SILENCE THERAPEUTICS

Oligo Oxford 2018

Development of innovative hepatocyte-targeted siRNA conjugates for the treatment of liver-related disorders.

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Group Leader Drug Delivery

10 APRIL 2018

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About Silence Therapeutics

Only quoted European RNA interference player

Key Performance Indicators:

> Net cash position of £43M at 2nd of Jan 2018

Headcount:

> 45 FTE (30 in Berlin, R&D and 15 London, Corporate and R&D)

Listing:

> AIM, London Stock Exchange

Our facilities

HQ in London



R&D in Berlin



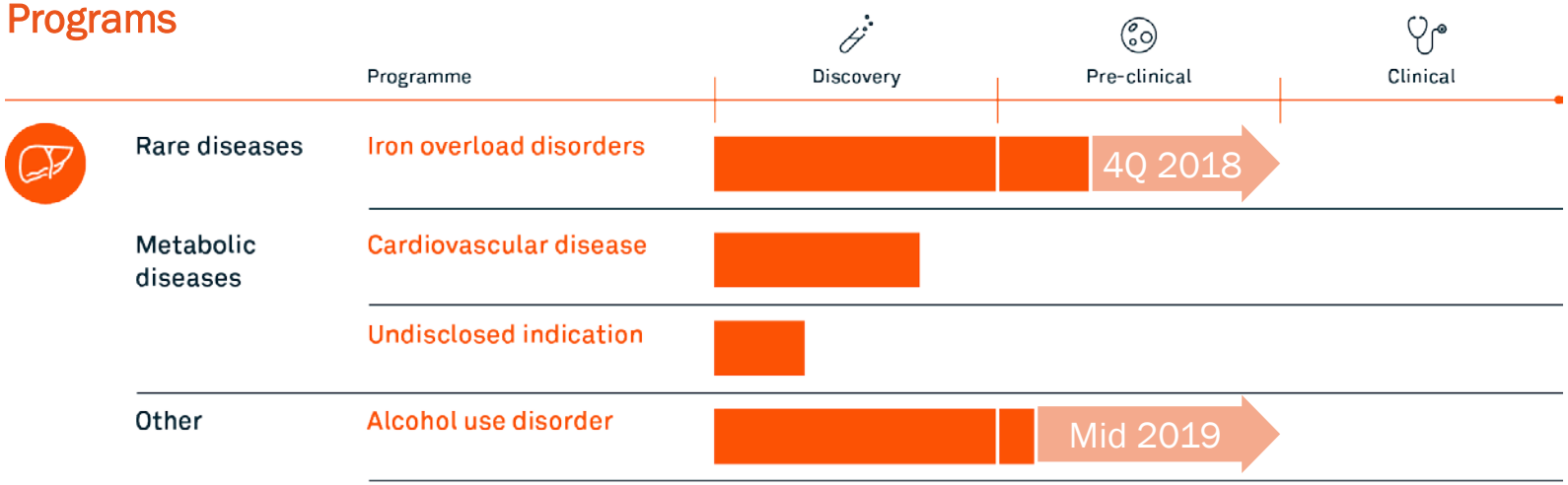
** As of 4 February 2018*

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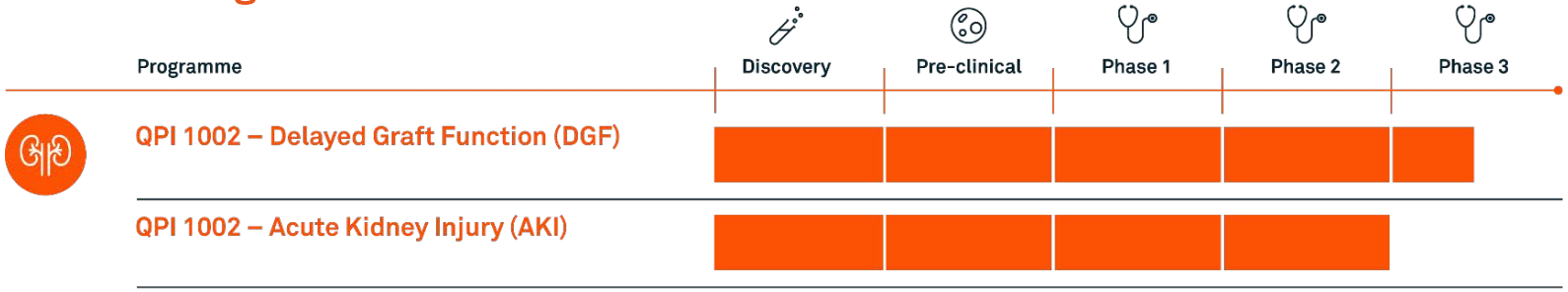
Pipeline

Building a proprietary portfolio, two projects advanced into preclinical development

Our Programs



Out-Licensed Programs

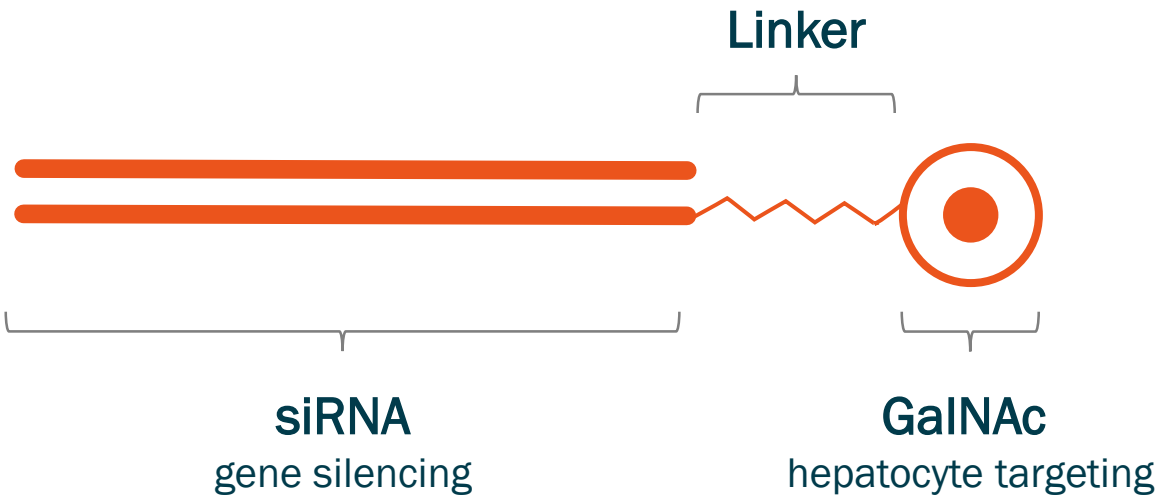


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GalNAc conjugated siRNA technology

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GalNAc-conjugated siRNA



Advantages of GalNAc-siRNA technology

> GalNAc targets therapeutic siRNA molecules **specifically to hepatocytes**

> Highly specific by targeting a **single transcript**

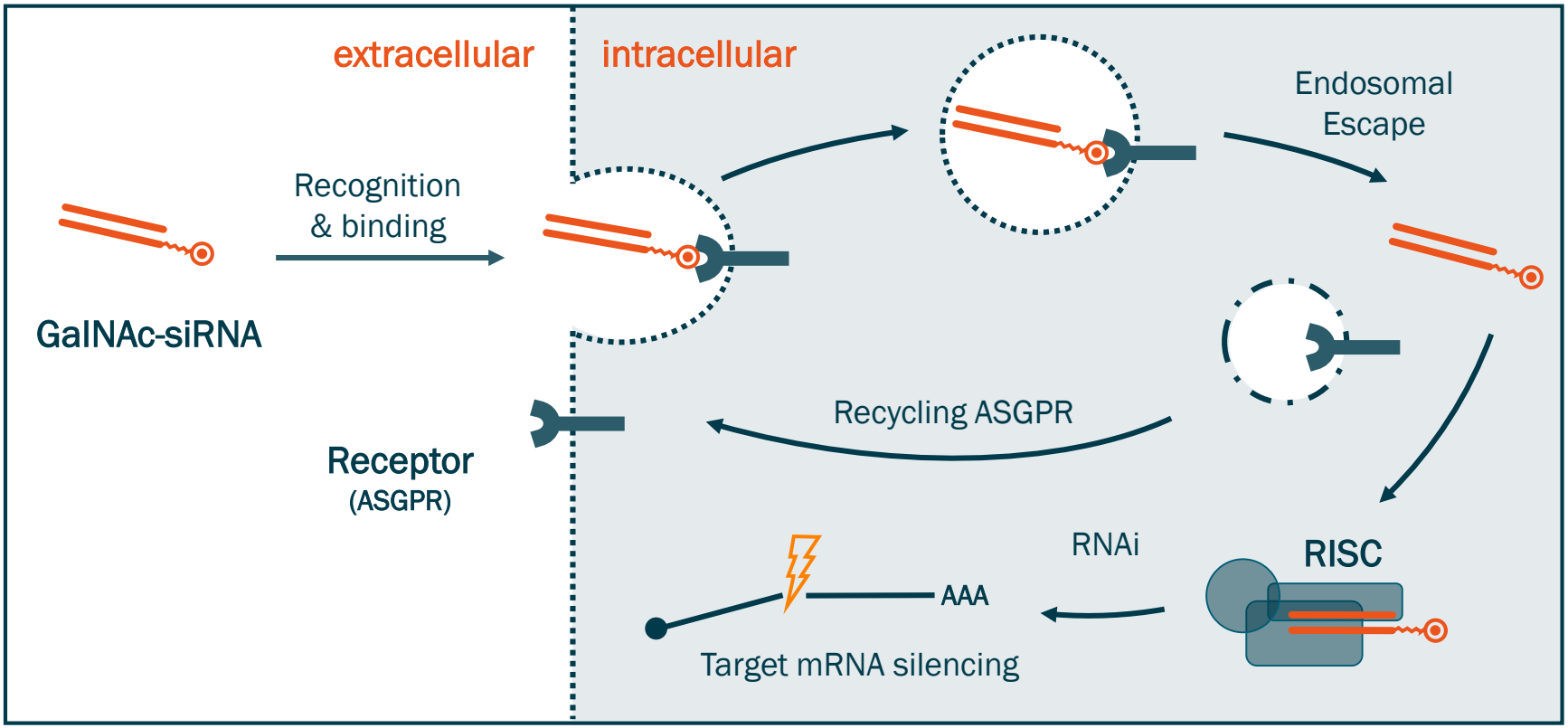
> Patient-friendly via **infrequent subcutaneous administration**

