SILENCE THERAPEUTICS

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Development of Novel Therapies Using Advanced GalNAc-siRNA Technology

Marie Wikström Lindholm, PhD,
Head of Technology Innovation

Forward looking statements

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Outline

1. About Silence Therapeutics
2. Case Study: SLN124 and iron overload disorders
3. Technology Innovation at Silence Therapeutics

About Silence Therapeutics

About Silence Therapeutics

Only quoted European RNA interference player

Key Performance Indicators:

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

> Market cap: £136.5M*

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*

Building a strong pipeline through the creation of a highly functional R&D organisation

Diverse technologies (CRISPR, mRNA, siRNA with LNP)

Decision to focus on GalNAc-siRNA platform

Building a GalNAc-siRNA therapeutic portfolio

Outsourcing routine work

2015 | 2016 | 2017 | 2018

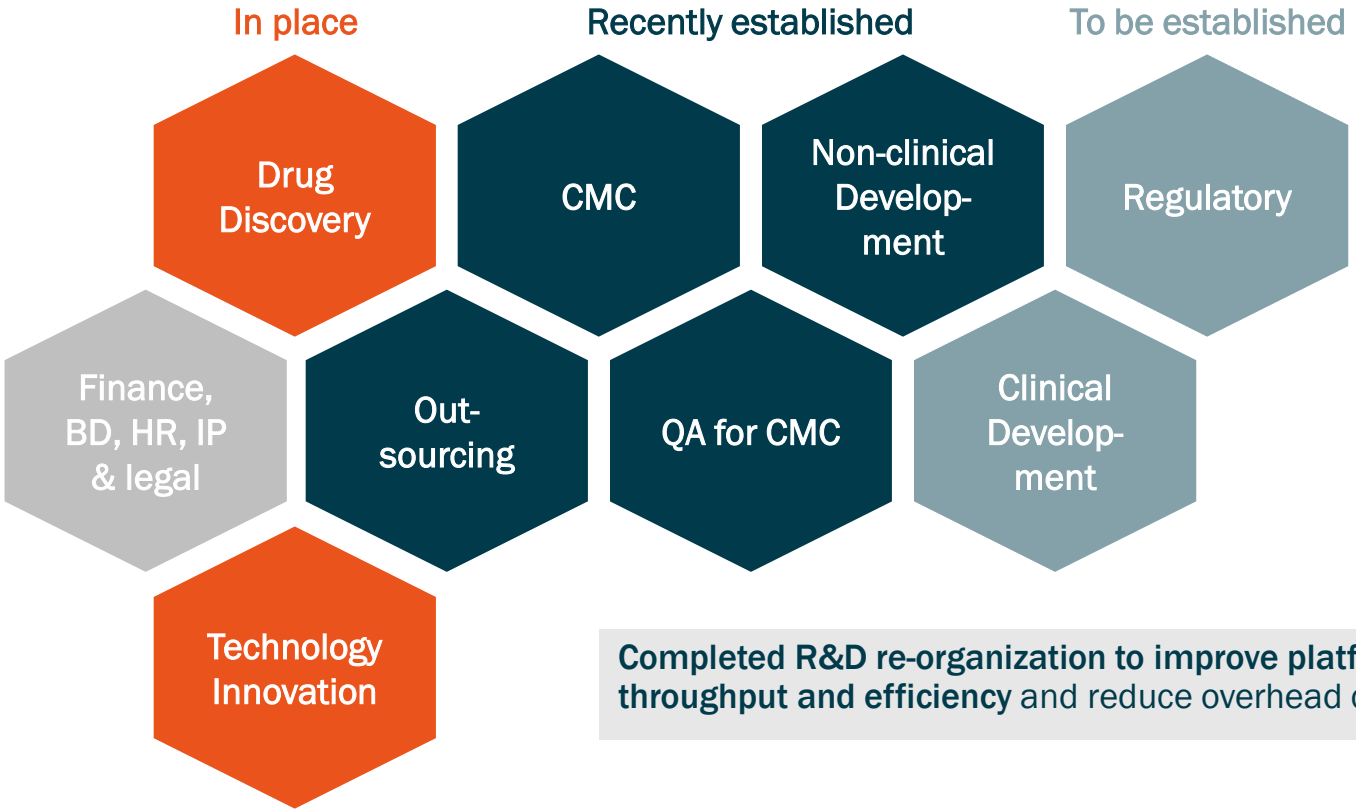
Technology-driven R&D organization

Drug Discovery team restructured

Technology Innovation group created

Experienced management team to execute strategy

Evolving modular R&D capabilities

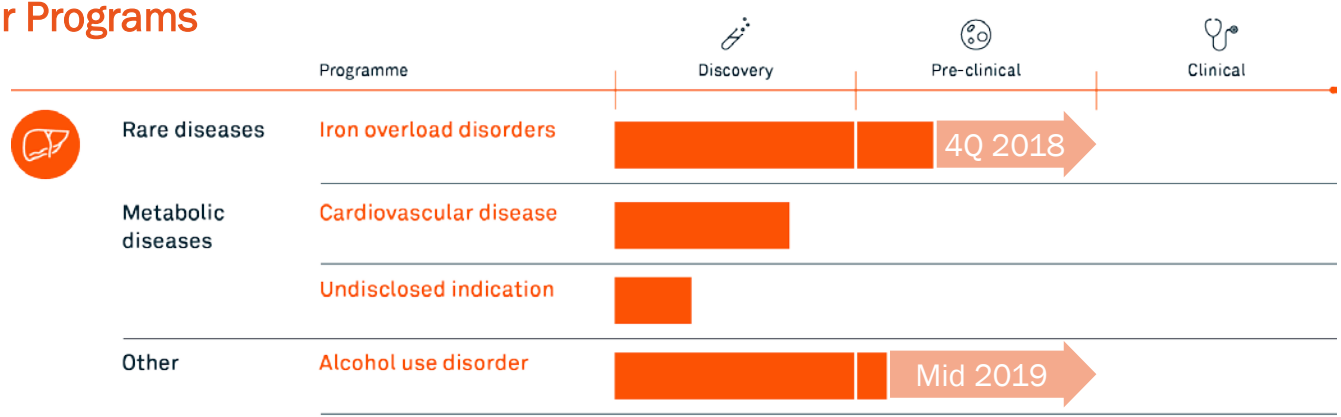


Completed R&D re-organization to improve platform throughput and efficiency and reduce overhead costs

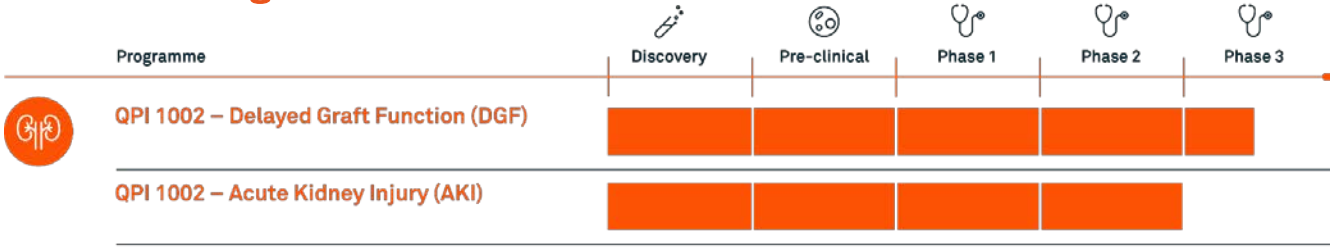
Pipeline

Building a proprietary portfolio, two projects advanced into preclinical development

