

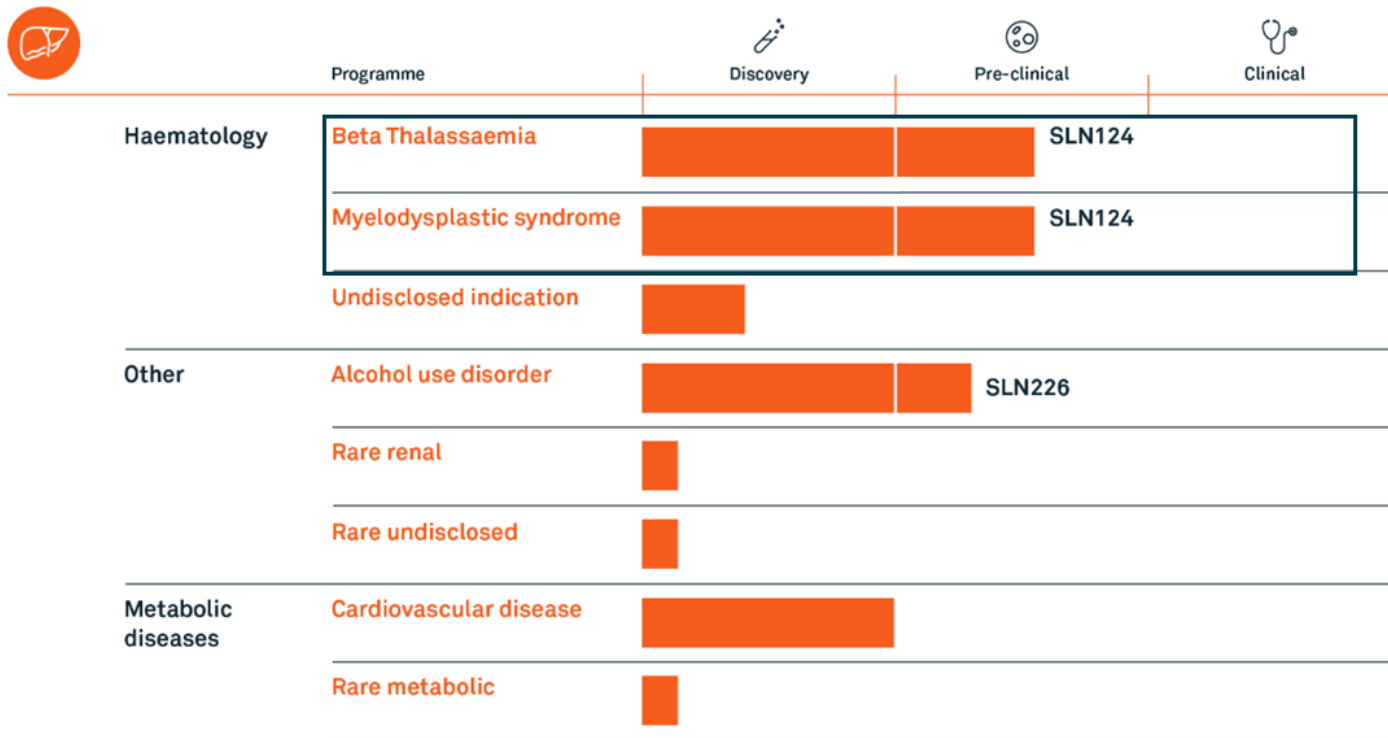


EHA June 14th to 17th 2018; Iron: from basic science to clinical application

Development of a GalNAc siRNA conjugate targeting TMPRSS6 for the treatment of iron overload disorders such as β -Thalassaemia

