.

### 4) Activin 2 Receptor Traps

Growth differentiation factors and activins are examples of transforming growth factor (TGF-) superfamily ligands that have been demonstrated to have an inhibitory effect on late-stage erythropoiesis [30-33]. In conditions characterized by inefficient erythropoiesis, such as -thalassemia [34] and myelodysplastic syndromes (MDS) [35], SMAD2/3 signaling can be reduced by the activin receptor ligand traps sotatercept and luspatercept. Activin receptor ligand traps have initially been thought to block GDF11-mediated signaling [36]. However, Guerra et al. recently demonstrated that in a mouse model of -thalassemia, the absence of GDF11 did not alleviate anaemia. The authors demonstrated that -thalassemia mice with a pan-cellular deletion of GDF11 or a deletion in the hematopoietic compartments responded to RAP-536 treatment, indicating that GDF11 is not the primary target of the activin receptor ligand trap and is probably not the main cause of ineffective erythropoiesis [37].



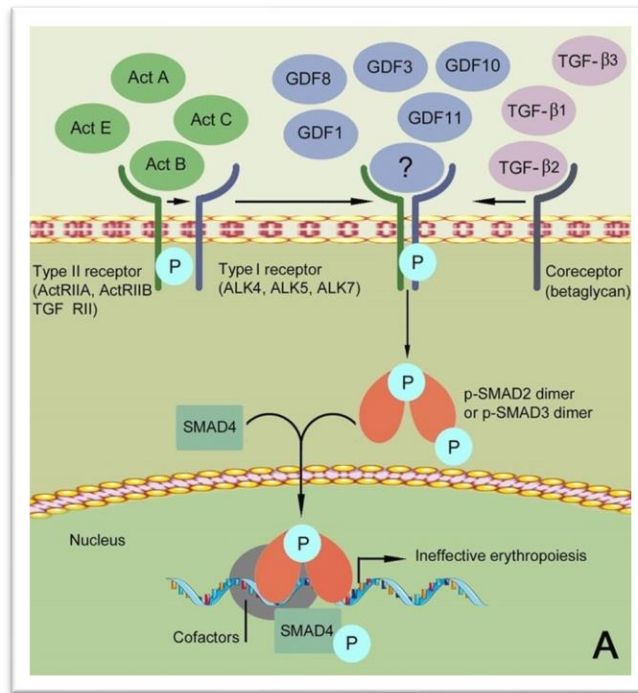


Fig. 4: New therapy approaches for beta-thalassemia targets. The ligand trap molecules for the activin receptor are directed at the  $\alpha$ SMAD2/3 signaling pathway. When type I and type II receptors bind to members of the transforming growth factor superfamily (TGF-), this results in multimerization. The type I receptor activates, resulting in the phosphorylation of SMAD2/SMAD3. This results in the gene being controlled and stimulating a cellular response with reduction of latestage erythropoiesis. It also causes dissociation from the type I receptor and oligomerization with SMAD4. By blocking the ligand from binding, lupaterecept and sotatercept inhibit this pathway and encourage late-stage erythropoiesis. JAK2 inhibitors, such as ruxolitinib, target the JAK2/STAT5 signaling pathway