Our Programs



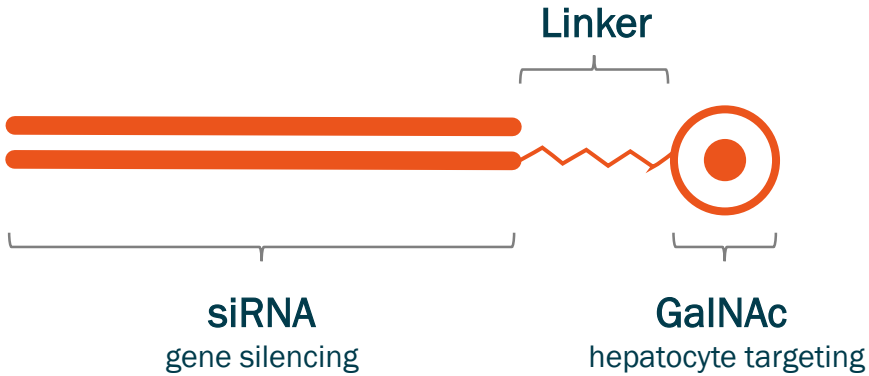
Out-Licensed Programs



Quark

GalNAc conjugated siRNA technology

GalNAc-conjugated siRNA



Advantages of GalNAc-siRNA technology

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

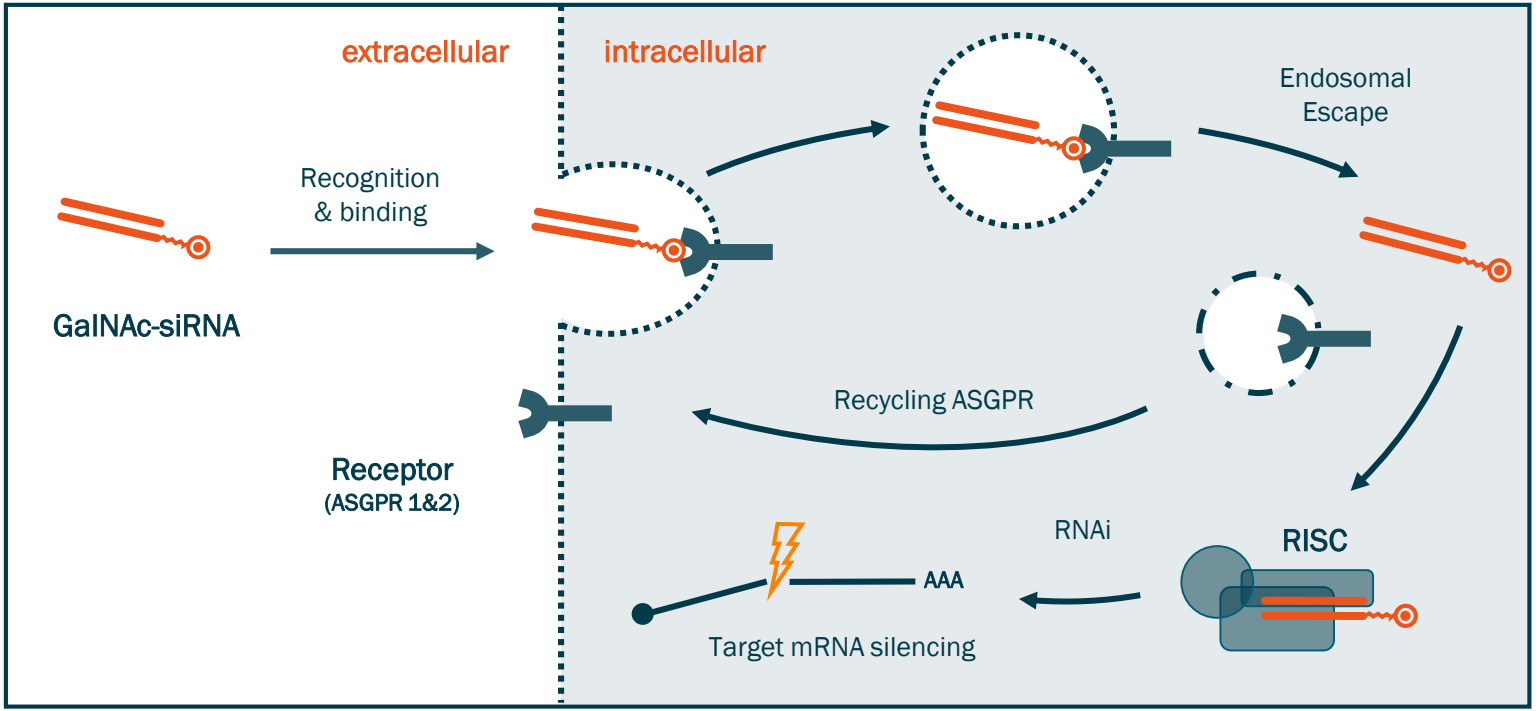
> Highly specific by targeting a **single transcript**

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

> Established **clinically validated technology**

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

Gene silencing with GalNAc-conjugated siRNA in hepatocytes



> Intracellular delivery mediated through receptor mediated endocytosis

Case study: SLN124 for the treatment of iron overload disorders

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

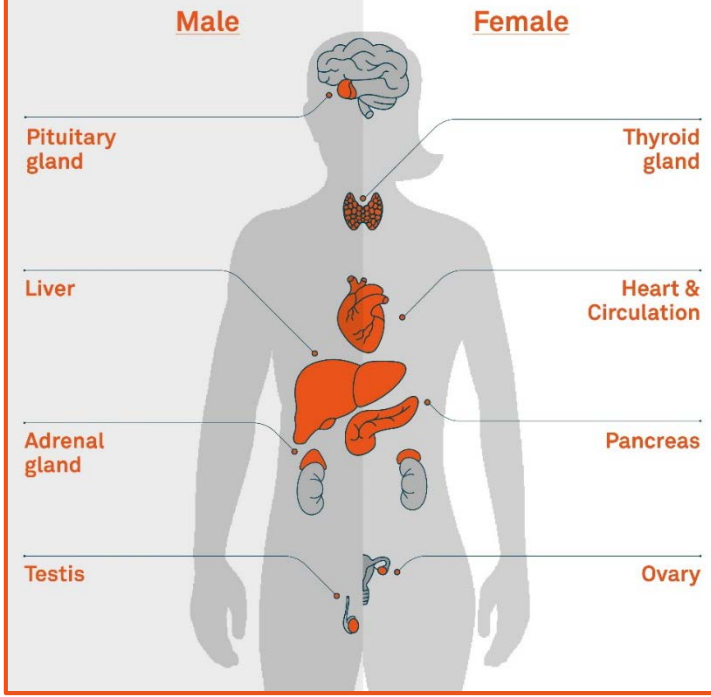
> Target a key modulator in iron regulation with a GalNAc-siRNA molecule providing a **highly specific, effective & safe** option through inhibition of a disease relevant target gene expressed in hepatocytes