> Established **clinically validated technology**

> Generally **well tolerated**, high therapeutic index

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Gene silencing with GalNAc-conjugated siRNA in hepatocytes



> Intracellular delivery mediated through receptor endocytosis

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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

RATIONALE

> Target 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

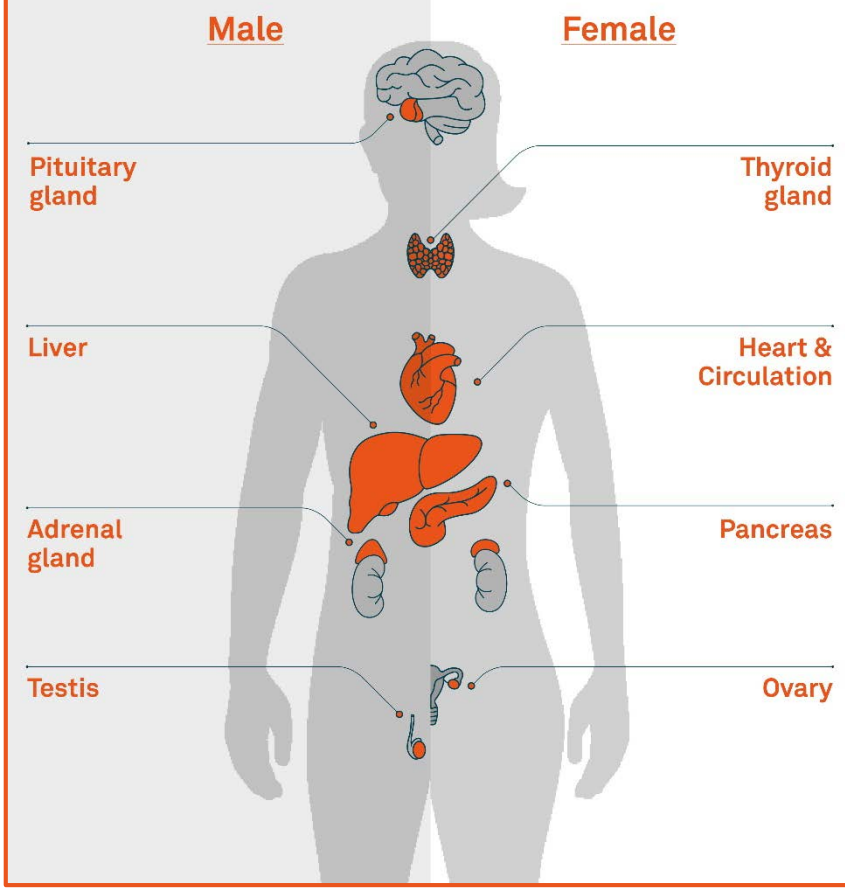
CURRENT STAGE

> Preclinical development with plans to enter clinical development in Q4/2018

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Iron Overload Disorders

Affected organs by iron overload



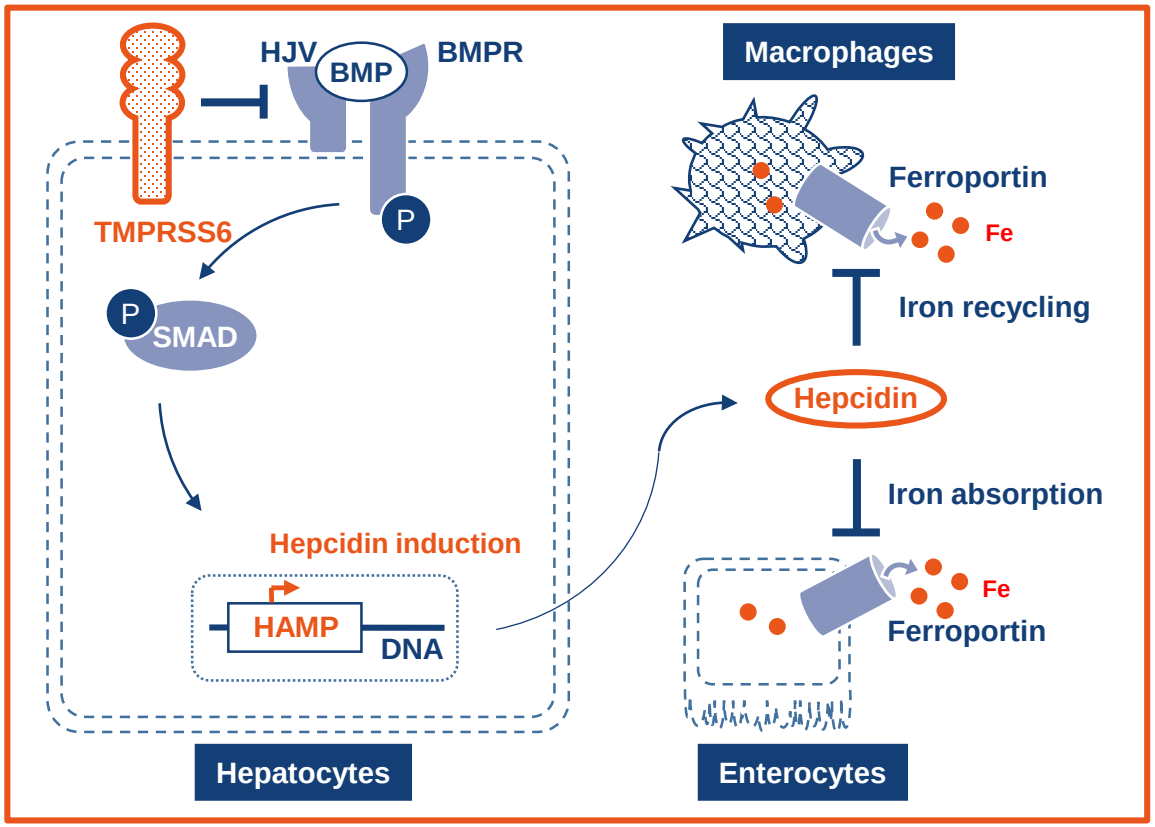
Diseases with iron overload

- β-Thalassemia
- Hereditary Haemochromatosis
- Myelodysplastic Syndrome
- Aplastic Anaemia
- Sideroblastic Anaemia

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

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SLN124 mechanism of action



> **TMPRSS6** (Transmembrane Protease, Serine 6) is a negative regulator of the BMP/SMAD signaling pathway

> Inhibition of TMPRSS6 in hepatocytes induces Hepcidin expression

> Hepcidin reduces absorption of dietary iron and the release of iron from cellular storage, thereby reducing circulatory iron levels

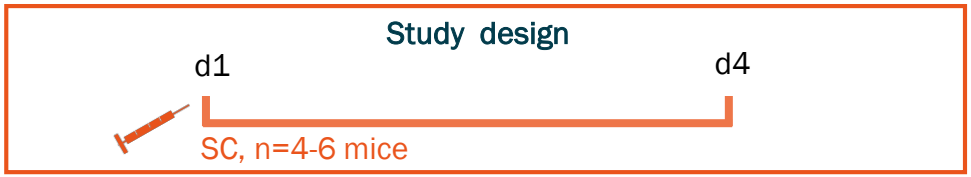
> The liver is the predominant source of Hepcidin

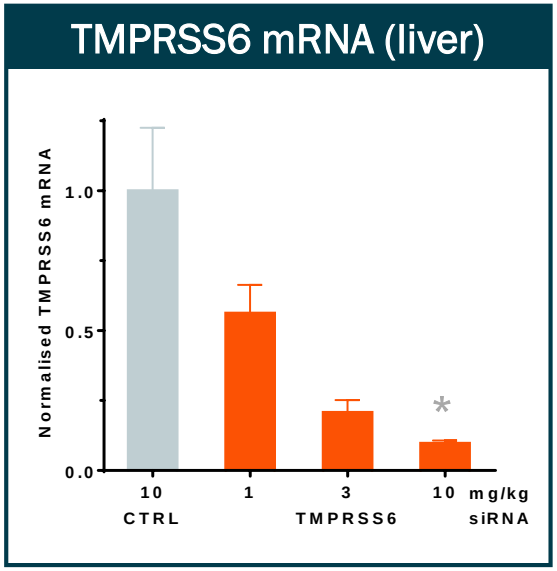
Silencing TMPRSS6

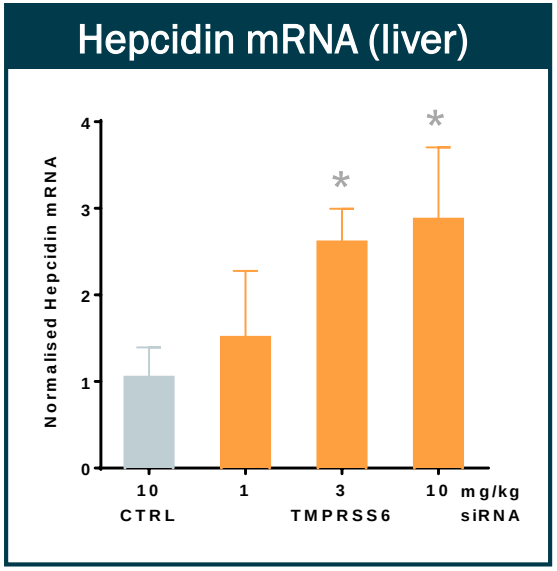
1. Increases Hepcidin levels
2. Reduces iron levels
3. Improves erythropoiesis
4. Reduces anaemia & iron overload

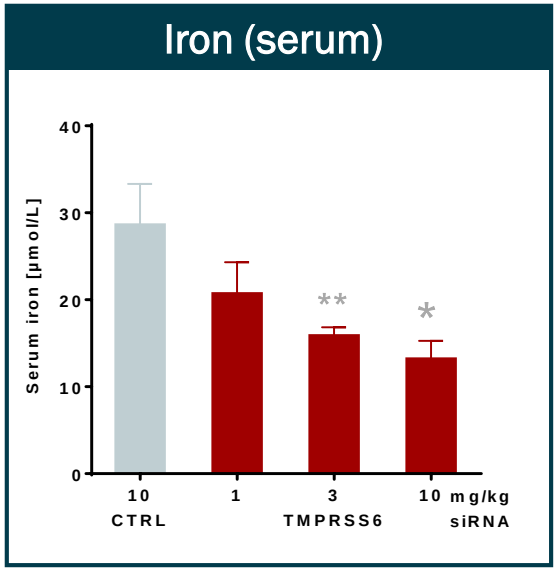
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Silencing TMPRSS6 lowers serum iron levels in mice