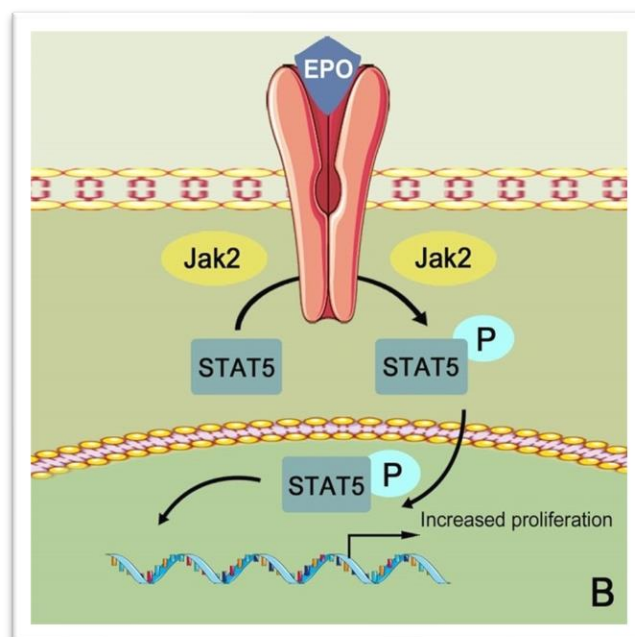


FIG 5: Erythropoietin (EPO) production is elevated in  $\alpha$ -thalassemia, which activates the JAK2/STAT5 pathway and affects erythroid progenitor proliferation and differentiation. c Mini-hepcidin and TMPRSS6 inhibitors aim to regulate hepcidin expression in hepatocytes. BMP6 and hemojuvelin (HJV) binding to the BMP6 receptor trigger a downstream signaling cascade through SMAD1, SMAD5, or SMAD8, which activate SMAD4. Then, SMAD4 will promote HAMP-encoded hepcidin transcription and expression. Other molecules, such as the transferrin receptor 2 (TFR2), which is associated with the human hemochromatosis protein (HFE) and the HJV, also control the SMAD signaling pathway. By cleaving HJV from the cell surface, transmembrane protease serine 6 (TMPRSS6) adversely regulates HAMP expression. The signaling route by which the production of erythroferrone (ERFE) reduces hepcidin expression is still unknown. Iron restriction is brought on by the injection of synthetic hepcidins and the suppression of TMPRSS6, which ultimately boosts hepcidin expression. Another class of medications that causes iron limitation is ferroportin inhibitors.

#### 4.1) Sotatercept (ACE-011)

By functioning as a ligand trap to block the TGF- $\beta$  superfamily's negative regulators of late-stage erythropoiesis, sotatercept or ACE-011 may be able to treat inefficient erythropoiesis. Between November 2012 and November 2014, a phase 2 study with sotatercept was carried out on 16 TDT patients and 30 NTDT patients in seven centers worldwide [38]. For TDT patients, the average treatment time was 13.8 months, whereas for NTDT or 1.0 mg/kg. Every three weeks, they were injected subcutaneously. Ten patients (63%) in the TDT group attained a transfusion burden, and two patients (13%), a reduction of 50%. The active dose of sotatercept in these individuals was 0.5 mg/kg, and the mean change in Hb level from baseline to the end of treatment was 0.7 g/dl.

On the other hand, in the NTDT group, 11 patients (37%) had a mean Hb increase of 1.5 g/dL sustained for 12 weeks, while 18 patients (60%) received sotatercept dosages ranging from 0.1 to 1.0 mg/kg and experienced a mean Hb increase of 1.0 g/dL [39]. The majority of patients accepted sotatercept well, and it had an overall positive safety profile. The prevalence of grade 3–4 adverse events was modest, and treatment discontinuation due to them was uncommon.

#### 4.2) Luspatercept

It is also known as ACE-536 or luspatercept, and it is a recombinant fusion protein that traps activin receptors. It has just received FDA approval for the treatment of TDT patients at the initial dose of 1 mg/kg administered subcutaneously once every three weeks. Overall, luspatercept was well tolerated and linked to a dose-dependent rise in Hb levels in healthy individuals. In a mouse model of  $\alpha$ -thalassemia, RAP-536, a murine analogue of luspatercept, was similarly demonstrated to lessen oxidative stress and anaemia.