CURRENT STAGE

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

Iron Overload Disorders

Affected organs by iron overload



Diseases with iron overload

> **β-Thalassemia**

> Myelodysplastic Syndrome

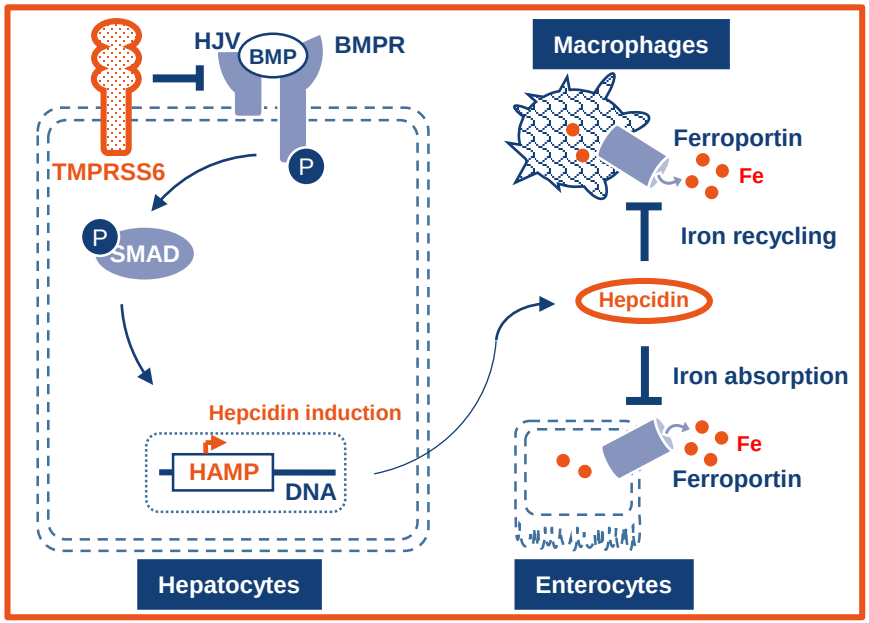
> Hereditary Haemochromatosis

> Aplastic Anaemia

> Sideroblastic Anaemia

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

SLN124 mechanism of action



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

> Inhibition of TMPRSS6 in hepatocytes induces Hepcidin expression

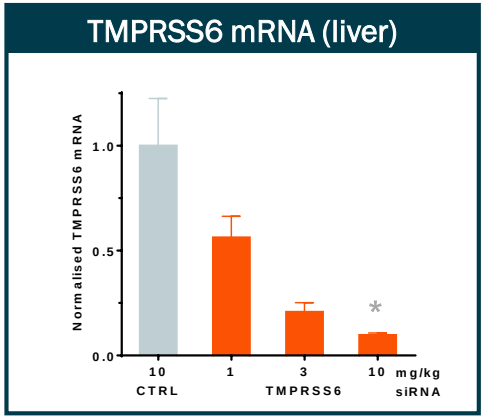
> Hepcidin reduces absorption of dietary iron and the release of iron from cellular storage, thereby reducing circulatory iron levels

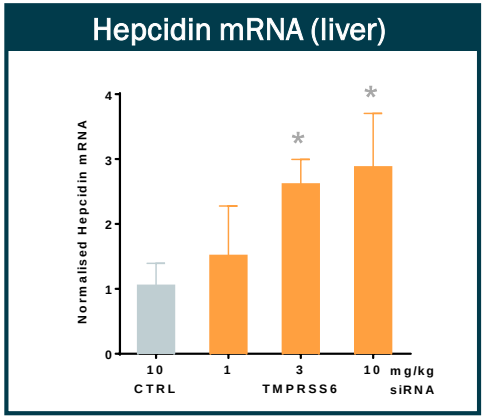
> The liver is the predominant source of Hepcidin