Ute Schaeper, PhD
Project Leader Drug Discovery

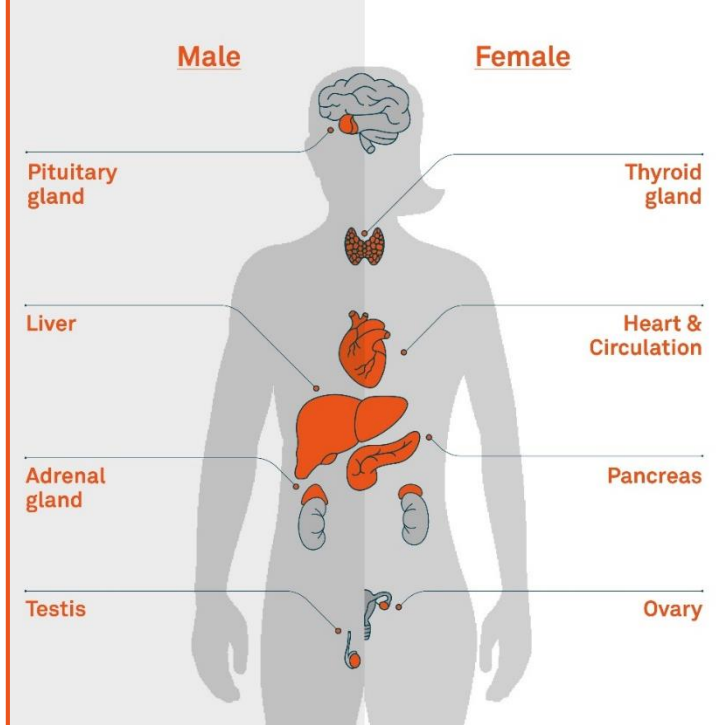
Our internal pipeline





Iron overload disorders

Organs affected by iron overload



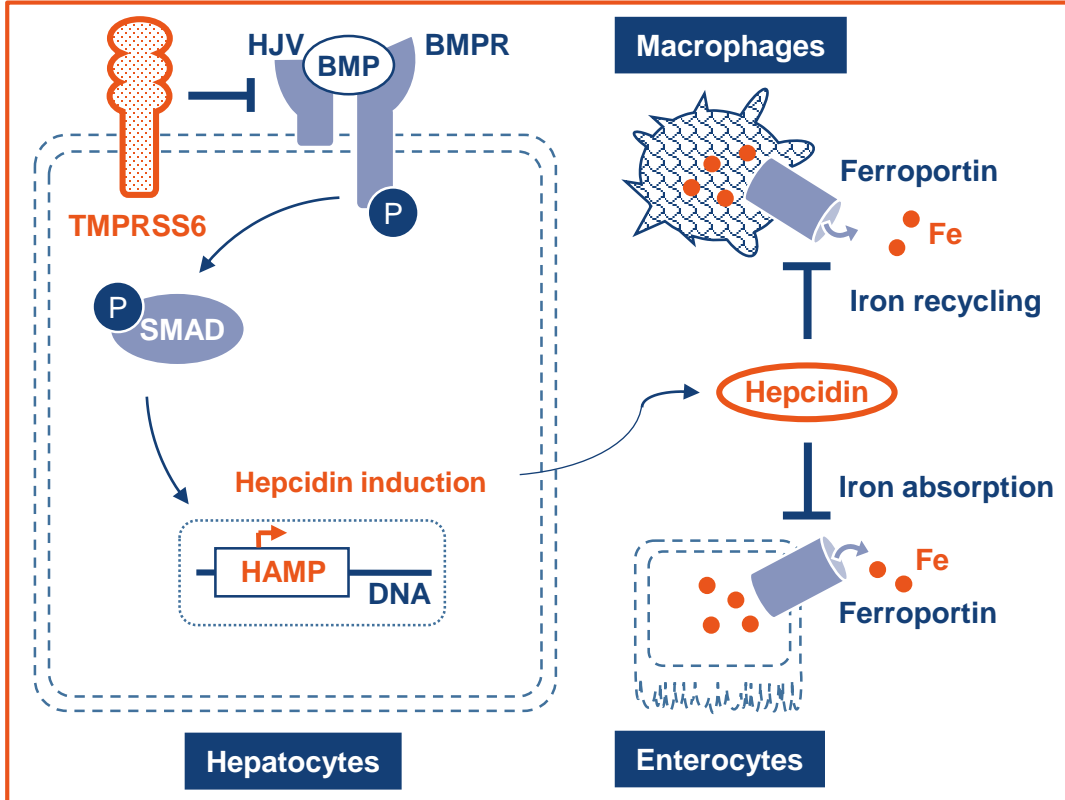
Diseases with iron overload

- > β -Thalassaemia
- > Myelodysplastic Syndrome
- > Hereditary Haemochromatosis
- > Aplastic Anaemia
- > Sideroblastic Anaemia