### 5) JAK2 Inhibitors

JAK2 has been implicated in a number of studies as a potential target for the treatment of erythropoiesis abnormalities [40]. JAK2 inhibition enhanced inefficient erythropoiesis in TDT and NTDT mouse models and also restored splenomegaly [41-42]. These results have led to the suggestion that ruxolitinib use may be advantageous for those with  $\alpha$ -thalassemia. Ruxolitinib's effectiveness and safety were evaluated in a phase 2a research in TDT patients with enlarged spleens. Ruxolitinib was administered to a total of 30 TDT patients at a beginning dose of 10 mg twice daily. Patients using ruxolitinib experienced a reduction in spleen size from the beginning of their treatment. Between baseline and weeks 12 (n=26) and 30 (n=25),

the mean change in spleen volume was 19.7% and 26.8%, respectively. One patient showed an increase in spleen volume at week 30 after originally experiencing a 15% drop. There were no clinically meaningful decreases in pre-transfusion Hb, which prevented any corresponding decrease in transfusion requirements. Furthermore, although hepcidin levels rose in the ruxolitinib treatment group over time, neither blood iron nor ferritin levels showed any discernible alterations [43]. The study did not enter phase 3 for all of the aforementioned reasons.

## 6) Modulating iron metabolism

Hepcidin is the primary regulator of iron metabolism [44], and despite iron overload, patients with thalassemia have low levels of hepcidin [45,46]. Preclinical investigations have looked into a significant variety of substances that boost hepcidin expression or activity and have found that they have positive effects [47,48]. Agents that directly target ferroportin can have a similar ferroportin-reducing impact by preventing the binding of hepcidin and preventing the internalization and destruction of the iron exporter protein. Approaches that disrupt the underlying regulatory mechanisms may be advantageous due to the homeostatic regulation of hepcidin expression [49]. One of these is the inhibition of matriptase 2 (MT2), which prevents haemojuvelin from being cleaved. [50,51].

### 6.1) Minihepcidin

Minihepcidin are known to limit iron absorption. They can therefore be applied to iron dysregulation. A 2016 young Hbbth3/+ mice, which have traits similar to the human NTDT phenotype, have inefficient erythropoiesis, anaemia, splenomegaly, and iron overload, as demonstrated by a study by Casu et al. However, the injection of Minihepcidin along with the iron chelator deferiprone was able to alleviate inefficient erythropoiesis, anaemia, and reverse splenomegaly in aged Hbbth3/+ mice.

### 6.2) Ferroportin inhibitors

The use of ferroportin inhibitors is a more modern strategy to combat inefficient erythropoiesis through the modification of iron metabolism. The ferroportin inhibitory small oral molecule VIT-2763 is a recently described chemical in the field. VIT-2763 inhibited the outflow of iron from cells, outcompeted hepcidin for ferroportin binding, and induced ferroportin internalization and ubiquitination. VIT-2763 enhanced erythropoiesis and reduced anaemia in Hbbth3/+mice.

Additionally, ROS levels were subsequently reduced, and the medication also reduced overall oxidative damage. The hypoxic cycle was inhibited and EPO synthesis was decreased by the treatment of VIT-2763 to Hbbth3/+mice, which also increased overall tissue oxygenation. The usage of this medication also reduced hepatic iron excess. Furthermore, after 3 weeks of dosing with VIT-2763, a considerable improvement in myelopoiesis was seen in the spleen of Hbbth3/+mice.

## 7) Phosphodiesterase 9 Inhibition

A novel therapy goal for sickle cell anaemia and thalassemia is to change intracellular cyclic guanosine monophosphate (cGMP). The cGMP-dependent pathway plays numerous roles in vascular biology and is important for the synthesis of HbF. Because phosphodiesterase (PDE) 9 specifically breaks down cGMP in erythropoietic cells, using PDE9 inhibitors can raise cGMP levels and reactivate HbF [52,53]. IMR-687 is a brand-new drug that was created to inhibit PDE 9. IMR-687 has recently been used orally in sickle cell disease patients, and it has been proven to boost HbF synthesis, improve Hb levels, and improve



haemolysis indicators<sup>[54]</sup> TDT and NTDT adult thalassemic patients have been enrolled in a comparable phase 2 research to assess the safety and tolerability of IMR-687 when administered once daily for 36 weeks.