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

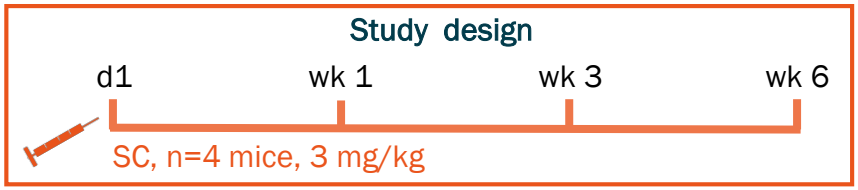
> Single subcutaneous administration reduces TMPRSS6 expression

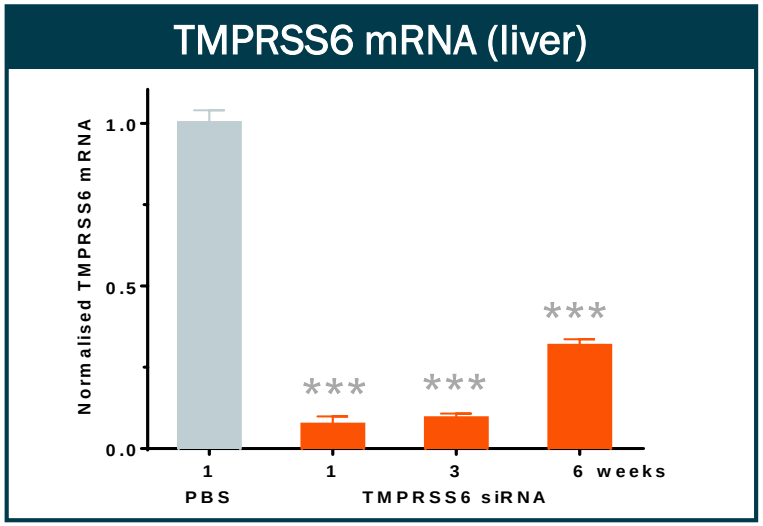
> Induction of Hepcidin causes reduction of blood iron levels

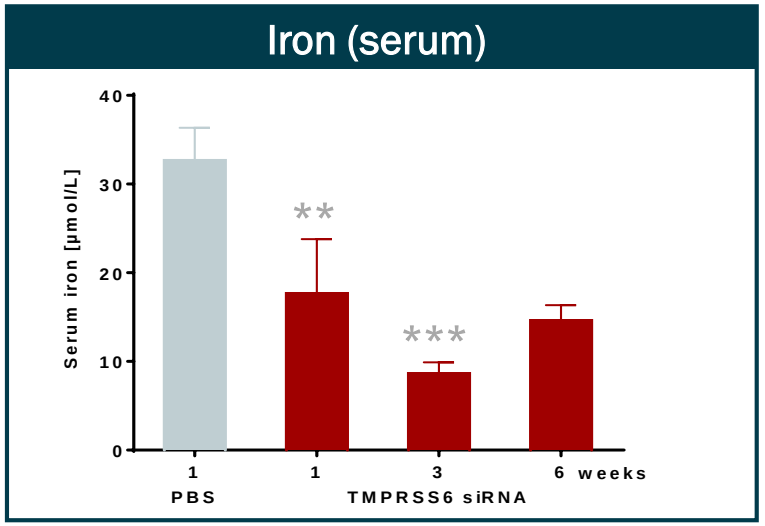
> **Proof of mechanism demonstrated**

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SLN124 lowers iron levels for at least 6 weeks after single administration in mice







2-way ANOVA multiple comparisons: shown to control CTRL groups (same time point)

> Long-lasting functional mRNA KD in liver

> Reduction of serum iron levels for at least 6 weeks

> **Well tolerated with long duration of action in mice**

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SLN124 - Summary

- Highly potent, selective and long acting GalNAc-siRNA
- Efficacious in lowering blood iron and well tolerated in healthy mice and non-human primates after single subcutaneous administration
- Demonstrated therapeutic efficacy in clinically relevant animal disease models
- Currently in preclinical development with plans to enter clinical development in Q4 2018

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

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Technology Innovation: making a good thing better

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R&D with focus on portfolio and innovation

Technology Innovation

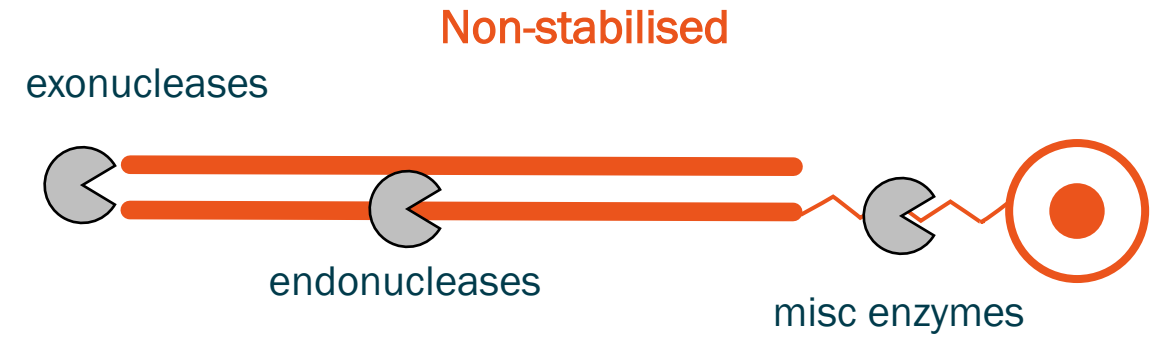
- Improve performance of our GalNAc-siRNA molecules
- Strengthen and broaden IP portfolio
- Expand RNAi horizon beyond hepatocytes
- Apply to therapeutic portfolio upon validation

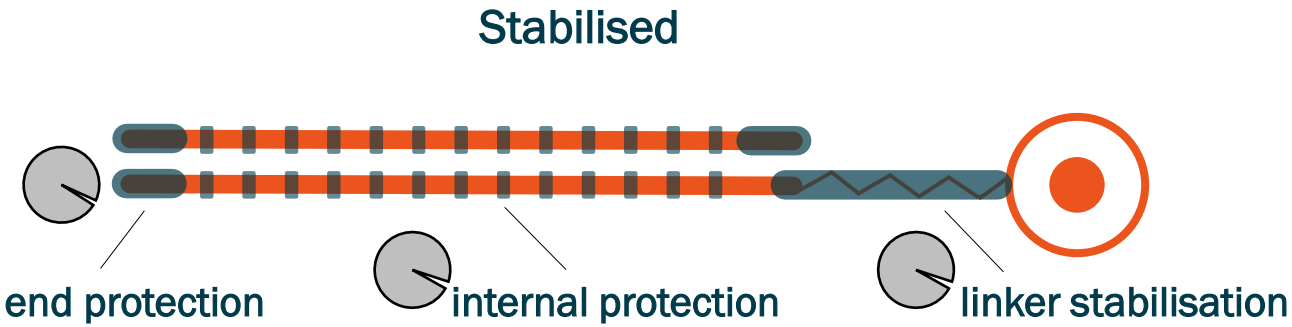
Drug Discovery & Development

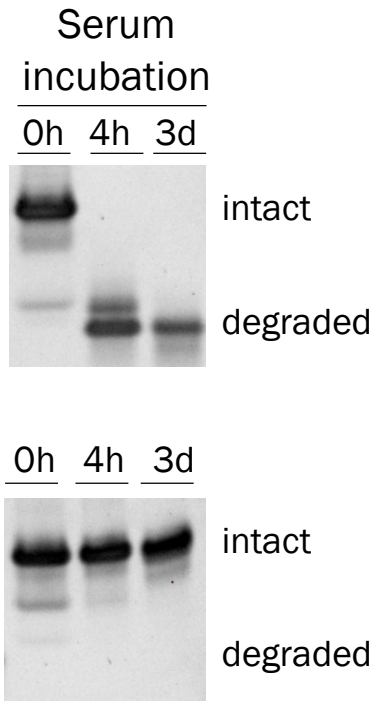
- Build a proprietary therapeutic portfolio by applying validated siRNA technologies
- Partner programs in a strategic manner
- Add new programs in a risk-diversified manner

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Unmodified GalNAc-conjugated siRNA is quickly degraded in biological fluids





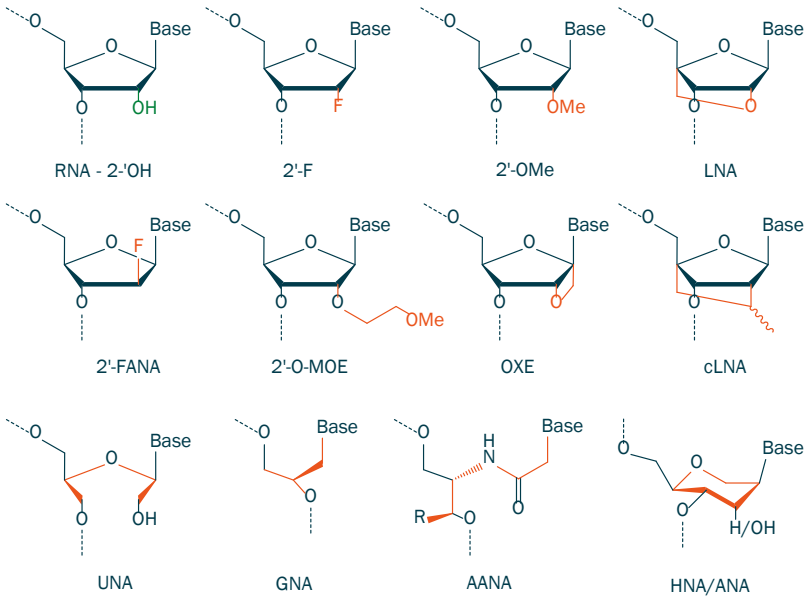


> Incorporation of chemically modified nucleotides can protect GalNAc-siRNA molecules from degradation

