SILENCE THERAPEUTICS

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Pipeline and platform progress for hepatocyte-targeted siRNAs

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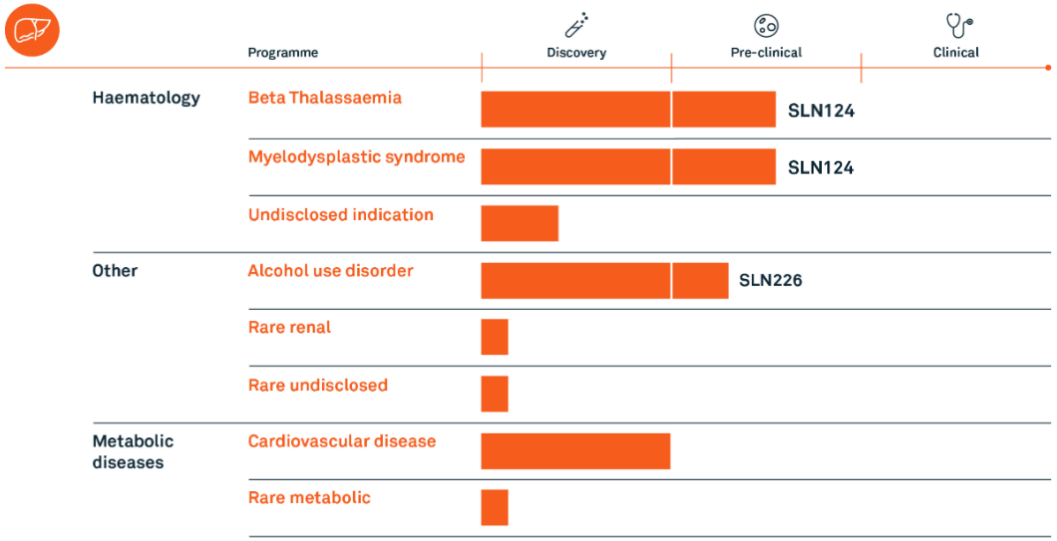
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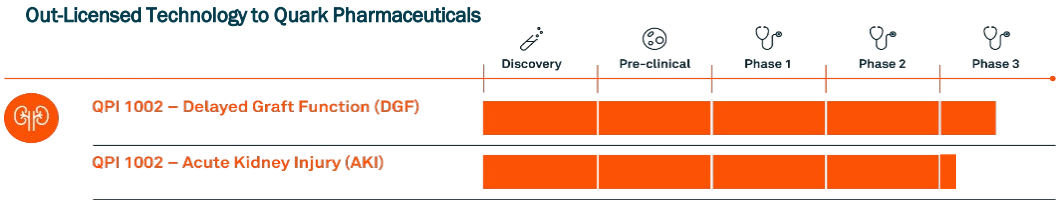
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Our pipeline





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SLN124 for the treatment of iron overload disorders

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Treatment of iron overload disorders

GOAL

> Provide an effective and safe novel treatment option for patients with iron overload conditions, such as β-Thalassemia and Myelodysplastic syndrome

RATIONALE

> Target TMPRSS6, a key modulator in iron regulation with a GalNAc-siRNA molecule providing a highly specific, effective & safe option through inhibition of a disease relevant target gene expressed in hepatocytes

CURRENT STAGE

> Preclinical development with plans to enter the clinic in 2019

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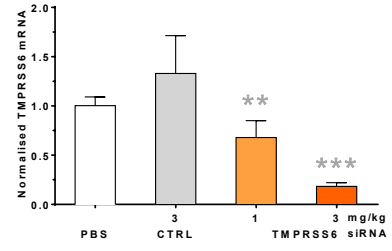
Therapeutic activity of SLN124 in a disease model for hereditary haemochromatosis ($HFE^{-/-}$ mice)

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

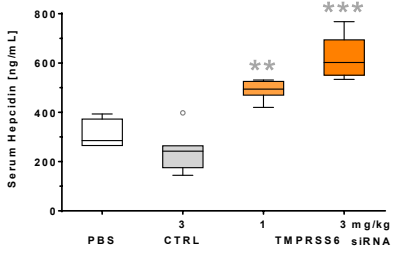
Study design



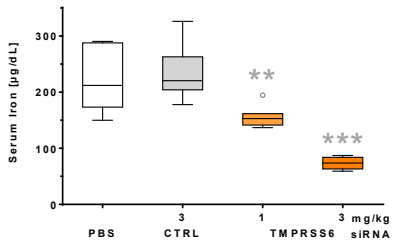
TMPRSS6 mRNA (liver)



