

THALASSAEMIA INTERNATIONAL FEDERATION (TIF)

14th International Conference
on Thalassaemia and Other Haemoglobinopathies
& 16th TIF Conference for Patients and Parents

17-19 November 2017 • Grand Hotel Palace, Thessaloniki, Greece

The TIF logo is a red teardrop shape containing a white world map. The letters "TIF" are written in white above the map. The teardrop is set against a background of a grey building silhouette and a red and white circular swoosh.

**Development of a GalNAc-siRNA Conjugate Targeting
TMPRSS6 for Treatment of Iron Overload**

Dr. Ute Schaeper

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Iron Overload in β -Thalassemia

- Mutations in HBB cause “stressed” erythropoiesis, hemolytic anemia & GI hyperabsorption of dietary iron
- Blood transfusions further enhance iron overload
- High iron levels worsen anemia and enhance dependency on blood transfusions
- Tissue accumulation of iron yields to organ damage & premature death

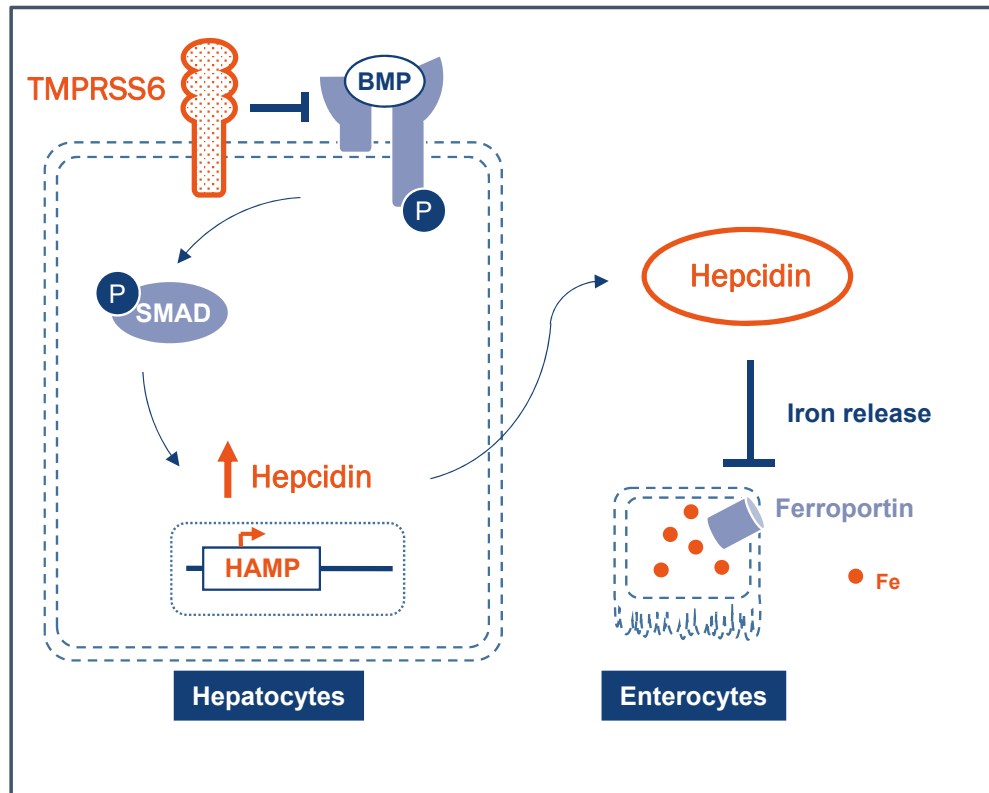
Medical Need:

- Reduce iron overload, improve erythropoiesis & reduce requirement for blood transfusions

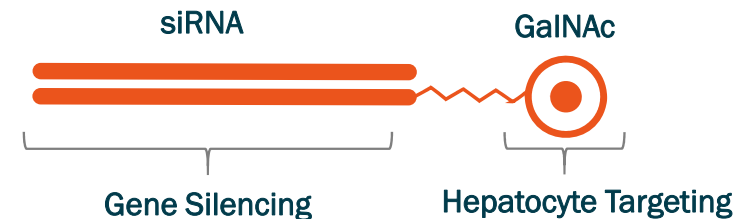
Project Goal:

- Target a key modulator of iron homeostasis by GalNAc siRNA approach

Rationale for Targeting TMPRSS6



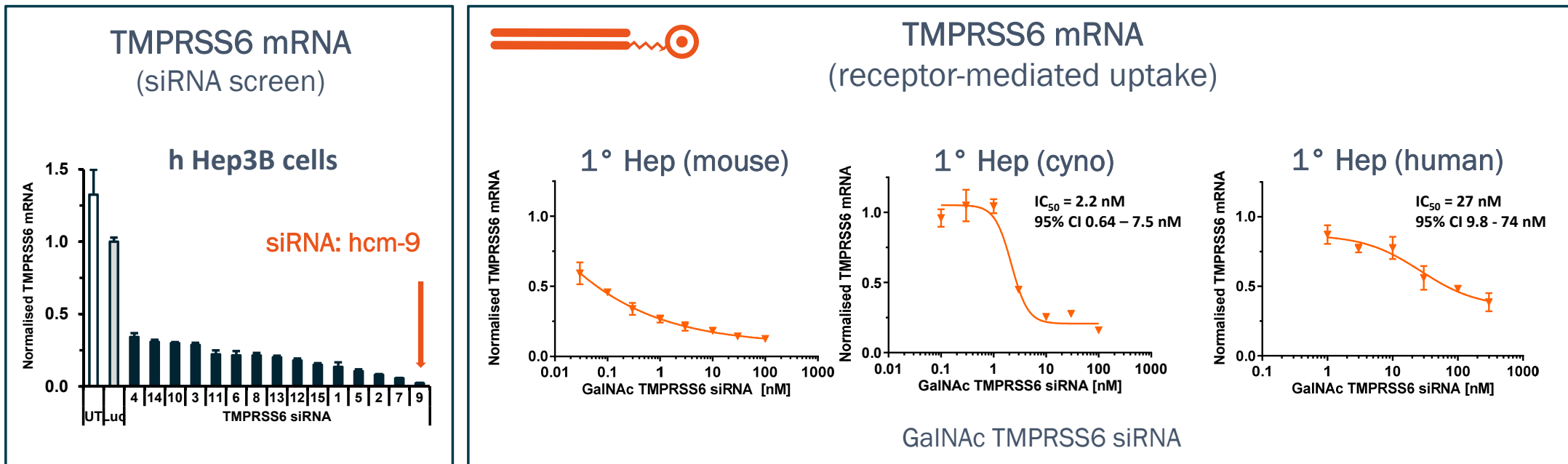
- > **TMPRSS6** is a negative regulator of the BMP/SMAD signaling pathway; activation of the pathway induces hepcidin expression
- > **Hepcidin** reduces uptake of dietary iron and the release of iron from cellular storage
- > **Hepcidin** levels are low in patients with iron loading anemias
- > **Inhibition of TMPRSS6** expression in the liver should raise hepcidin and reduce iron absorption
- > **GaINAc siRNA** approach for gene silencing in the liver



→ Silencing TMPRSS6 in the liver increases hepcidin expression, reduces systemic iron levels & improves erythropoiesis

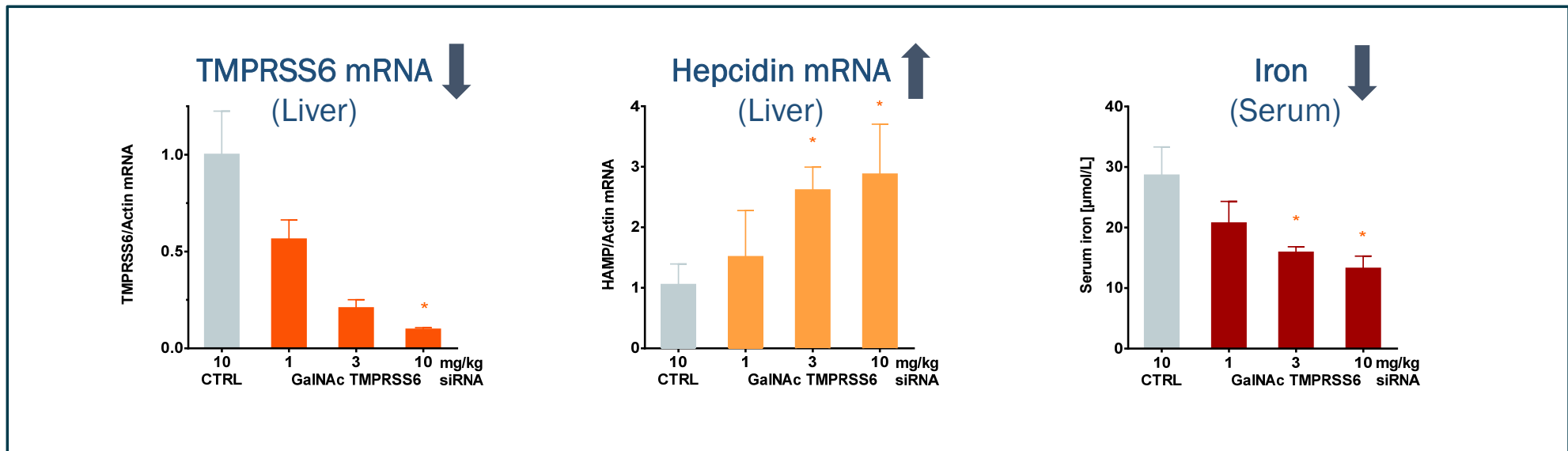


GaINAc siRNA Conjugate Inhibits TMPRSS6 Expression in 1° Hepatocytes by Receptor-Mediated Uptake