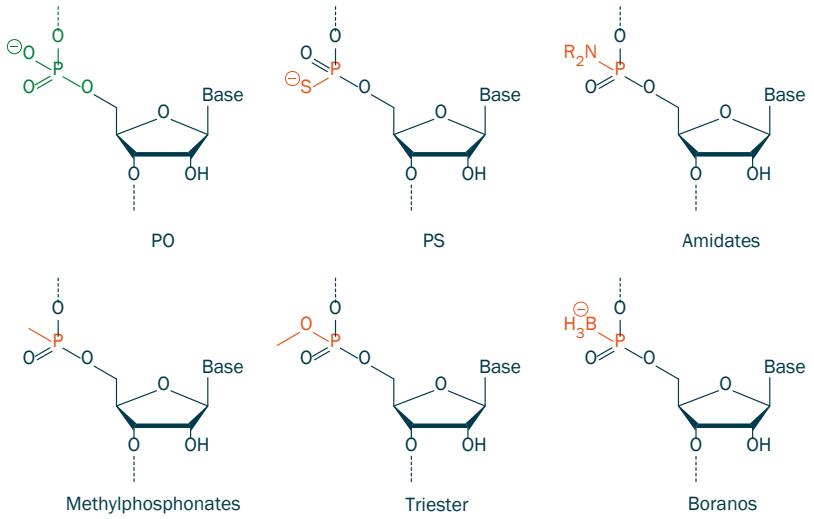
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Examples of stabilising chemically modified nucleotides

Modified 2'-OH



Modified phosphate

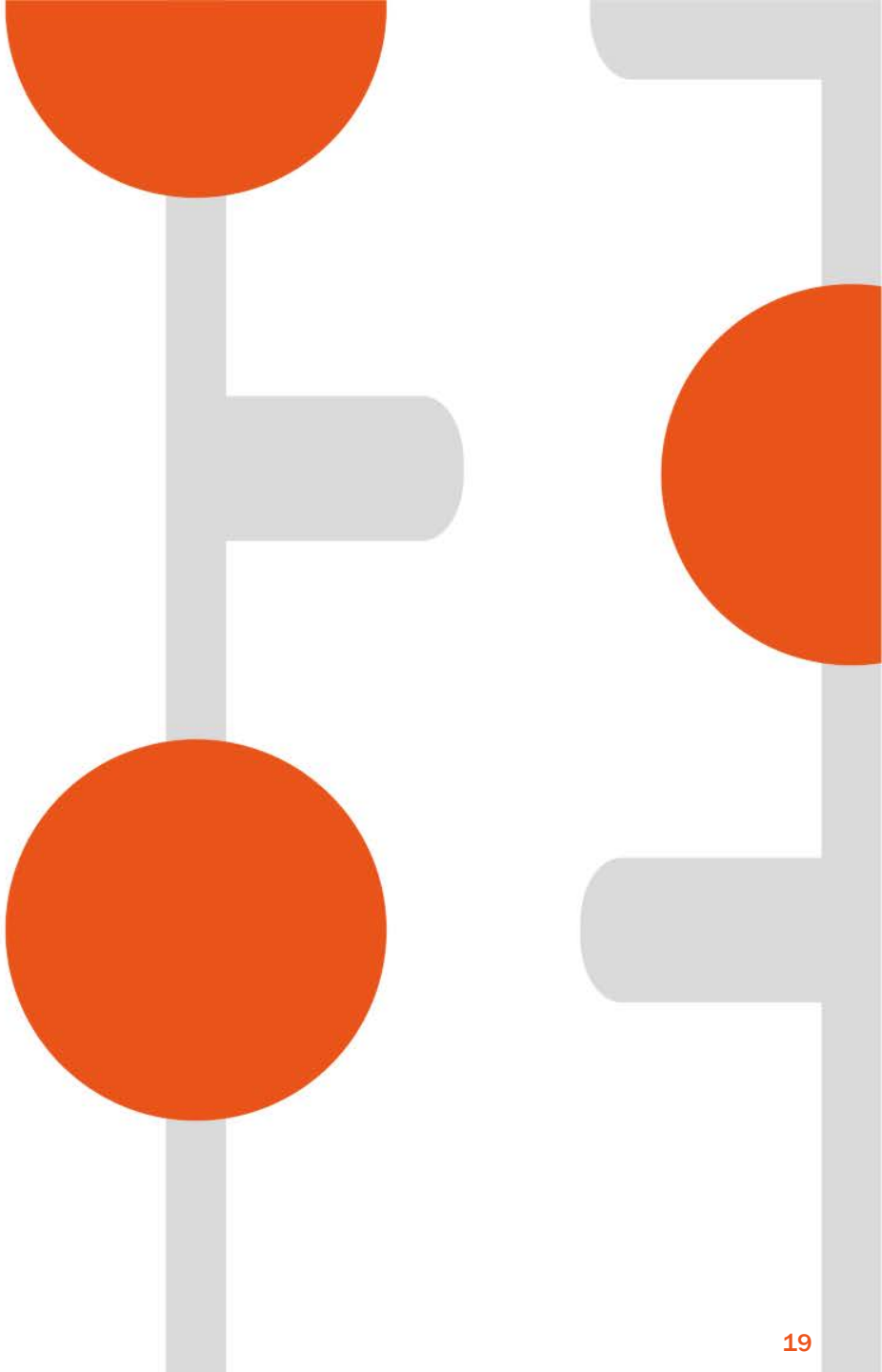


> Most are not naturally occurring and may cause **non-specific effects** and **reduce silencing activity**

> Our strategy is to minimise the use of non-natural nucleotides while preserving or improving both stability and potency

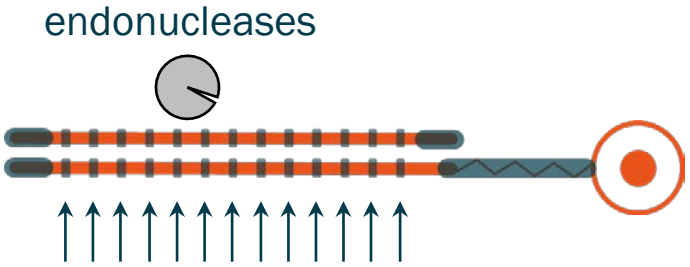
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Internal siRNA modifications for endonuclease protection

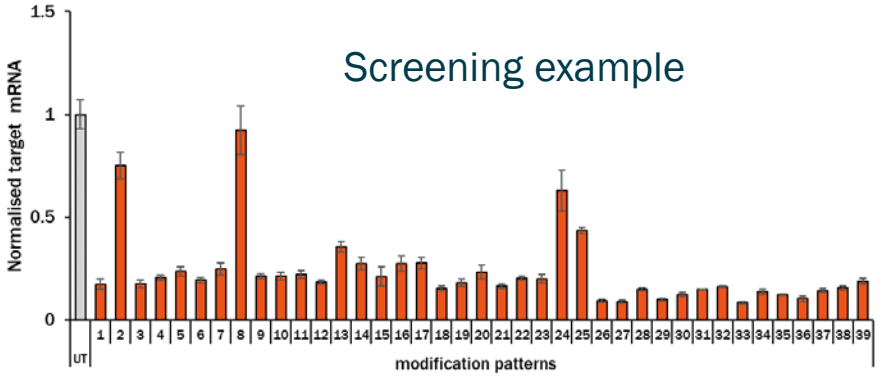


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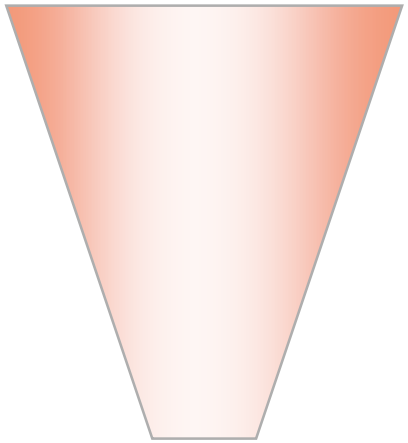
Minimising the use of non-natural nucleotides



Internal siRNA modifications



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

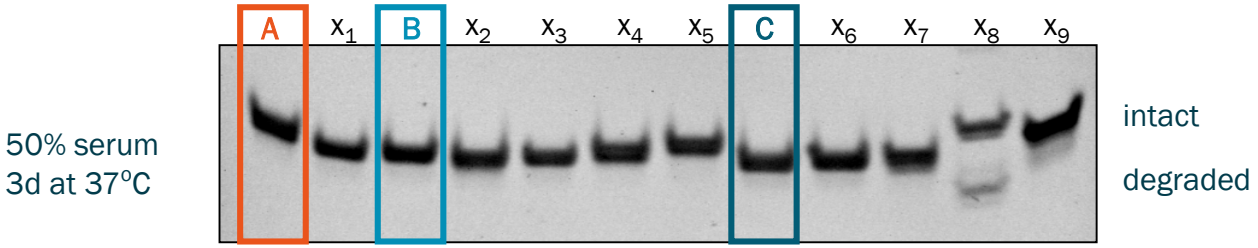
Animal activity: with GalNAc

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

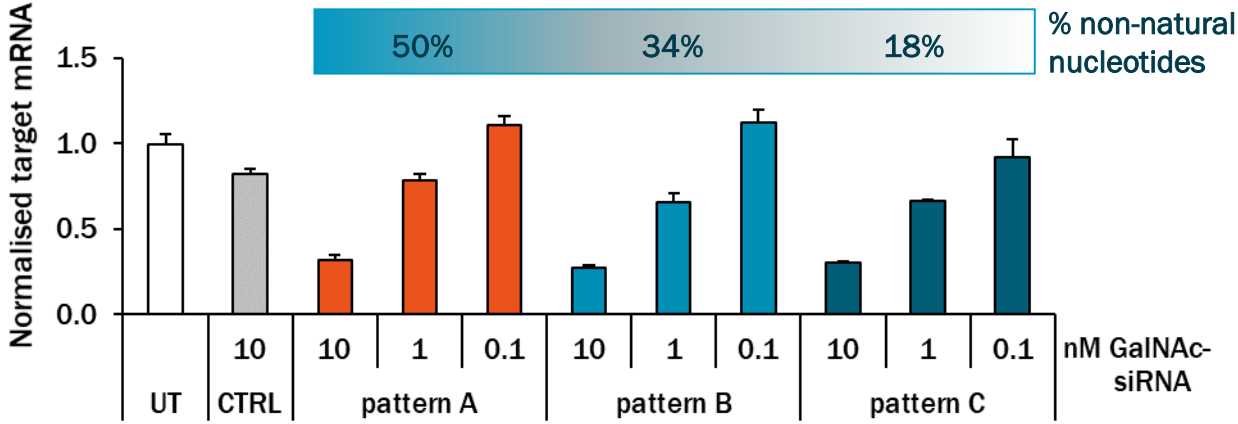
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Serum stability and activity of molecules with reduced non-natural nucleotide content