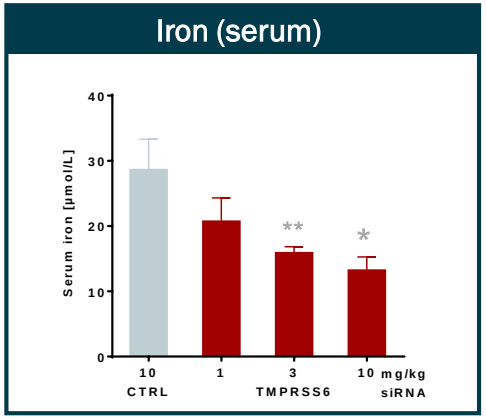
Silencing TMPRSS6

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

Silencing TMPRSS6 lowers serum iron levels in mice







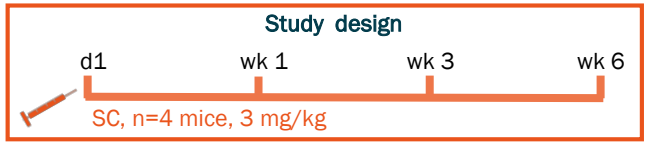
Kruskal-Wallis test with Dunn's multiple comparisons test against non-targeting control CTRL

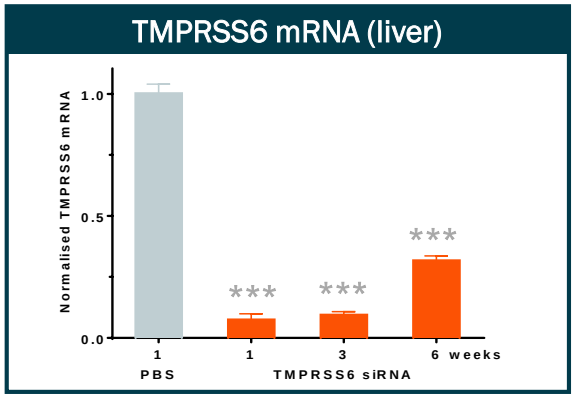
> Single subcutaneous administration reduces TMPRSS6 expression

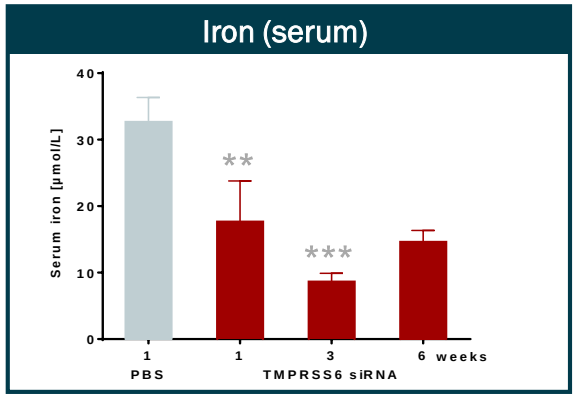
> Induction of hepcidin causes reduction of blood iron levels

> Proof of mechanism demonstrated

SLN124 lowers serum iron levels for at least six weeks after single injection 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

SLN124 - Summary

- Highly potent, selective and long acting GalNAc-conjugated siRNA
- Efficacious in lowering blood iron and well tolerated in healthy mice after single subcutaneous injection
- 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