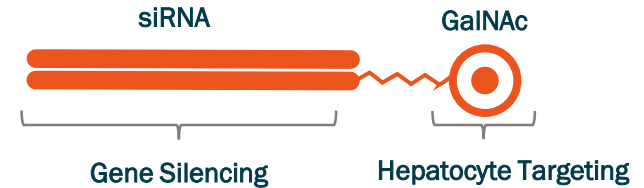
If untreated, iron accumulation in organs leads to severe damage, e.g. heart, liver & endocrine organs



Rationale for targeting TMPRSS6 in iron overload disorders



- > **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 storage cells
- > **Hepcidin** levels are low in patients with hereditary haemochromatosis and in patients with iron loading anaemias, like β -thalassaemia
- > **Therapeutic hypothesis:** inhibition of TMPRSS6 expression in the liver will raise hepcidin and reduce iron absorption
- > **GaINAc siRNA approach** for gene silencing in the liver



Therapeutic activity of SLN124 in a disease model of Hereditary Haemochromatosis type 1 (1/2)

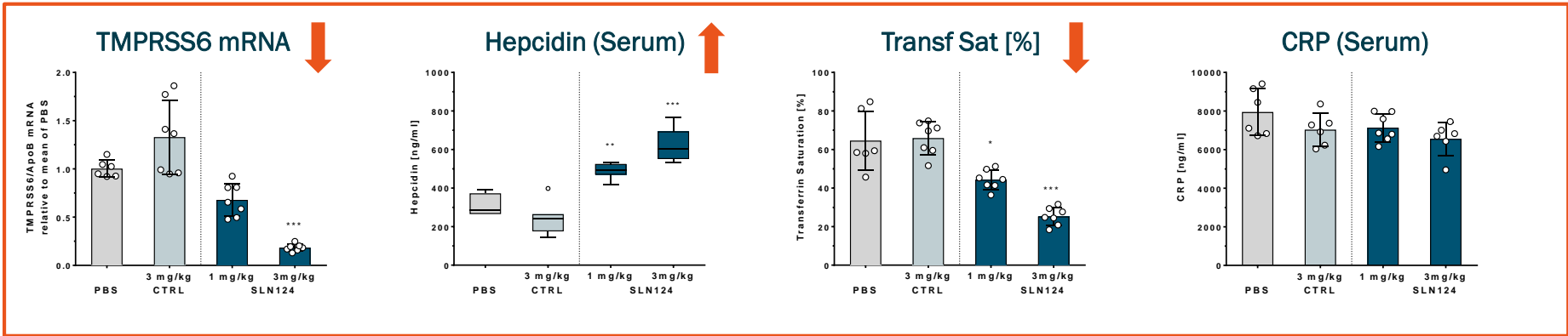


Study design



Hfe^{-/-} mice
model of HH type 1

Collaboration with
Prof. Dr. Martina Muckenthaler
Heidelberg University, Germany



- > Dose-dependent and robust silencing of TMPRSS6 mRNA in the liver
- > Induction of hepcidin expression and normalisation of iron levels and transferrin saturation
- > No induction of inflammatory marker, C-reactive protein

Therapeutic activity of SLN124 in a disease model of Hereditary Haemochromatosis type 1 (2/2)