Serum stability



Silencing activity in primary hepatocytes



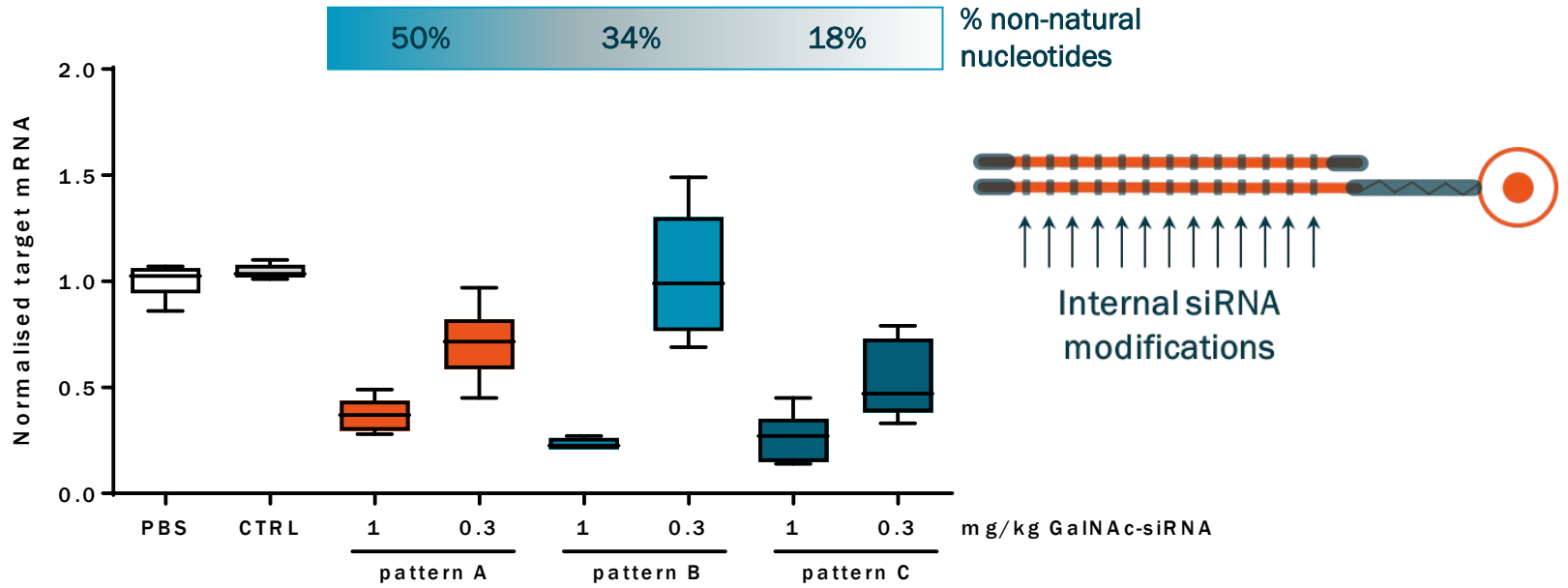
> Molecules with dramatically reduced non-natural nucleotide content retain excellent nuclease resistance and activity in primary hepatocytes

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In vivo activity of GalNAc-siRNA molecules with reduced non-natural nucleotide content



Silencing activity in mice (target mRNA levels in liver tissue)



> Molecules with dramatically reduced non-natural nucleotide content produce outstanding gene silencing in vivo

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Summary – Internal GalNAc-siRNA modifications for endonuclease protection

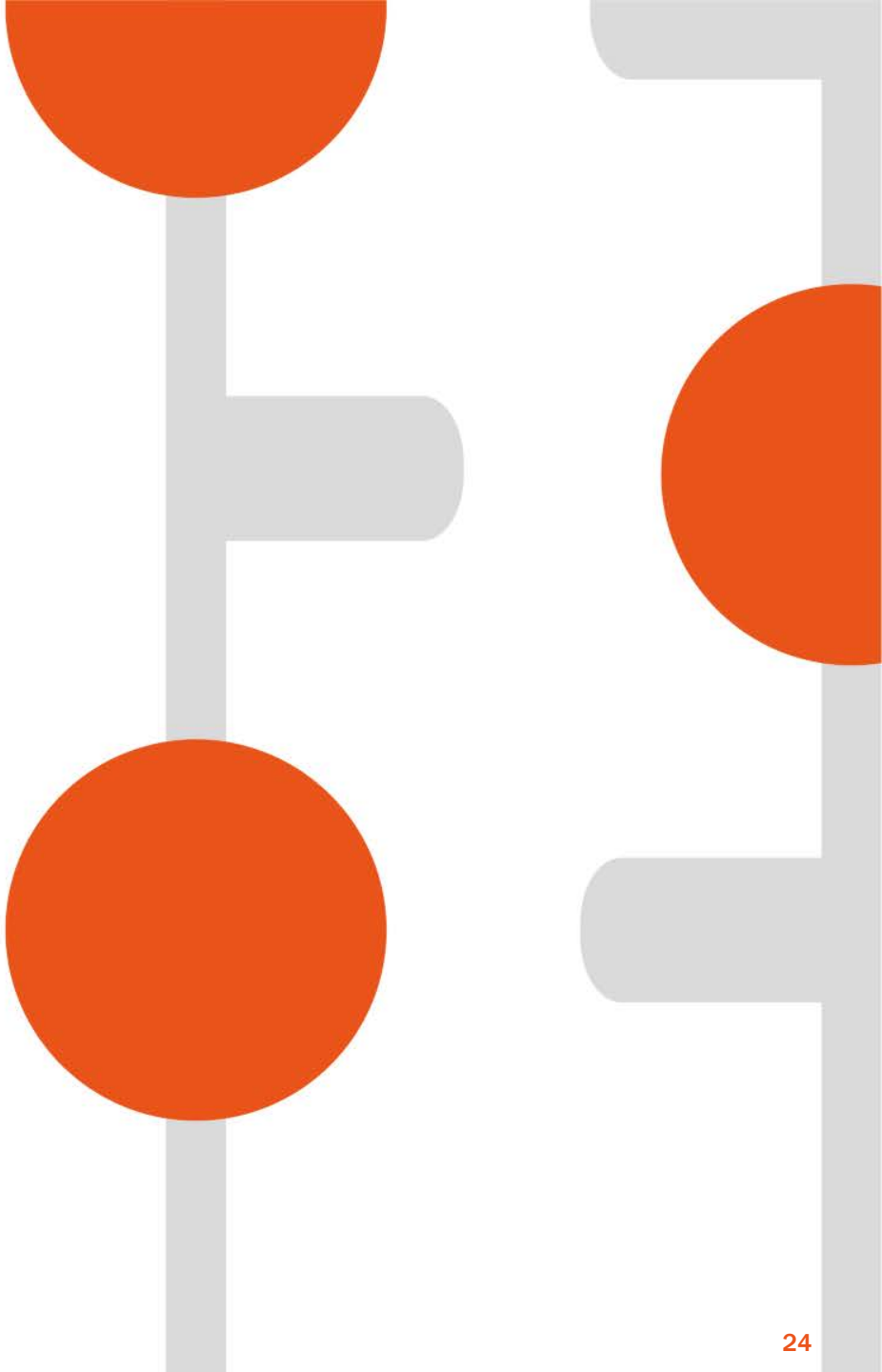


Identified chemical modification patterns that

- Reduce dramatically non-natural nucleotide content from ≥50% to less than 15%
- Retain outstanding nuclease stability, as well as robust silencing activity in vitro and in vivo
- Reduce the costs of siRNA building blocks by >25%
- **Can be applied to any siRNA sequence**, permitting accelerated lead optimisation

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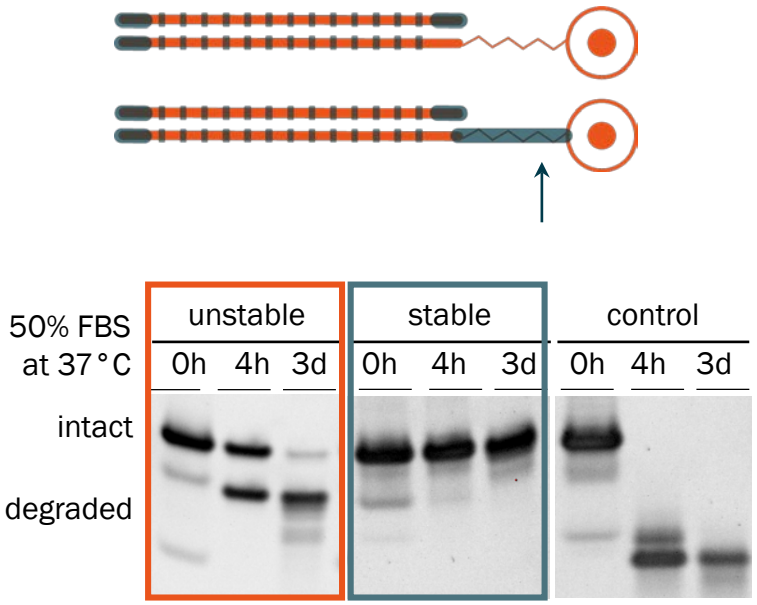
Stabilisation of the linker