Technology Innovation: making a good thing better

R&D with focus on portfolio and innovation

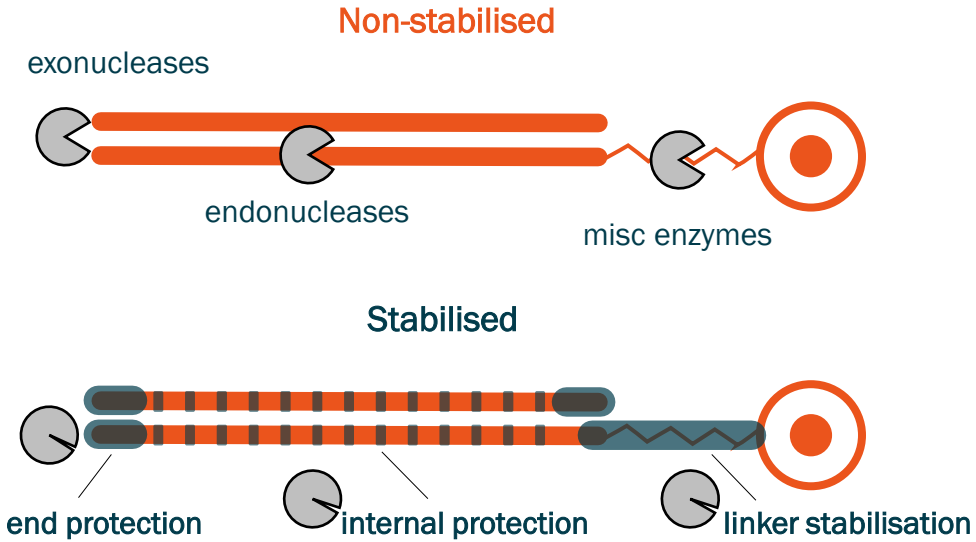
Technology Innovation

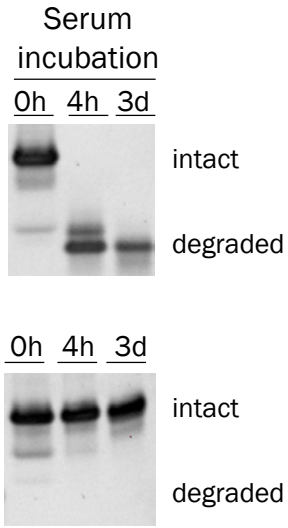
- Improve performance of our GalNAc-siRNA molecules
- Strengthen and broaden IP portfolio
- Expand RNAi horizon beyond hepatocytes
- Apply to therapeutic portfolio upon validation

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

Unmodified GalNAc-conjugated siRNA is quickly degraded in biological fluids

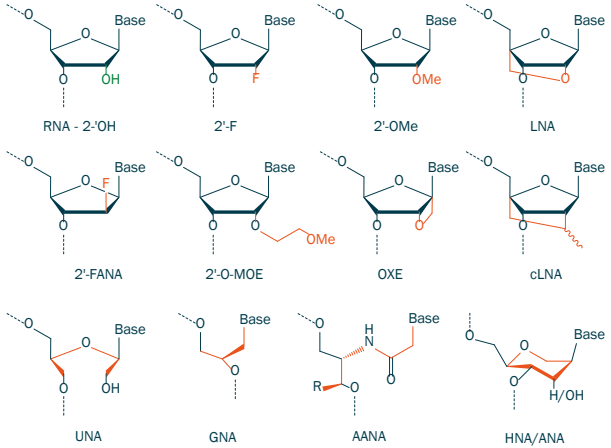




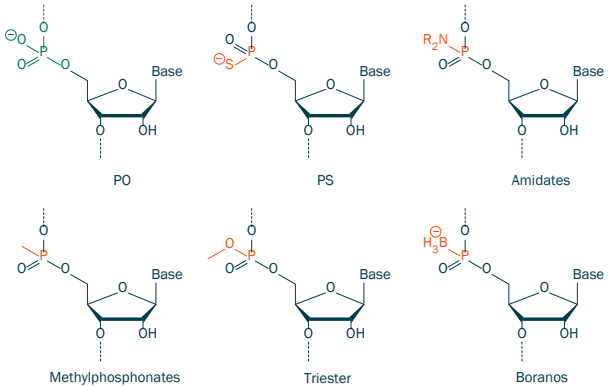
Incorporation of chemically modified nucleotides can protect GalNAc-conjugated siRNA from degradation

Most “stabilising chemically modified nucleotides” are not naturally occurring in humans

Modified 2‘-OH



Modified phosphate

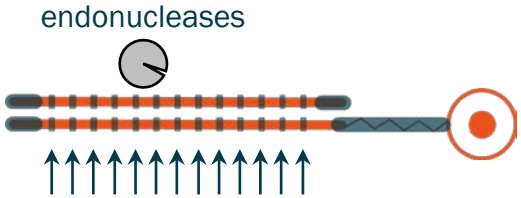


> May potentially cause **non-specific effects** and **affect silencing activity**

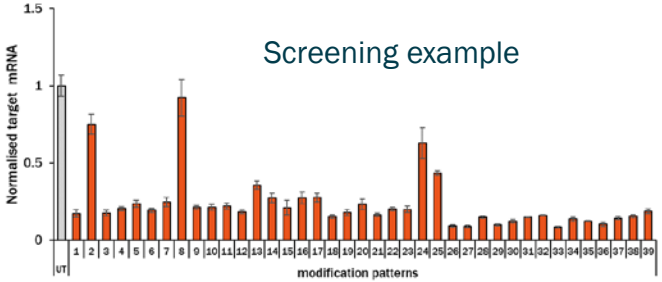
> Our strategy is to minimize the use of non-natural nucleotides while preserving or improving both stability and potency

siRNA modifications for endonuclease protection

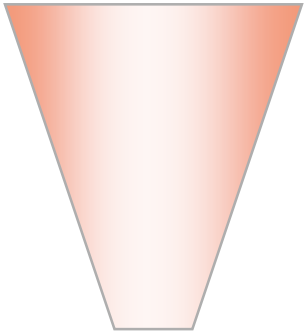
Minimizing the use of non-natural nucleotides



