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

<table>
<thead>
<tr>
<th>Programme</th>
<th>Discovery</th>
<th>Pre-clinical</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta Thalassaemia</td>
<td></td>
<td></td>
<td>SLN124</td>
</tr>
<tr>
<td>Myelodysplastic syndrome</td>
<td></td>
<td></td>
<td>SLN124</td>
</tr>
<tr>
<td>Undisclosed indication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol use disorder</td>
<td></td>
<td></td>
<td>SLN226</td>
</tr>
<tr>
<td>Rare renal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rare undisclosed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolic diseases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rare metabolic</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Iron overload disorders

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.
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.

GalNAc 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

d1 wk 3

1X sc, HFE⁻/⁻ mice, females, 6 wks, n=6-7

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

© Silence Therapeutics 2018
Therapeutic activity of SLN124 in a disease model of Hereditary Haemochromatosis type 1 (2/2)

Study design

Hfe⁻/⁻ mice model of HH type 1

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

Kidney 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<sup>th3/+</sup> mice model of β-thalassaemia intermedia
- Collaboration with Dr. J. Vadolas & Dr. G. Grigoriadis
  Monash Medical Centre/Melbourne, Australia

> 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

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

**Study design**

Hbb<sup>th3/+</sup> mice model of β-thalassaemia intermedia

Collaboration with Dr. J. Vadolas & Dr. G. Grigoriadis
Monash Medical Centre/Melbourne, Australia

**Reactive Oxygen Species**

- Hbb<sup>th3/+</sup> CTRL
- Hbb<sup>th3/+</sup> SLN124
- wt PBS

**Reactive Oxygen Species**

- ROS [FI]
- p < 0.0001

© Silence Therapeutics 2018
SLN124 ameliorates RDW and normalises proportion of reticulocytes in β-thalassaemia intermedia model

Study design

d1, wk 2, wk 5
sc, Hbb\textsuperscript{th3/+} & wt mice. n=5-8

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

Collaboration with Dr. J. Vadolas & Dr. G. Grigoriadis
Monash Medical Centre/Melbourne, Australia

Red Cell Distribution Width

\begin{align*}
\text{RDW [\%]} & \\
\text{PBS} & \downarrow & \text{CTRL} & \downarrow & \text{SLN124} \\
\text{th 3/+} & \downarrow & \text{wt} & \\
\end{align*}

\text{p < 0.0001}

Reticulocytes

\begin{align*}
\text{Reticulocytes [%]} & \\
\text{PBS} & \downarrow & \text{CTRL} & \downarrow & \text{SLN124} \\
\text{th 3/+} & \downarrow & \text{wt} & \\
\end{align*}

\text{p < 0.0001}

\text{> 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
2: basophilic normoblast
3: polychromatophilic normoblast
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

Silence Therapeutics

Heidelberg University
Prof. Dr. M. Muckenthaler
Dr. S. Altamura

Monash Medical Centre/Melbourne
Dr. J. Vadolas
Dr. G. Grigoriadis

S. Dames
Dr. K. Löffler
M. Eisermann
Dr. S. Schubert
Dr. C. Frauendorf
Dr. L. Bethge
N. Roeder
M. Aleku
Dr. U. Zügel