Study design

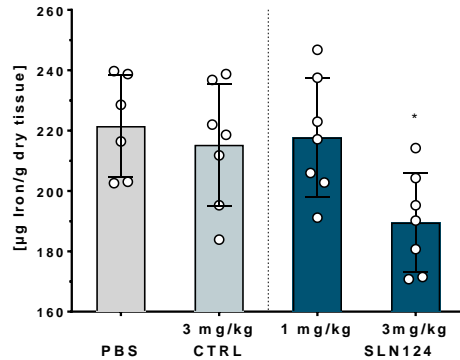


Hfe^{-/-} mice
model of HH type 1

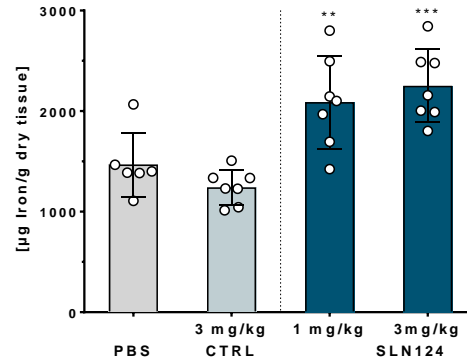
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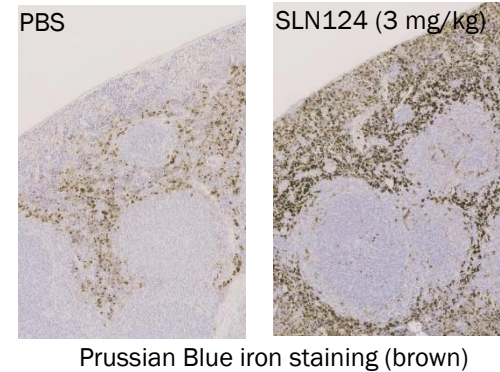
Kidney Iron



Spleen Iron



Spleen Iron

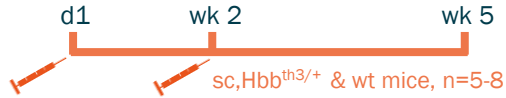


> Reduction of tissue iron levels and redistribution to spleen (storage compartment)

SLN124 improves anaemia and normalises spleen size in a murine model of β -thalassaemia intermedia



Study design

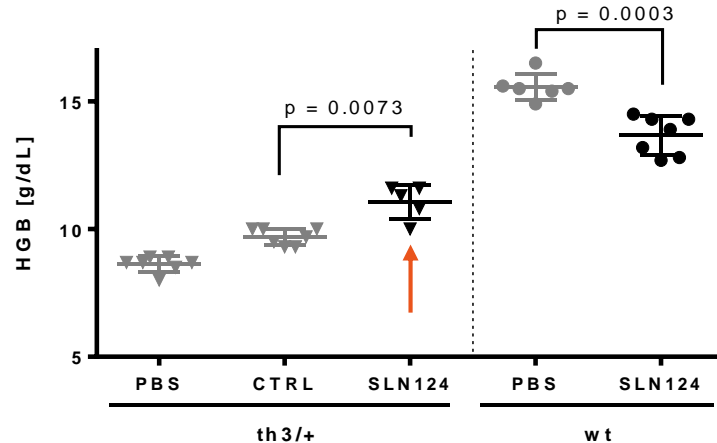


$Hbb^{th3/+}$ mice
model of β -thalassaemia
intermedia

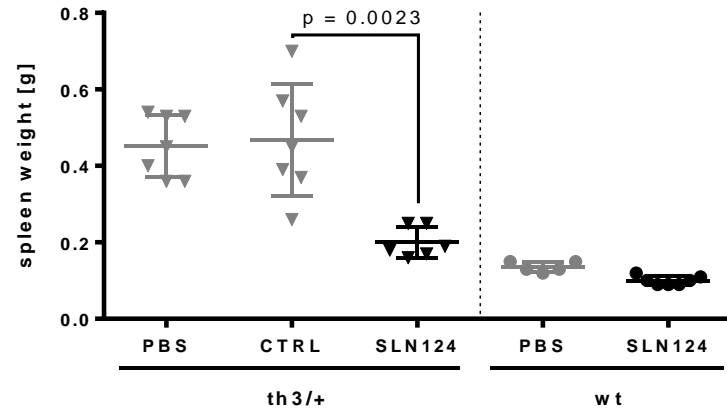
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Haemoglobin