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

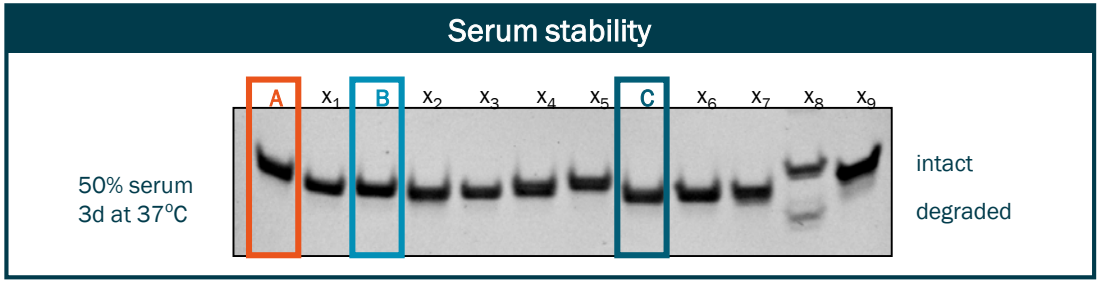
Serum stability: with or without GalNAc

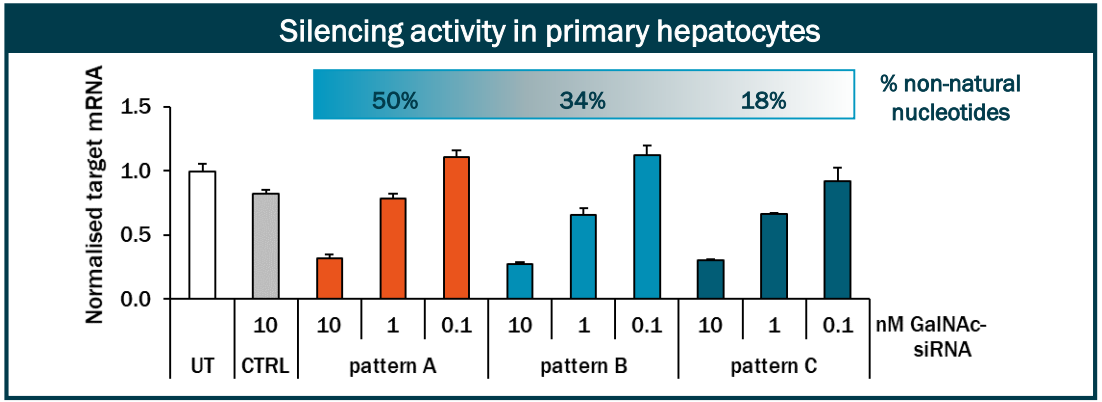
Primary hepatocyte activity: with GalNAc

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%

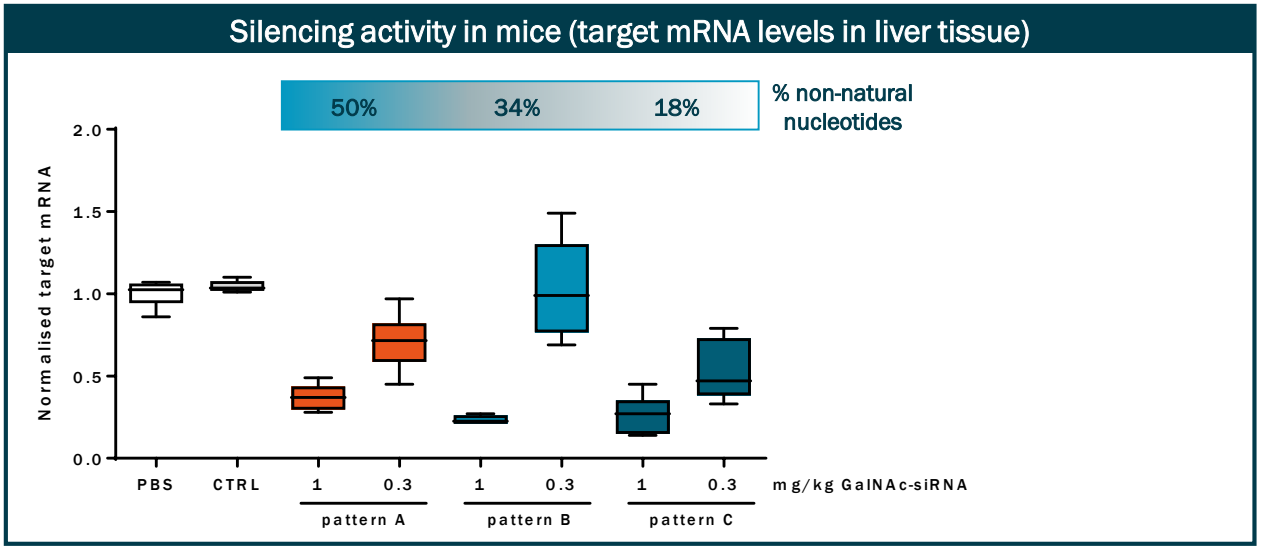
Serum stability and activity of molecules with reduced non-natural nucleotide content