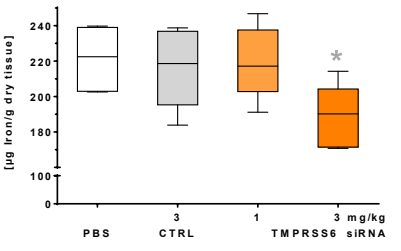
Hepcidin (serum)



Iron (serum)



Iron (kidney)



Kruskal-Wallis test with uncorrected Dunn's test against non-targeting control CTRL

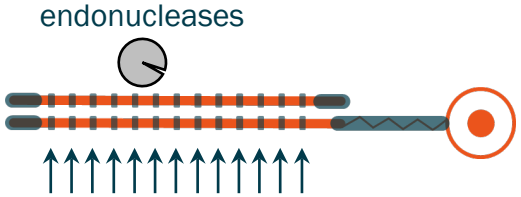
- Dose-dependent and robust silencing of TMPRSS6 mRNA in the liver
- Increase in serum hepcidin levels
- Reduction of serum and kidney iron levels to physiological values

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Making a good thing better:
when less is more

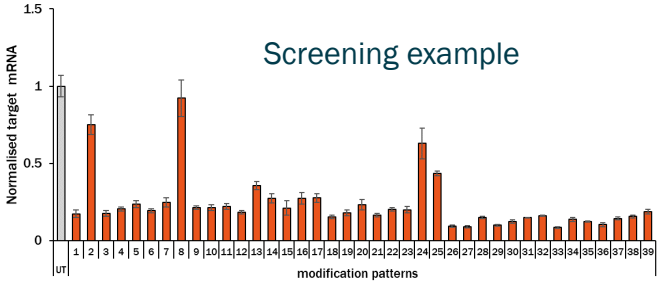
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Minimizing the use of non-natural nucleotides

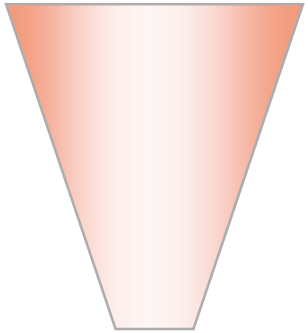


Internal siRNA modifications

Screening example



Hundreds of chemical modification patterns
~50% non-natural



Unique chemical modification patterns
<15% non-natural

***In vitro* activity**: without GalNAc, with various modifications, patterns, sequences

Serum stability: with or without GalNAc

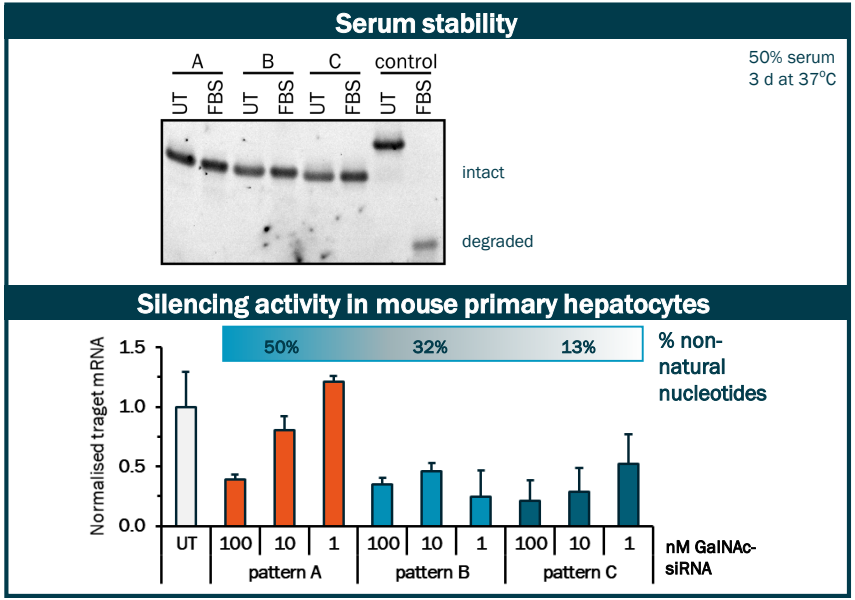
Primary hepatocyte activity: with GalNAc