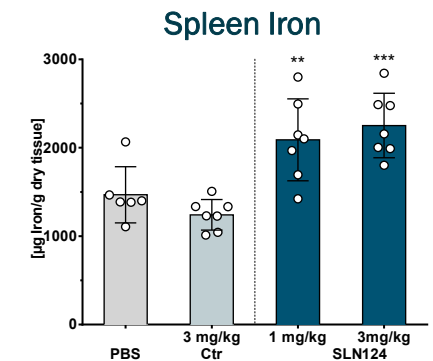
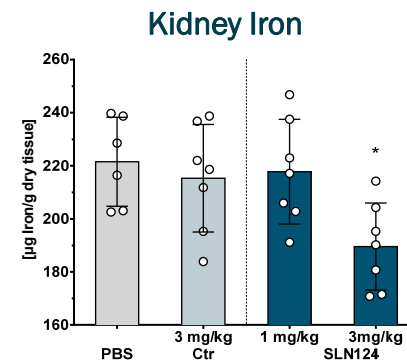
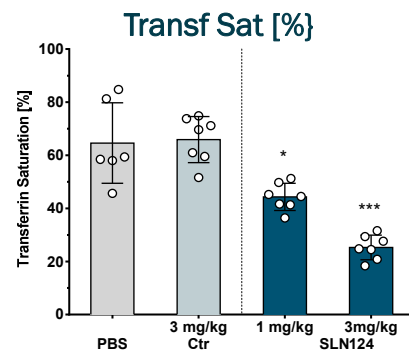
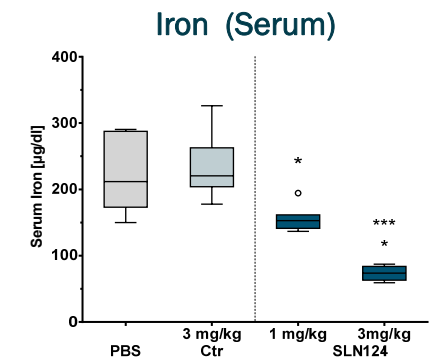
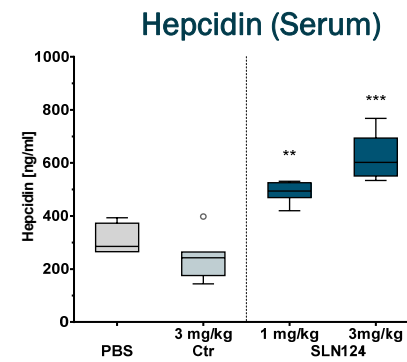
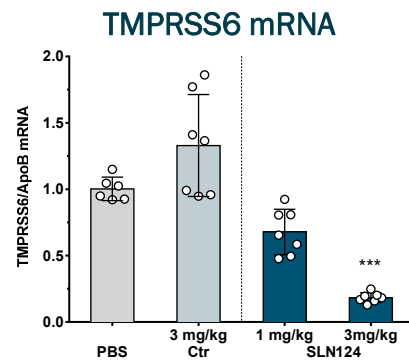
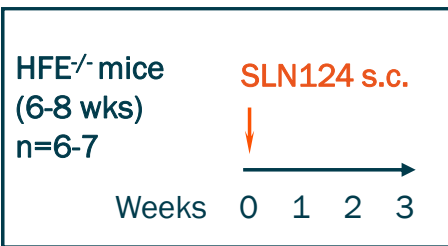
- Lead siRNA for TMPRSS6 identified (picomolar IC_{50} by transfection)
- GaINAc siRNA conjugate is functional in 1° hepatocytes from different species (mouse, human, cynomolgus)

TMPRSS6 siRNA Conjugate is Functional in vivo (Mice)



→ POM: Silencing of TMPRSS6 in the liver induces Hepcidin expression and lowers serum iron levels in mice

SLN124 Lowers Serum Iron Levels and Modulates Tissue Iron Distribution in Rodent Model for Hereditary Hemochromatosis



