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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

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

Dr. Ute Schaeper

Nov 19th 2017

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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

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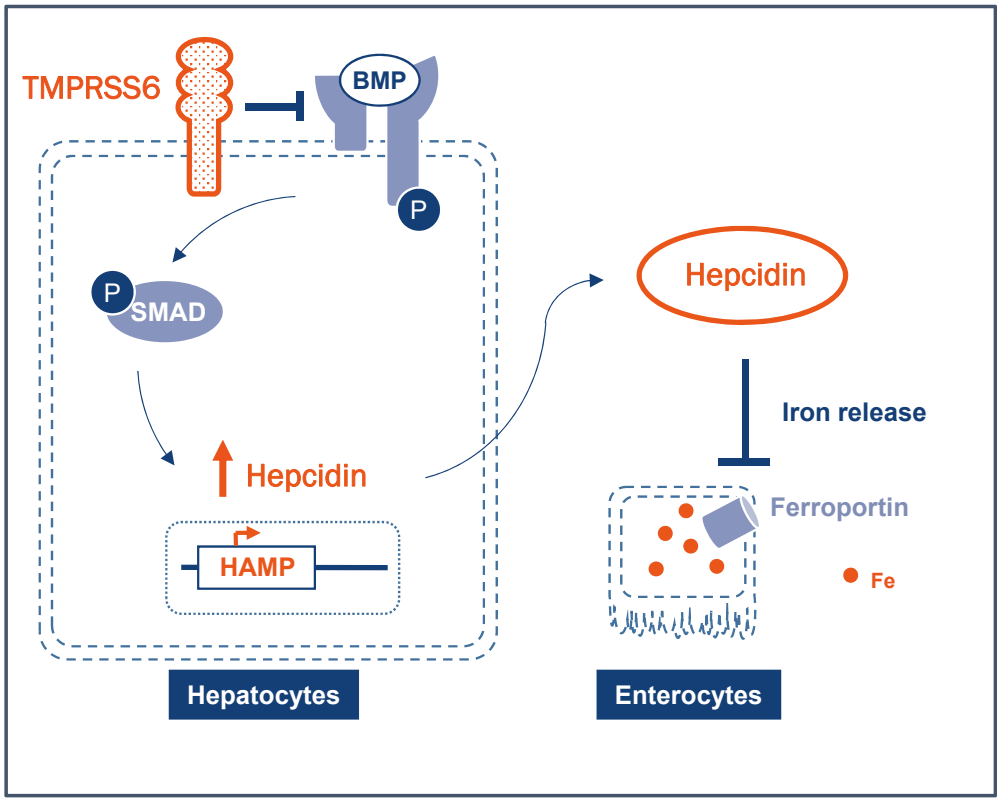
Rationale for Targeting TMPRSS6



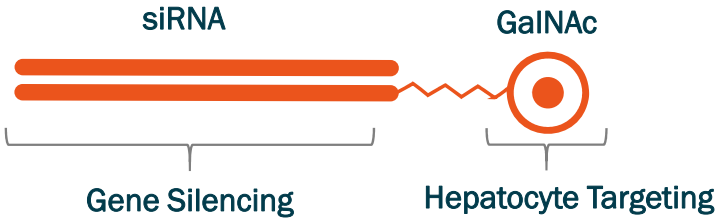
> **TMPRSS6** is a negative regulator of the BMP/SMAD signaling pathway; activation of the pathway induces Hepcidin expression

> **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

> **GalNAc siRNA approach** for gene silencing in the liver



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

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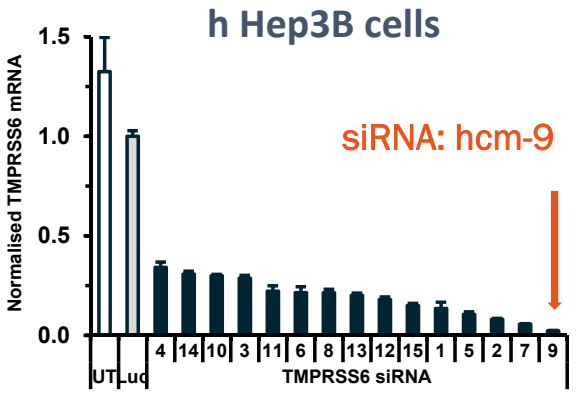
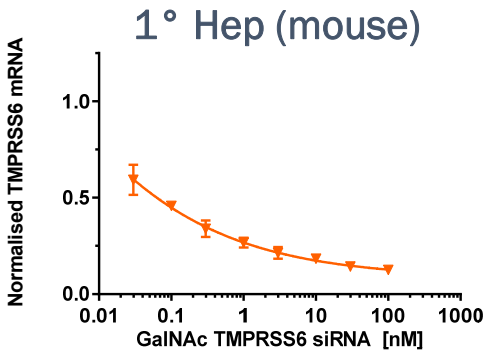
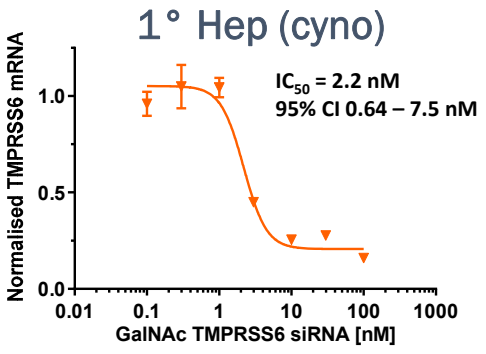
GalNAc siRNA Conjugate Inhibits TMPRSS6 Expression in 1° Hepatocytes by Receptor-Mediated Uptake