### 8) Transmembrane protease serine 6 (TMPRSS6)

Increasing hepatic hepcidin production is one of the cutting-edge treatment strategies to address iron imbalance. The TMPRSS6 gene can be suppressed to do this. It has been demonstrated that infective erythropoiesis, anaemia, and splenomegaly can all be improved in Hbbth3/+ mice by deleting the TMPRSS6 gene. In Hbbth3/+ mice, the targeting of TMPRSS6 with second-generation antisense oligonucleotides (ASOs) has also been documented. Targeting TMPRSS6 by ASO can modify the expression of the hepcidin antimicrobial peptide (HAMP), according to a study by Guo et al. Using mice with hemochromatosis (Hfe-/-), the ASO-treated group displayed significant improvements in inefficient erythropoiesis, a considerable reduction in iron parameters and liver iron buildup, decreased erythropoietin levels, a decrease in splenomegaly, and higher Hb levels<sup>[55]</sup>. Another work by Schmidt et al. demonstrated that TMPRSS6 can be downregulated by using small interfering RNAs (siRNA). They demonstrated that treating Hbbth3/+ mice with lipid nanoparticles-TMPRSS6 siRNA caused hepcidin to be produced and reduced the levels of tissue and serum iron. Ionis Pharmaceuticals will soon begin a phase 2a research in patients with NTDT 18 years of age utilizing TMPRSS6 inhibitors. Patients will receive IONIS TMPRSS6-LRx subcutaneously every four weeks as part of this trial. The proportion of individuals whose plasma Hb increased by less than 1.0 g/dL from baseline at week 27 will be one of the study's primary outcome measures. Silence Therapeutics is also working on SLN124, a GalNAc attached double-stranded completely modified siRNA that targets the TMPRSS6 messenger RNA (mRNA) The safety, tolerability, pharmacokinetics, and pharmacodynamic response of SLN124 are being studied in an adult patient population with NTDT and very low- and low-risk myelodysplastic syndrome (MDS) in a randomized, single-blind, placebo-controlled, phase 1b, single-ascending and multiple-dose study.

### 9) New iron chelation

The prognosis of beta-thalassemia major has significantly improved over the past 30 years thanks to conventional treatment, which generally consists of routine blood transfusions and iron chelation therapy with desferrioxamine (DFO). Effective parenteral DFO delivery decreases or prevents iron buildup and iron-mediated organ damage, which consistently lowers morbidity and mortality. Chelation with DFO, however, could not be sufficient for a number of reasons. The exorbitant costs of the medication and the materials required for its administration prevent most patients in developing Middle Eastern and Far Eastern nations, where thalassemia is a significant public health issue, from accessing it. DFO is reportedly only given for 25,000 of the 72,000 thalassemia major patients who receive blood transfusions on a regular basis worldwide. Despite the widespread availability of DFO in Western nations, some patients find it difficult to adhere to the recommended course of treatment because the effective chelation regimen is uncomfortable and time-consuming and necessitates repeated daily subcutaneous or intravenous administration.

Additionally, some patients may experience adverse effects of varying severity that impair compliance or occasionally force a halt to therapy. In a recent study, 105 of 328 North American patients who had previously undergone chelation therapy with DFO reported problems that necessitated changing the

chelator's dose or route of administration, and 20 reported quitting DFO. Iron overload could cause mortality if a person cannot handle the strenuous and demanding long-term use of DFO.

Alternative iron chelators are being sought after because DFO is unavailable for the majority of thalassemia major patients and the recommended therapy does not work to stop problems in other people. More than 1000 molecules with synthetic, microbial, or plant origins have been examined in vitro and in vivo during the past 25 years, and a number of intriguing compounds have been discovered. Deferiprone (DFP), one of them, has been on the market for 9 years in India and 5 years in Europe, while the others are the subject of active clinical research. The rate of iron accumulation varies by organ, and each organ has a unique susceptibility to the harm caused by reactive iron species like intracellular labile iron pool (LIP) and nontransferrin bound iron (NTBI).