Prof. Muckenthaler
 Heidelberg University

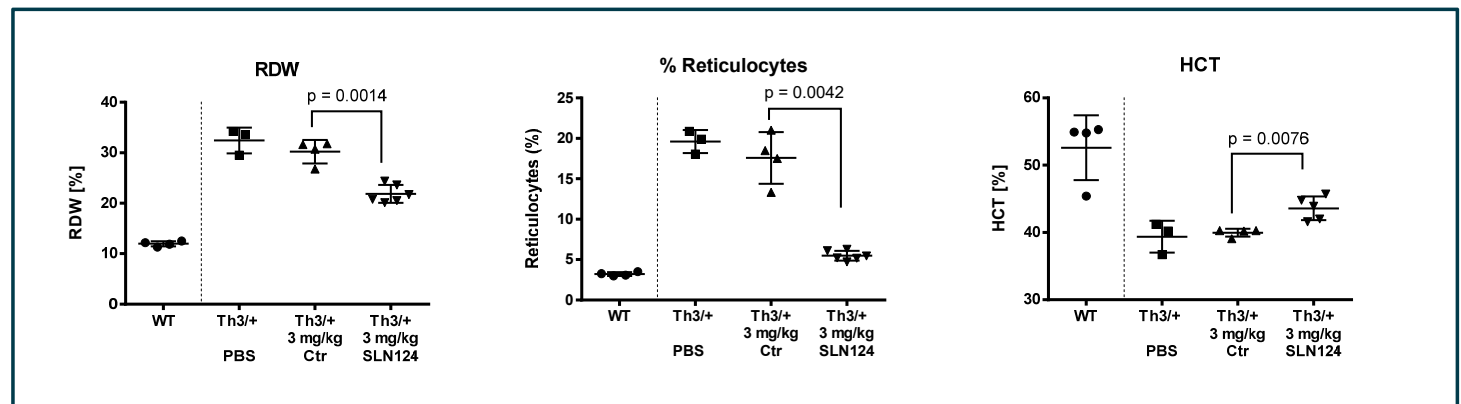
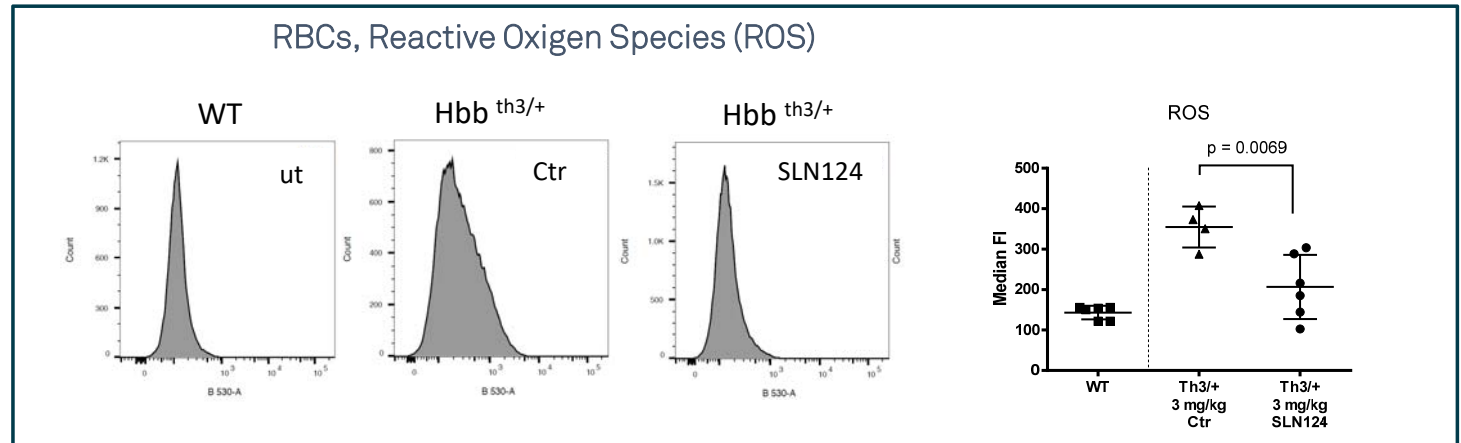


SLN124 Normalises ROS and Improves RBC Parameters in β -Thalassaemia Intermedia Disease Model ($Hbb^{th3/+}$ Mice)

$Hbb^{th3/+}$ mice
(6-8 wks)
n=3-6

SLN124 s.c.

Weeks 0 1 2 3 4 5





Summary & Conclusion

SLN124 a GalNAc siRNA conjugate targeting TMPRSS6 expression in the liver

- > Highly potent, with durable activity by single s.c. application
 - > Lowers serum iron levels, transferrin saturation and reduces tissue iron accumulation in rodent model of hereditary hemochromatosis
 - > Normalises ROS in RBC, improves RBC parameter in rodent model for β -Thalassemia intermedia
 - > Is well tolerated in mice & NHP's after single dose
 - > Non-Clinical Development and CMC has started in Q2/2017
 - > Start of Clinical Development is planned for Q4 2018
- SLN124 represents a promising therapeutic candidate for patients with iron overload disorders, such as β -Thalassemia and Hereditary Hemochromatosis



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