Spleen Weight

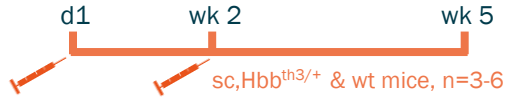


- > The amelioration of anaemia leads to a significant reduction in spleen size and correction of splenomegaly

SLN124 reduces ROS in red blood cells of β -thalassaemia intermedia mice



Study design

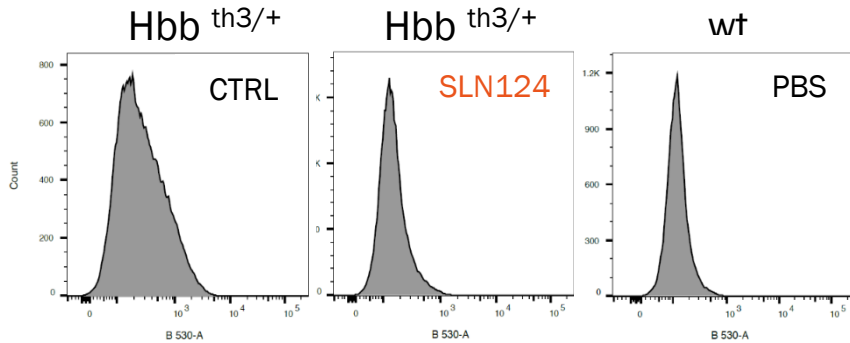


Hbb^{th3/+} mice
model of β -thalassaemia
intermedia

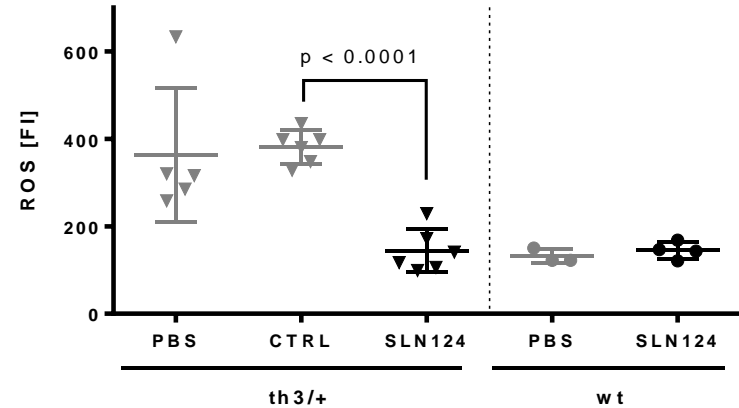
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Reactive Oxygen Species



Reactive Oxygen Species

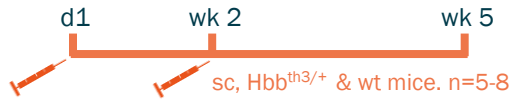


> SLN124 normalises ROS levels in animal model for β -thalassaemia

SLN124 ameliorates RDW and normalises proportion of reticulocytes in β -thalassaemia intermedia model