Understanding the relative accessibility of iron chelators to those various pools requires more research. Methods for measuring these iron species are becoming more accessible and sensitive, and they may help us better understand how different chelators work and make it easier to create customized chelation plans. These findings suggest a role for specialized chelators that remove iron from particular organs. Since cardiac illness is one of the most significant life-limiting effects of iron overload in thalassemia, effective chelation should also target a decrease in iron in certain organs, especially the heart.

Development of iron chelation

Ex: Deferiprone

Desferrithiocin

Hydroxybenyl-ethlenediamino-diacetic acid

Prriodoxalisonicotinoyl hydrazone

### CLINICAL TRIALS OF NOVEL TREATMENT IN B THALASSEMIA

Treatment Modality	Mechanism	Route	Phase	ClinicalTrials.gov (8 may 2021)	Status	Institution/ Developer
Luspatercept	Ligand trap TGF beta superfamily	Subcutaneous	2  2 Extensi on Study	NCT01749540  NCT02268409 NCT03342404 NCT04143724	Comple ted  Comple ted Open Not yet	Acceleron Pharma, Celgene Corporation
Mitapivat	Pyruvate kinase activation	Orel	2	NCT03692052	Open	Agios Pharmaceutic als
TMPRSS6L Rx	Matriptase-2 inhibition Hepcidin activation	Subcutaneo us	2	NCT04059406	Open	Ionis Pharmaceutic als

SLN124	Matriptase-2 inhibition Hepcidin activation	Subcutaneous	2	NCT04718844	Open	Silence Therapeutics Plc
PTG-300	Hepcidin Analog	Subcutaneous	2	NCT04054921	Completed	Protagonists Therapeutics, Inc.
VIT-2763  HSCT	Ferroportin Inhibition  Reduced intensity Conditioning	Oral  Matched Sibling donor  Family related Matched Donor or cord	2  1,2  2	NCT04364269  NCT00920972, NCT01050855,  NCT00408447	Open  Open  Recruiting	Vifor (International ) Inc US, Canada US, Canada  University, USA
IMR-687	Phosphodiesterase 9 inhibitions, HbF stimulation	Oral	2	NCT04411082	Completed	Imara, Inc

HSCT	Matched unrelated		2	NCT01049854	Completed	New York Medical College , USA
HSCT	Nonmyeloablative haploidentical	Haploidentical Transplants	1,2	NCT00977691	Completed	National heart, lungs And blood Institute (NHLBI)
HSCT	Nonmyeloablative Peripheral blood mobilized	Allogeneic Peripheral Blood stem cell	1,2	NCT02105766	Open	National heart,lungs And blood Institute (NHLBI)

HSCT	Umbilical cord blood	Umbilical Cord stem cells	1	NCT02126046	Open	Nanfang Hospital of southern medical university
HSCT CordIn™	Umbilical cord blood -derived ex vivo stem cells	Ex vivo Umbilical cord Stem cells	1	NCT02504619	Completed	Gamida cell ltd

### CONCLUSION

New therapeutic strategies that aim to directly repair the imbalance between the  $\alpha$ - and  $\beta$ -globin chains through gene therapy or address inefficient erythropoiesis operating on several pathways have been made possible by the advancement in our understanding of  $\beta$ -thalassemia pathogenesis. On the other hand, because of the complexity of genes and the less inefficient erythropoiesis component, the therapy of  $\beta$ -thalassemias is less advanced than for  $\alpha$ -thalassemias. While the loss of three genes, or illness, is phenotypically an  $\alpha$ -thalassemia, the most severe type of  $\beta$ -thalassemia (missing of the four genes), i.e., Hb Bart's, which results in hydrops fetalis, necessitates in utero intervention.

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