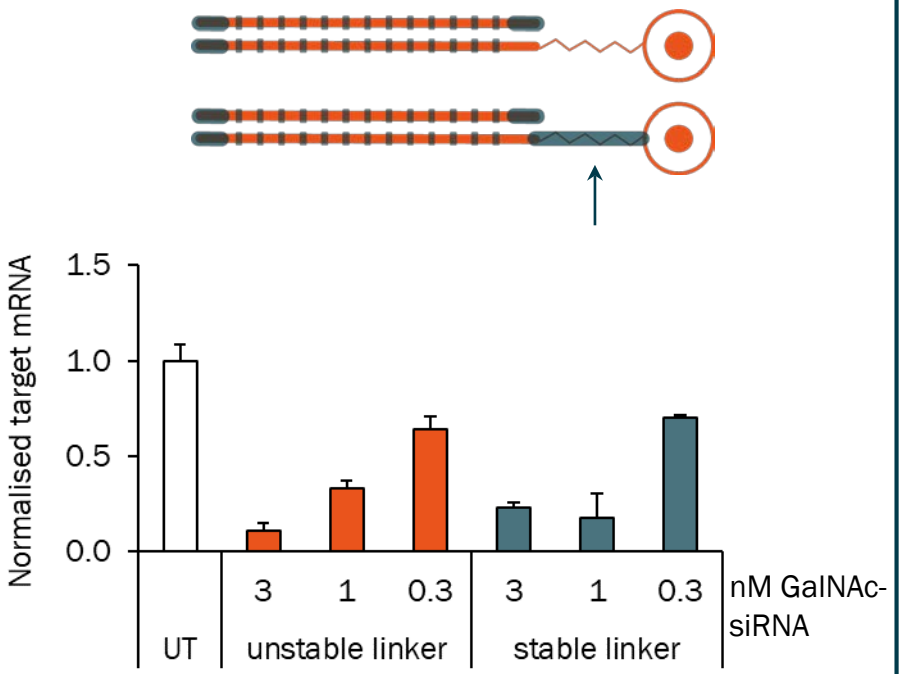
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Performance of GalNAc-siRNA molecules with stabilised linker

Serum stability



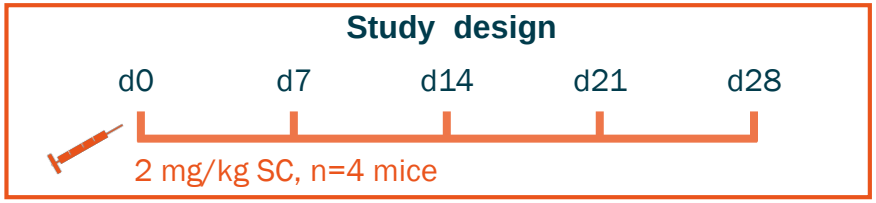
Silencing activity in primary hepatocytes



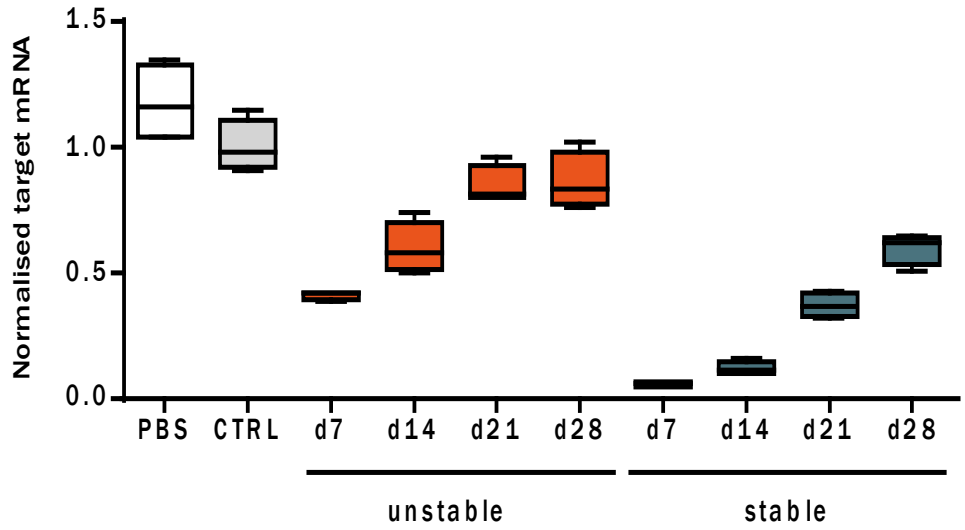
> GalNAc-siRNA with stabilised linker produces robust silencing activity in primary hepatocytes

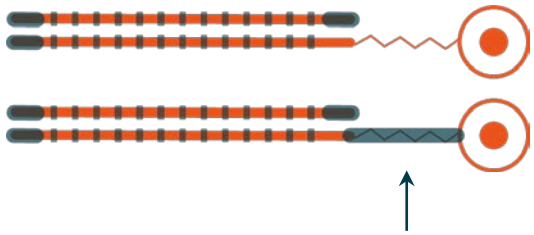
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In vivo activity of GalNAc-siRNA molecules with stabilised linker



Silencing activity in mice (target mRNA in liver)





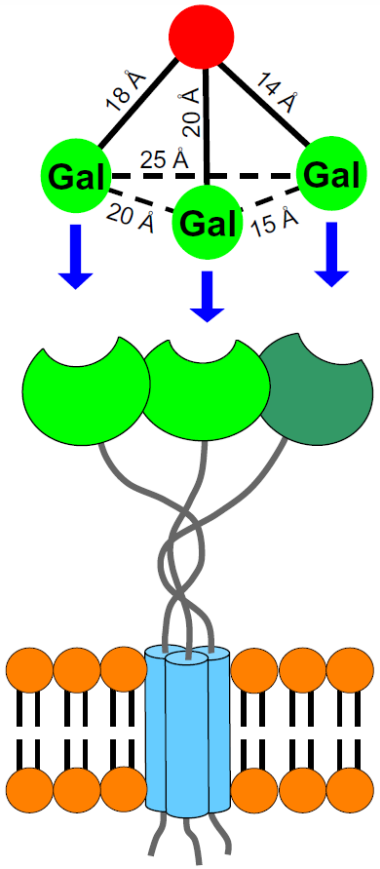
> GalNAc-siRNA with stabilised linker yields stronger and prolonged target silencing in vivo

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Antisense GalNAc-siRNA Conjugates

Background:
Affinity of the ligand to the ASGPR was reported to increase dramatically from monomeric to dimeric and trimeric but not much add on was shown by tetrameric clusters. Hence, triantenary GalNAc clusters with distances of 15-25Å between the carbohydrates are preferred.

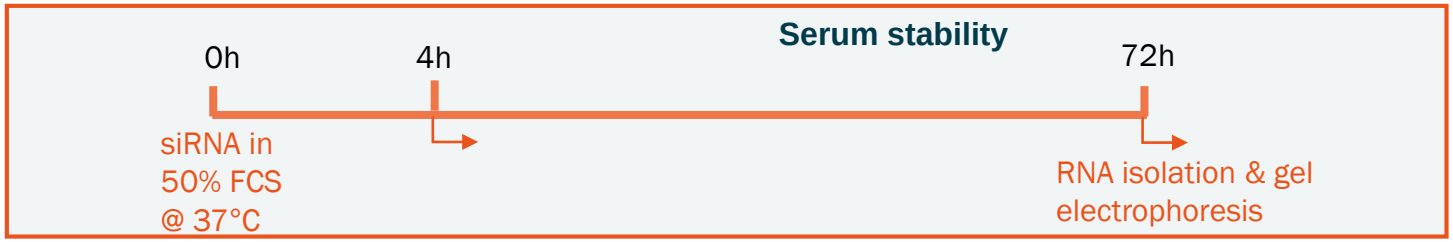
Objective:
Test different valences (n = 1 to 4) at sense and antisense strand for functional siRNA delivery.



Khorev et al. (2008) https://doi.org/10.1016/j.bmc.2008.03.017

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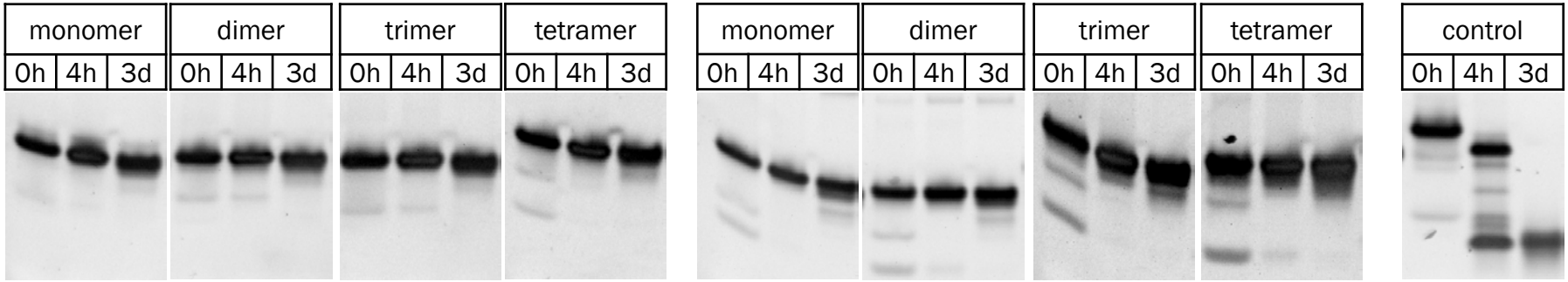
Serum stability of siRNA-GalNAc conjugates