Study design

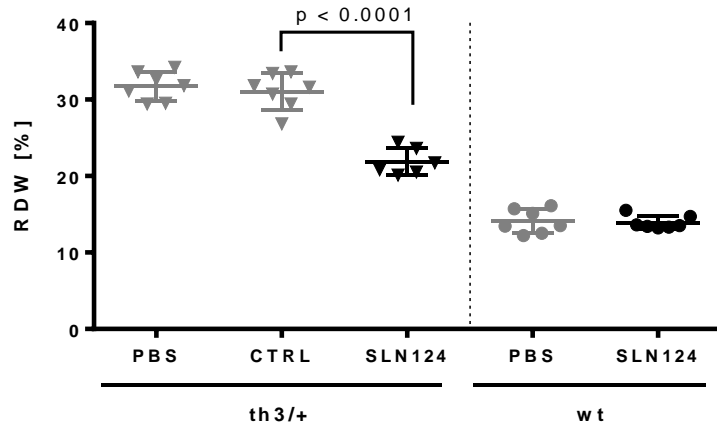


Hbb^{th3/+} mice
model of β -thalassaemia
intermedia

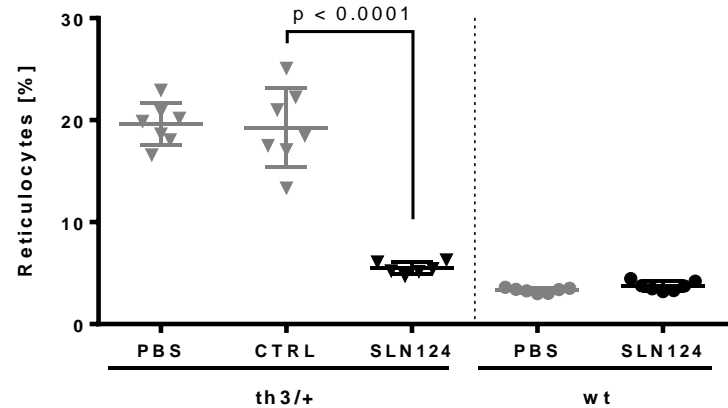
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Red Cell Distribution Width

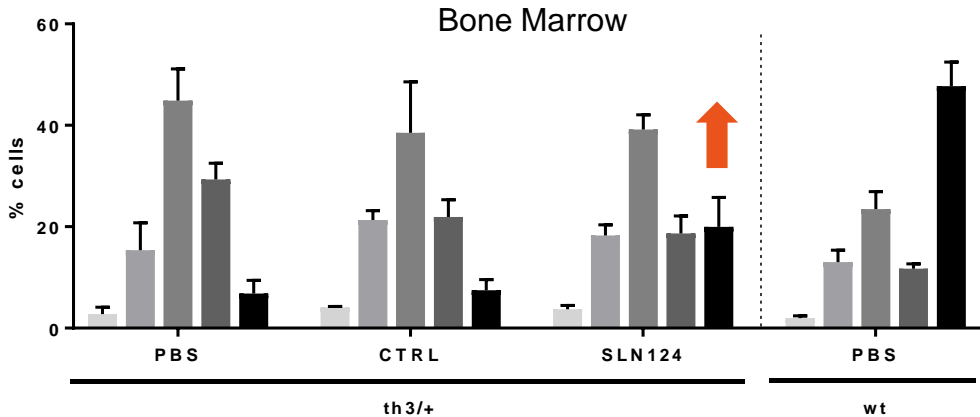
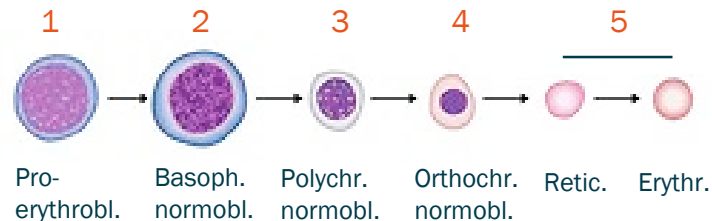
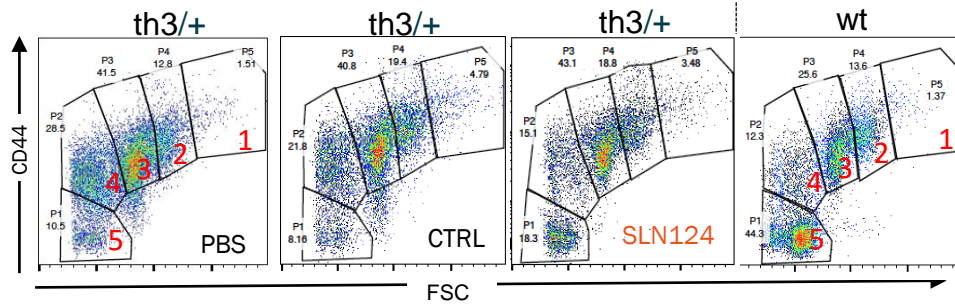