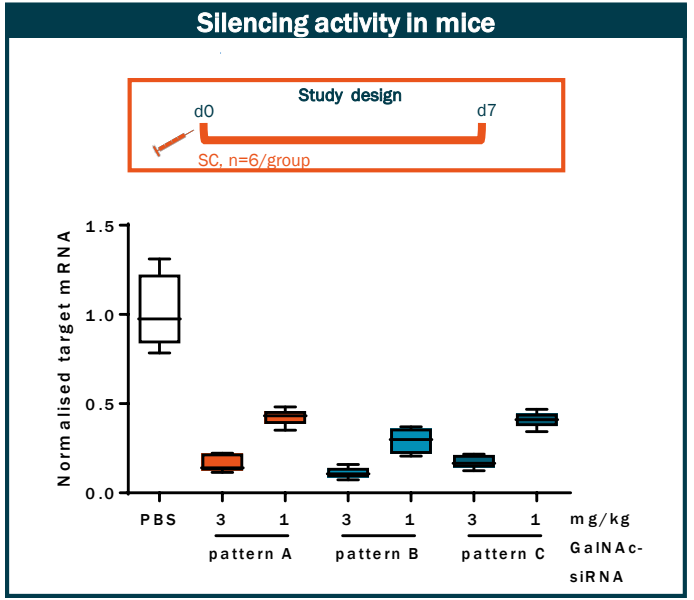
Animal activity: with GalNAc

> Hundreds of variations (chemical modifications, patterns, sequences) were tested to identify patterns with reduced non-natural nucleotide content from ~50% to less than 15%

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GalNAc-conjugated siRNA with reduced 2'F modified nucleobase content





- Non-natural siRNA modifications can be dramatically reduced with retained serum stability, and activity in primary hepatocytes, compared to molecules with 50% non-natural modifications
- GalNAc-conjugated siRNA with reduced non-natural nucleotide content demonstrate similar or improved dose-dependent reduction of target transcript in livers of treated mice (compared to 50% non-natural modifications)

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Optimizing number and position of GalNAc units

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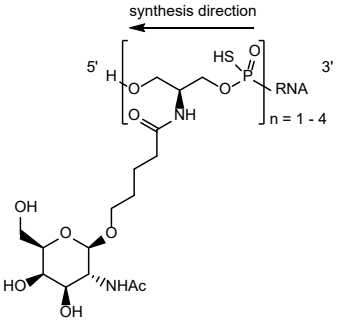
Stepwise path to new design

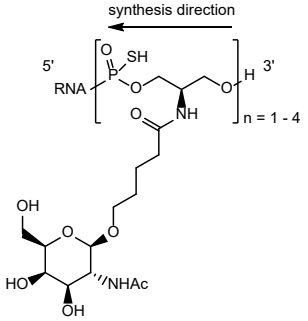
> **Step 1:** investigating optimal number and location for “serial clusters”
  - 1-4 serinol-linked GalNAc units were conjugated to 3’ or 5’ sense or antisense strand
  - All conjugates were screened for stability (tritosomes) and *in vitro* activity (primary mouse hepatocytes), several conjugates were also tested *in vivo* (mice)

> Result from step 1:
  - 5’ antisense conjugates are stable but inactive *in vitro*
  - All other positions gave stable conjugates with only minor differences between 2-4 GalNAc units and a triantennary control compound

> **Step 2:** investigating optimal distance between two 3’ antisense positioned GalNAc units
  - Similar *in vitro* activity (primary mouse hepatocytes) for two serinol linked GalNAc units comparing short or long spacing (longest spacer a C12 carbohydrate chain)