serum stability over three days

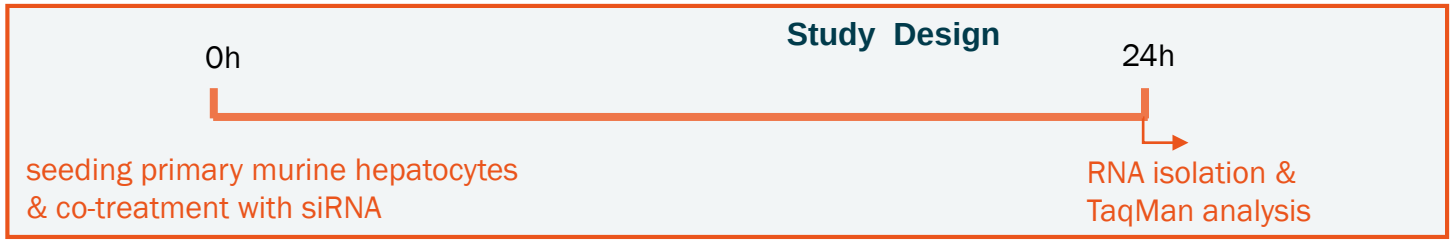






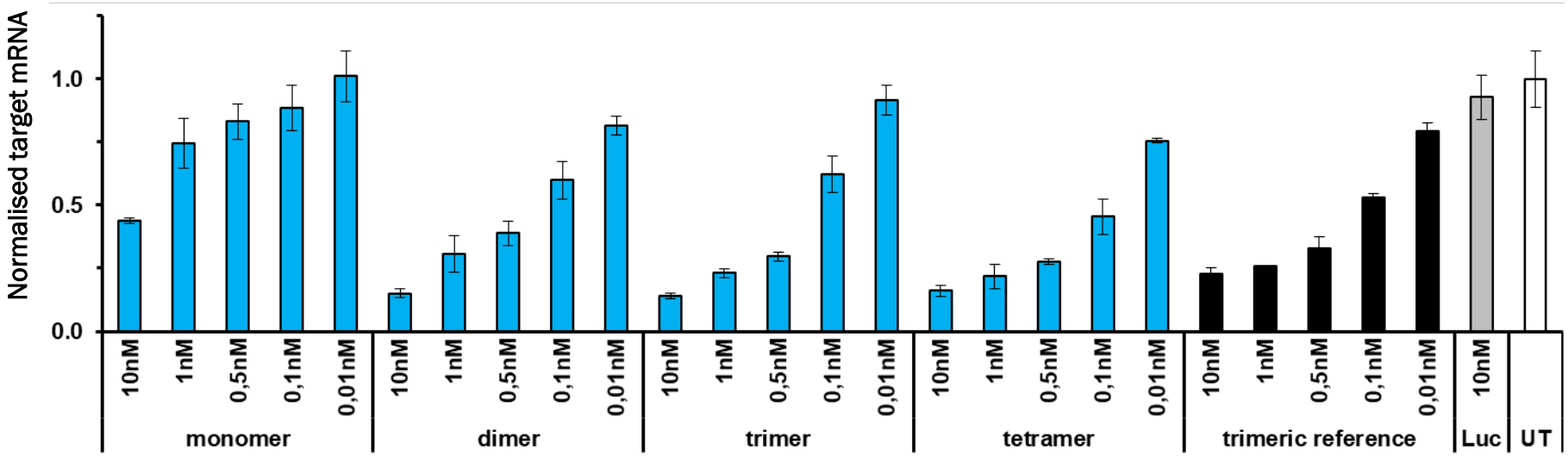
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In vitro activity of 3‘ anti-sense conjugates



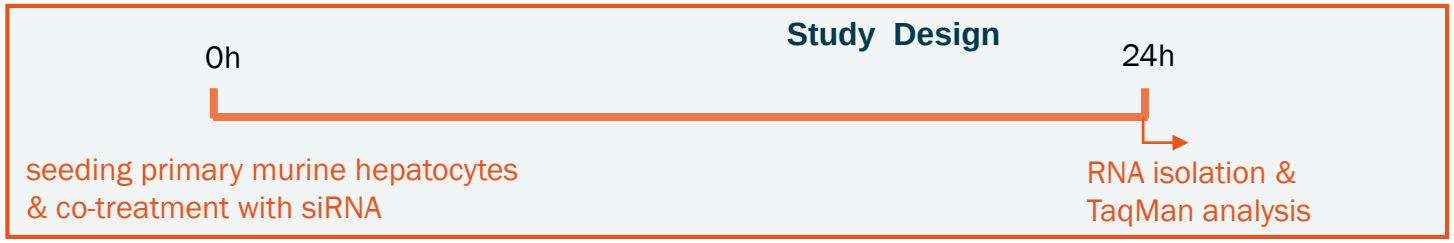
3’ anti-sense GalNAc-conjugates





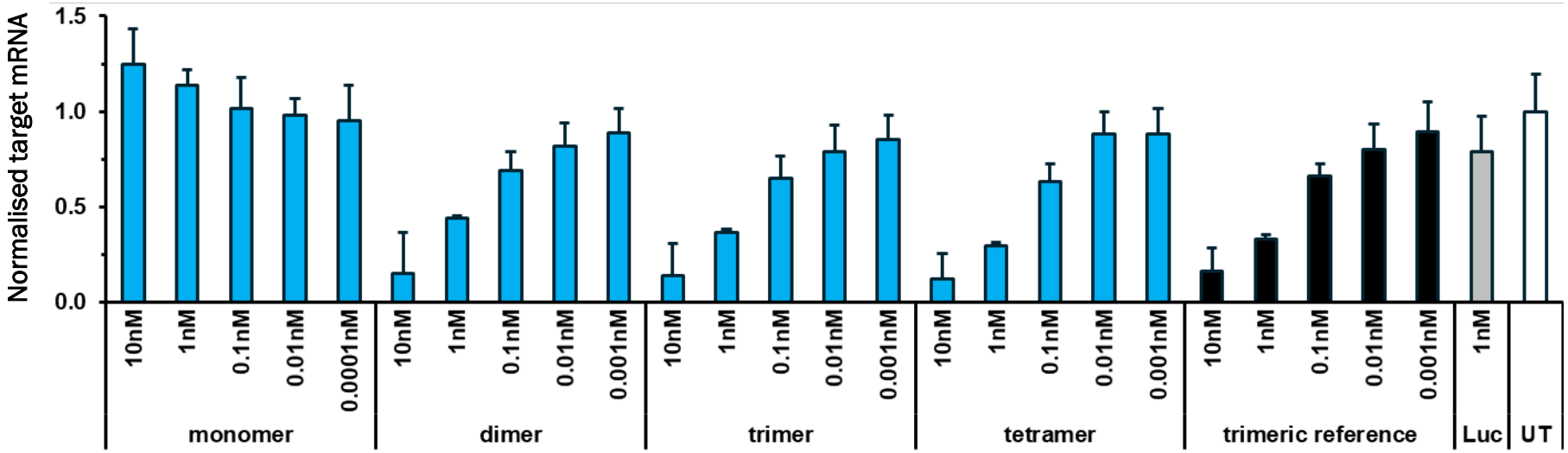
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In vitro activity of 5‘ sense conjugates



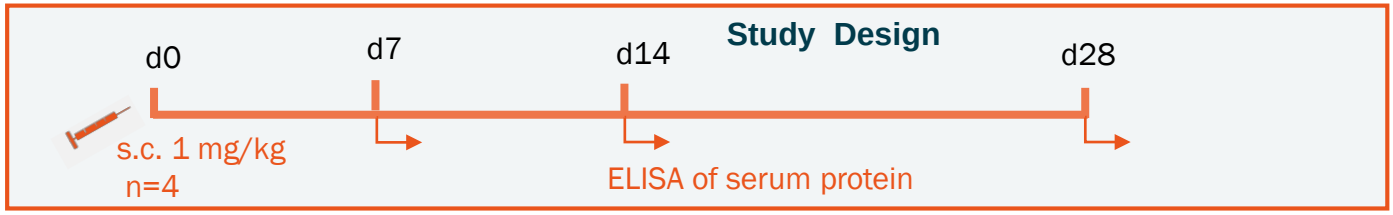
5’ sense GalNAc-conjugates



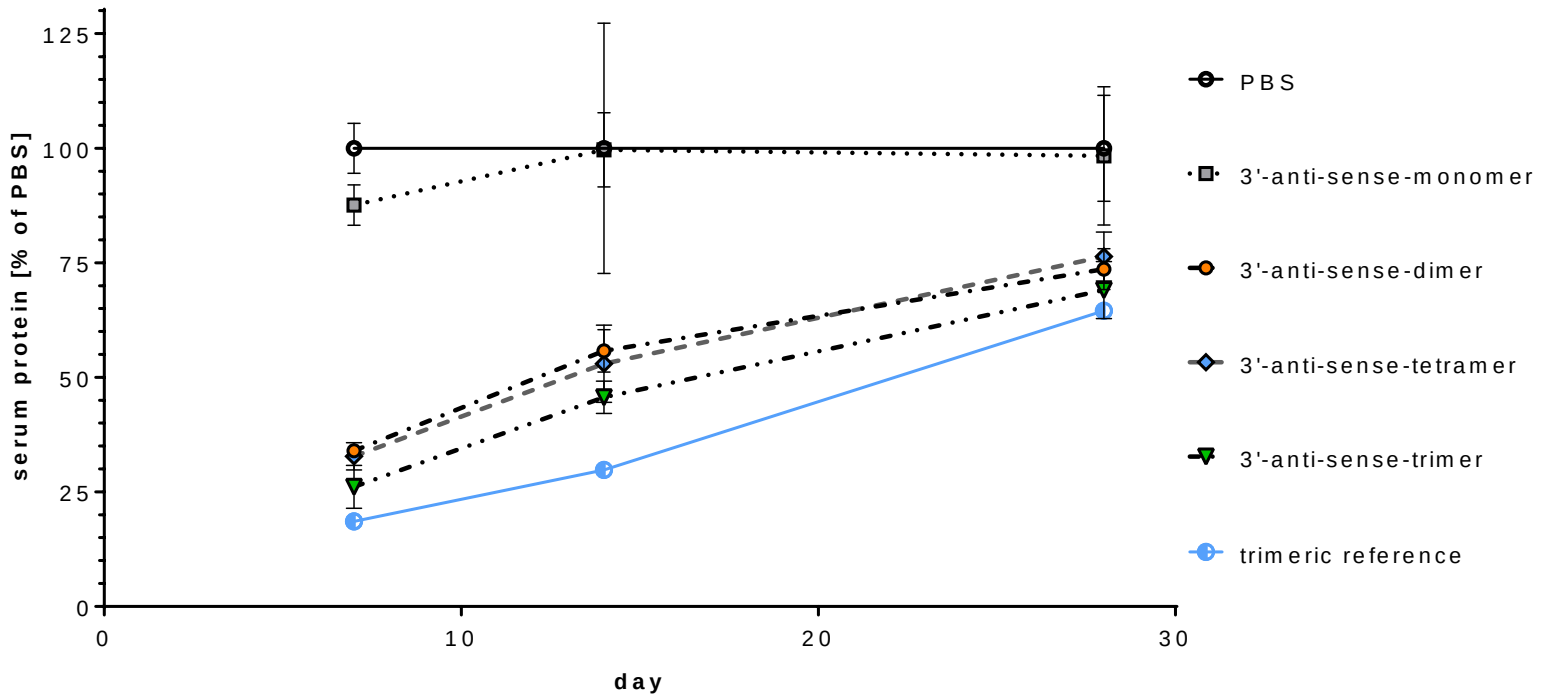


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Duration of target knock down *in vivo* following single dose of GalNAc conjugates