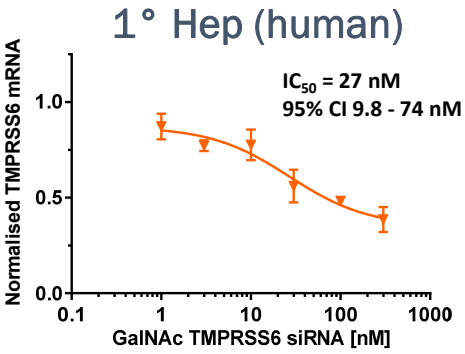
TMPRSS6 mRNA (siRNA screen)



TMPRSS6 mRNA (receptor-mediated uptake)







GalNAc TMPRSS6 siRNA

→ Lead siRNA for TMPRSS6 identified (picomolar IC_{50} by transfection)

→ GalNAc siRNA conjugate is functional in 1° hepatocytes from different species (mouse, human, cynomolgus)

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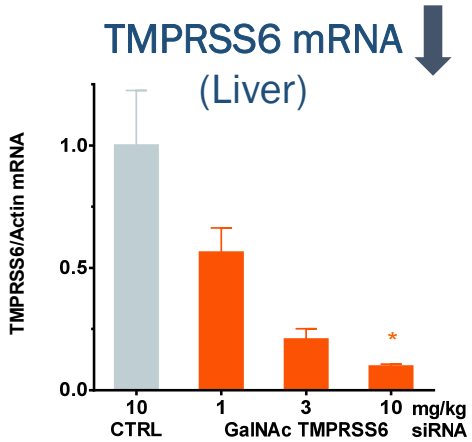
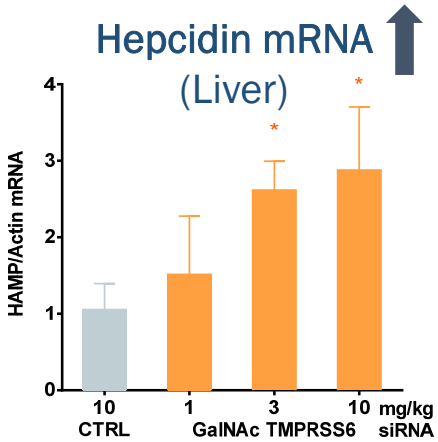
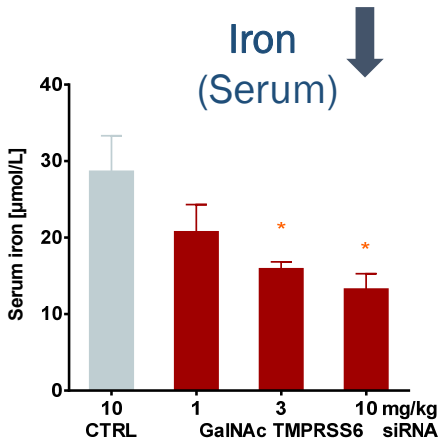
TMPRSS6 siRNA Conjugate is Functional in vivo (Mice)







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

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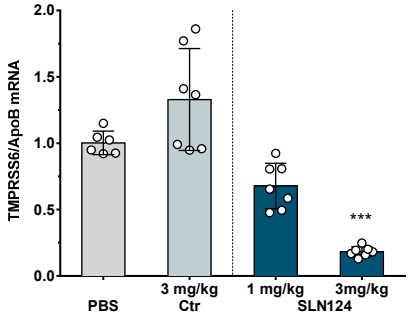
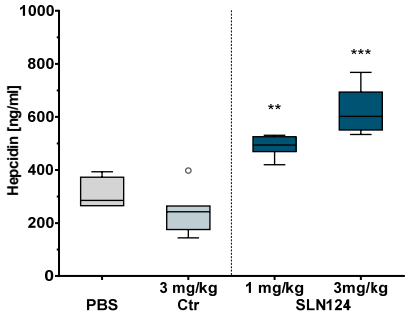
SLN124 Lowers Serum Iron Levels and Modulates Tissue Iron Distribution in Rodent Model for Hereditary Hemochromatosis