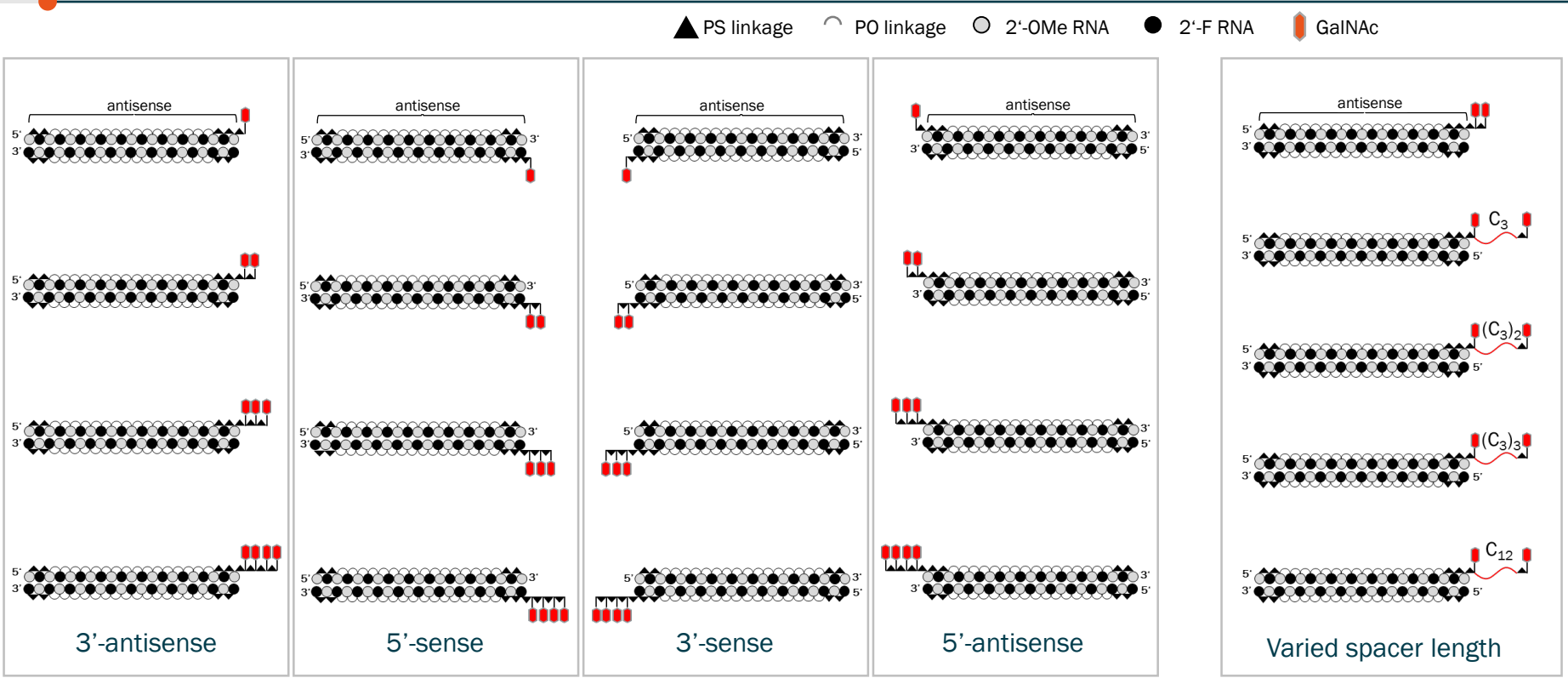
> **Step 3:** Asking the question “If two GalNAc units, close or spaced far between, are sufficient for *in vitro* activity, what will happen if we position single GalNAc units at different end locations in the siRNA?”





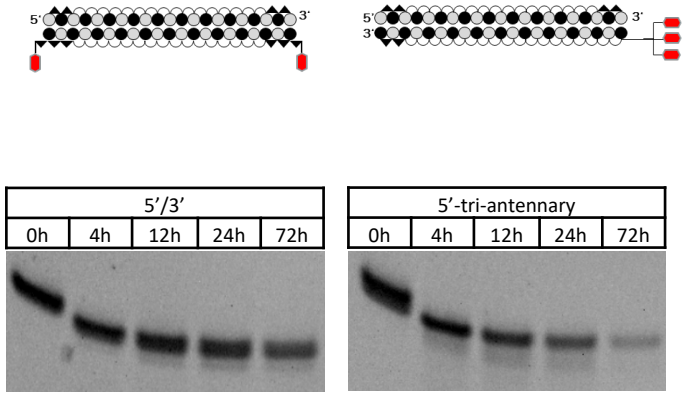
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Serial serinol linked conjugate designs steps 1-2