Reticulocytes



> SLN124 improves red blood cell maturation

SLN124 ameliorates RBC maturation in bone marrow

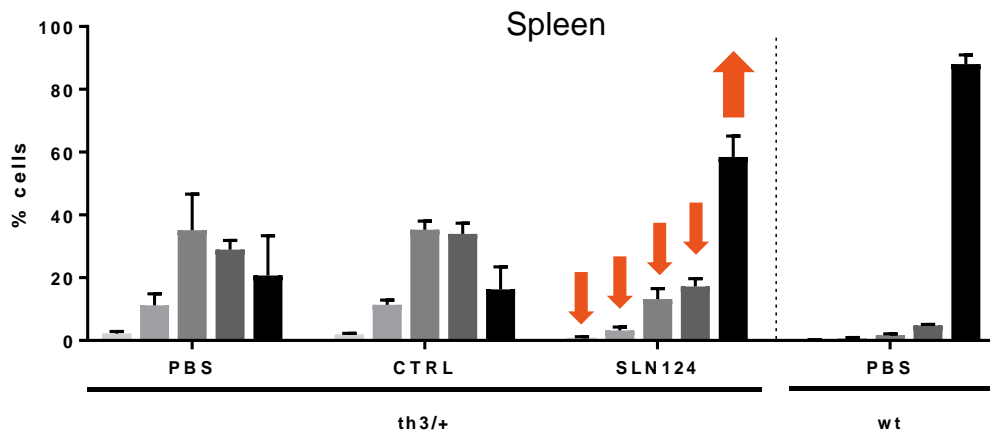
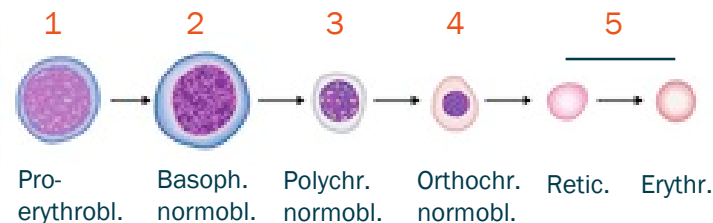
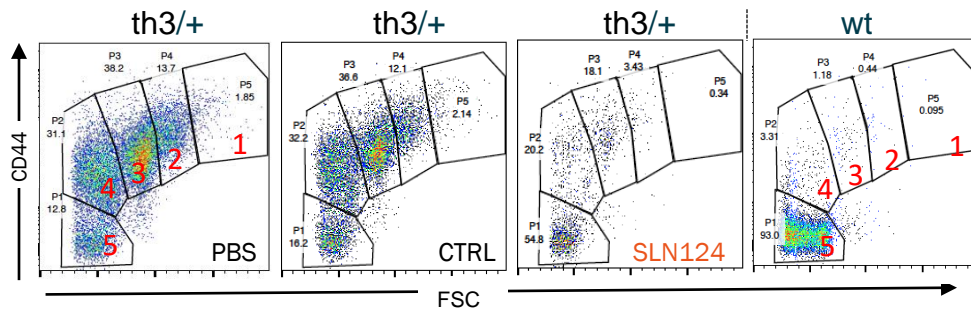


Erythroid subpopulations

- 1: proerythroblast
- 2: basophilic normoblast
- 3: polychromatophilic normoblast
- 4: orthochromatic normoblast
- 5: erythrocytes + reticulocytes



SLN124 reduces ineffective erythropoiesis in spleen



Erythroid subpopulations

- 1: proerythroblast
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- 4: orthochromatic normoblast
- 5: erythrocytes + reticulocytes



SLN124 - Summary

- > Highly potent, specific, safe and long-acting GalNAc-siRNA conjugate
- > Efficacious in lowering systemic iron levels and improving erythropoiesis and RBC parameters in murine disease models
- > Demonstrated therapeutic efficacy in clinically relevant animal models for β -thalassaemia intermedia and hereditary haemochromatosis
- > Currently in preclinical development with plans to enter the clinic in 2019

SLN124 represents a highly valuable therapeutic candidate for patients with iron overload disorders, such as β -thalassaemia

Acknowledgements



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