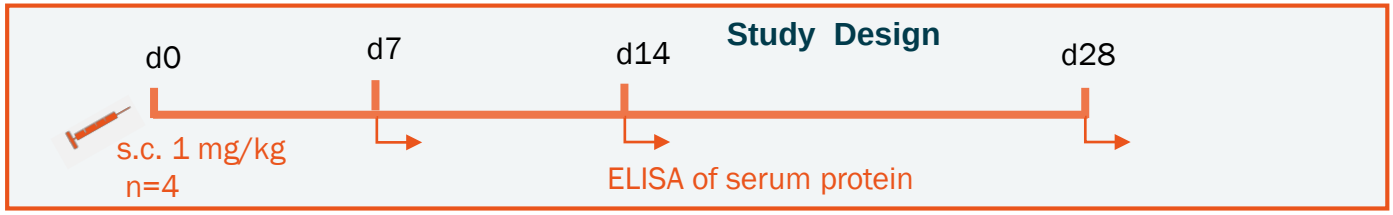


3’ anti-sense GalNAc-conjugates

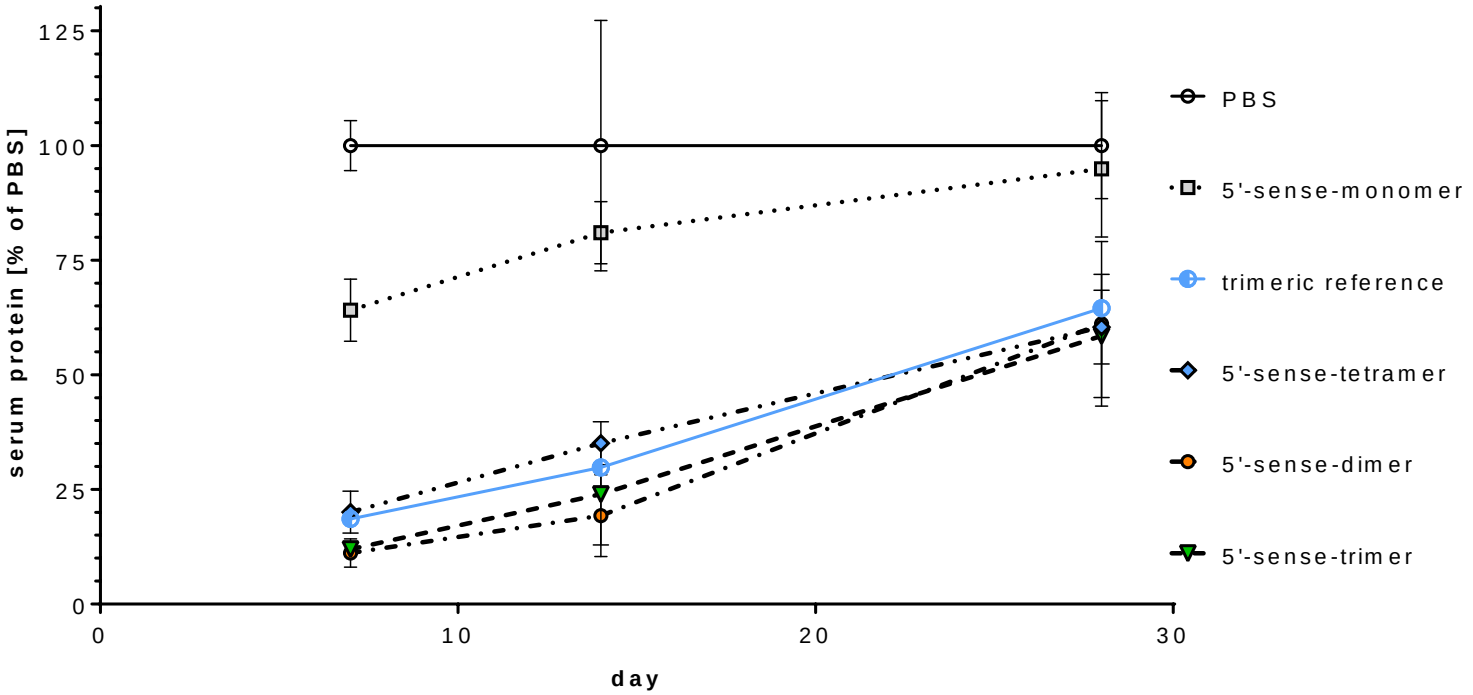


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Duration of target knock down *in vivo* following single dose of GalNAc conjugates

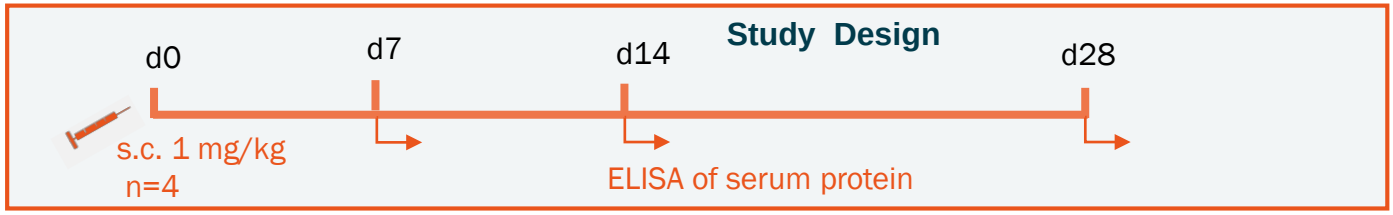


5’ sense GalNAc-conjugates

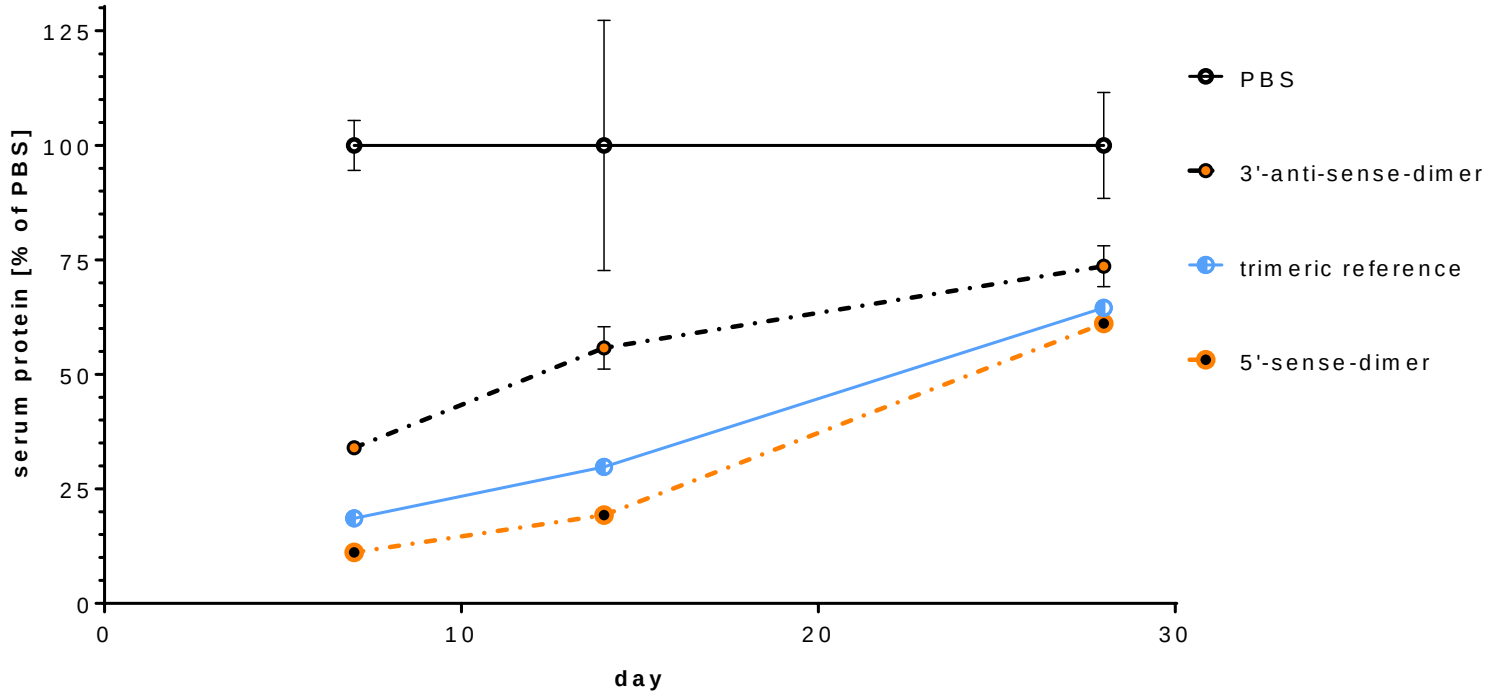


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Duration of target knock down *in vivo* following single dose of GalNAc conjugates

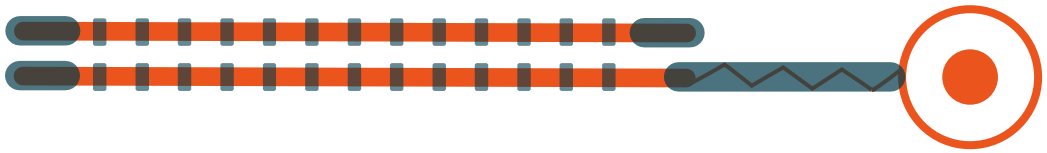


dimeric GalNAc-conjugates



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Summary – valency of GalNAc-cluster and postion



GalNAc-clusters

> with two carbohydrates are as good clusters of as tree and four

> conjugation to the sense strand results in better in vivo performance

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Technology Innovation: Summary

- highly stable and potent GalNAc molecules (*in vitro* and *in vivo*)
- reduced internal non-natural nucleotides by up to 80%
- internal patterns are universally applicable
- reduced COG of building blocks: by >25%
- improved GalNAc-linker designs for simpler synthesis
- supported by fundamental IP, issued in US/EU 2016/17/18
- 10+ additional patent applications filed

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