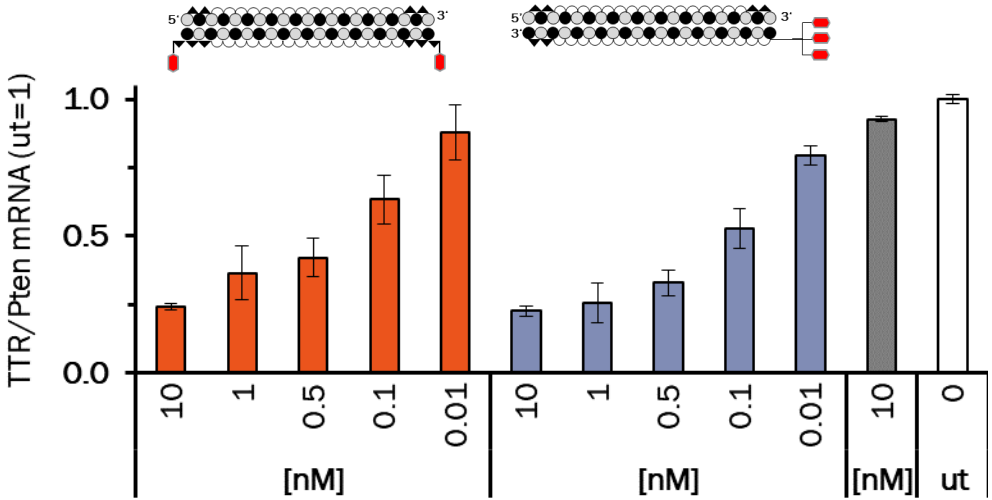


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Step 3: GalNAc conjugated siRNA with single GalNAc unit 3’ and 5’ sense strand location



Rat liver tritosome stability at 37 °C and pH=5

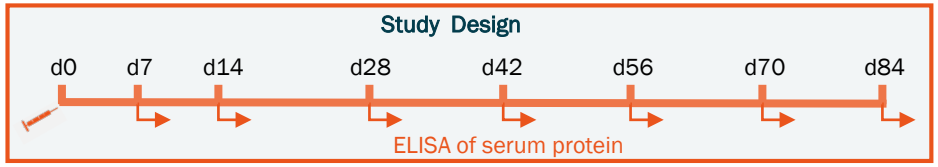


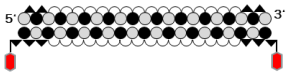
Mouse hepatocytes incubated for 24h
Grey bar: non-targeting control, white bar: untransfected cells.

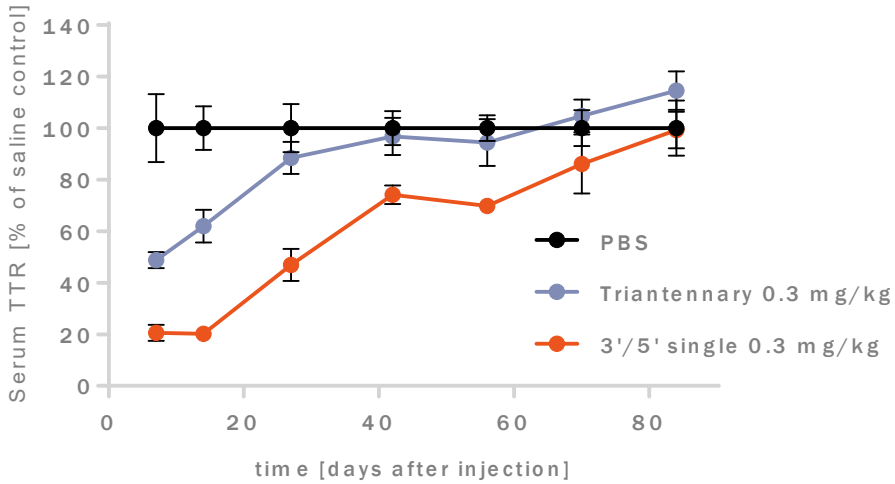
> Single GalNAc unit with 3’ and 5’ sense strand location are remarkably stable and demonstrate equal, or slightly reduced, *in vitro* activity compared to a tri-antennary GalNAc cluster conjugate of the same siRNA

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Two single GalNAc units with 3’ and 5’ sense strand location increase *in vivo* activity







> The new conjugate design is 2-3 times more active *in vivo* compared to a tri-antennary GalNAc cluster conjugate of the same siRNA

> Similar increase in *in vivo* activity has been demonstrated for three other test sequences

> Evaluation is in progress for combination with other new design features, i.e. reduced 2’F nucleobase content

C57Bl/6J mice injected s.c. d0, n=4/group. Data represents mean±SD.
Data presented as percent of saline control at respective time point.

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Summary – GalNAc-conjugated siRNA design



- Reduced non-natural nucleotide content to minimum 15% with retained or increased activity
- Surprisingly, two single GalNAc units with 3’ and 5’ sense strand location resulted in increased stability and *in vivo* activity
- Ongoing work includes evaluation of combination of design elements, most of which demonstrates that “less is more”
- 10 siRNA design patent applications filed 2017-18

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