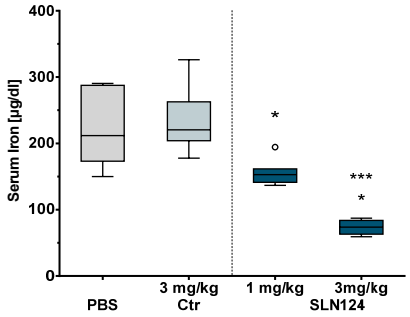
HFE$^{-/-}$ mice
(6-8 wks)
n=6-7

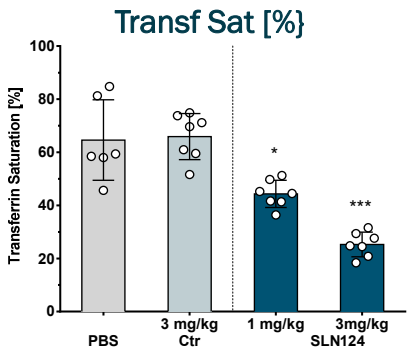
SLN124 s.c.

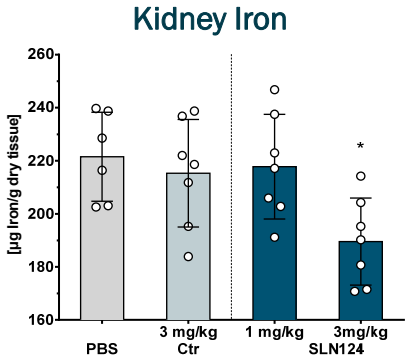
Weeks 0 1 2 3

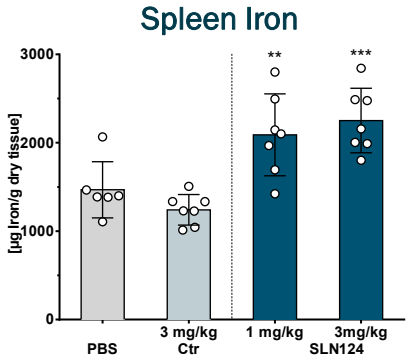












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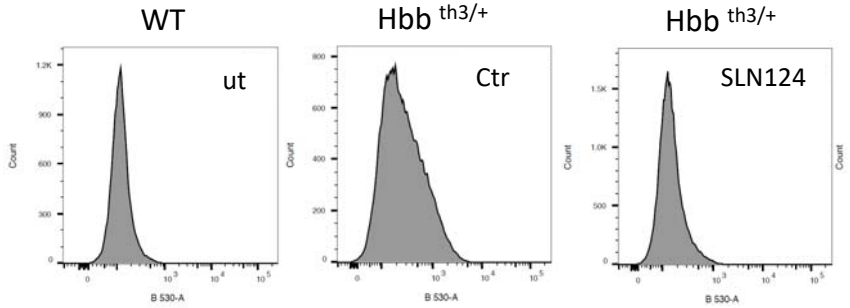
SLN124 Normalises ROS and Improves RBC Parameters in β–Thalassemia Intermedia Disease Model ($Hbb^{th3/+}$ Mice)

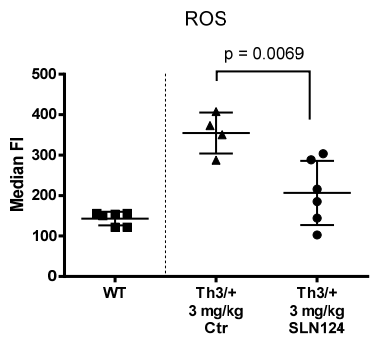
$Hbb^{th3/+}$ mice
(6-8 wks)
n=3-6

SLN124 s.c.

Weeks 0 1 2 3 4 5

RBCs, Reactive Oxigen Species (ROS)





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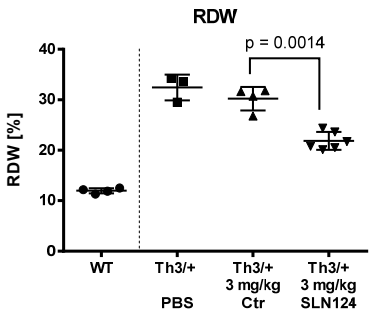

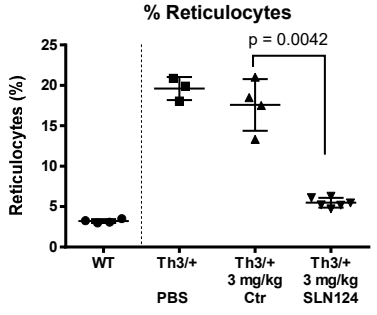

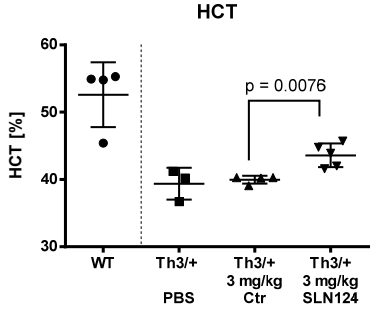

Summary & Conclusion

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

Acknowledgements

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