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

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



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

Summary –GalNAc-conjugated siRNA modifications for endonuclease protection

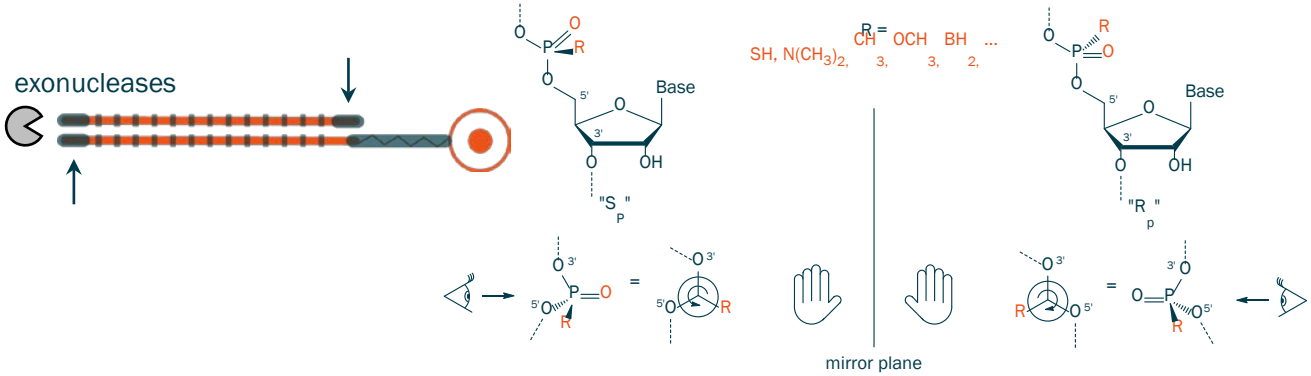
Identified chemical modification patterns that

- Reduce 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*
- Can be applied to any siRNA sequence, permitting accelerated lead optimisation

End protection against exonucleases

Challenges associated with the use of non-natural end-protecting moieties

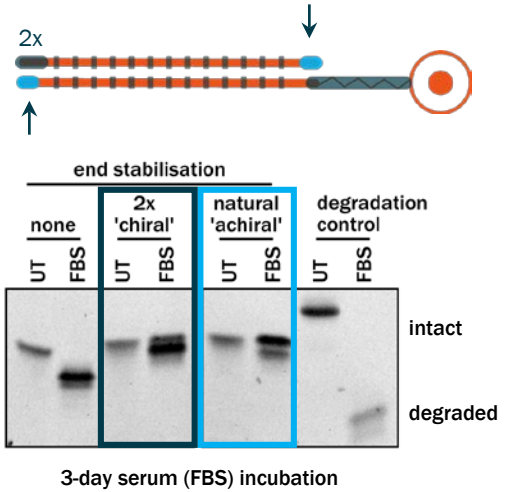
- Most siRNA end-protecting moieties are not naturally occurring in the human body, and may cause side effects
- End-protecting moieties can add undefined chiral centres that may increase complexity of compound manufacturing and characterisation



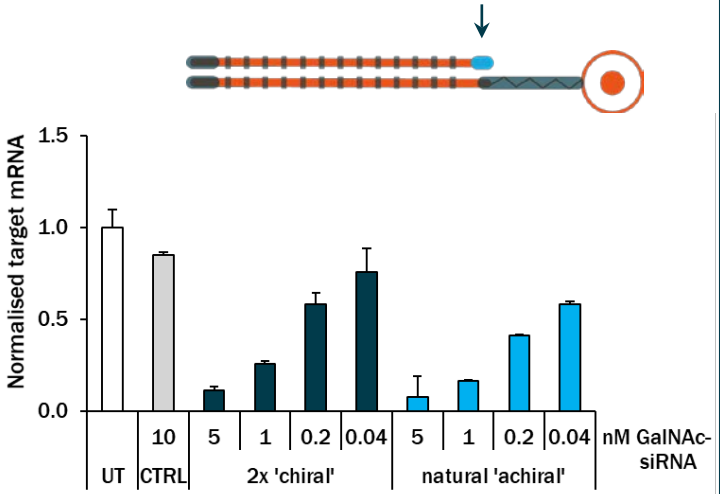
- The goal is to identify and apply naturally occurring moieties for the end protection, which do not add stereogenic complexity (‘achiral’)

Performance of GalNAc-conjugated siRNA with natural ‘achiral’ end-protecting moieties

Serum stability

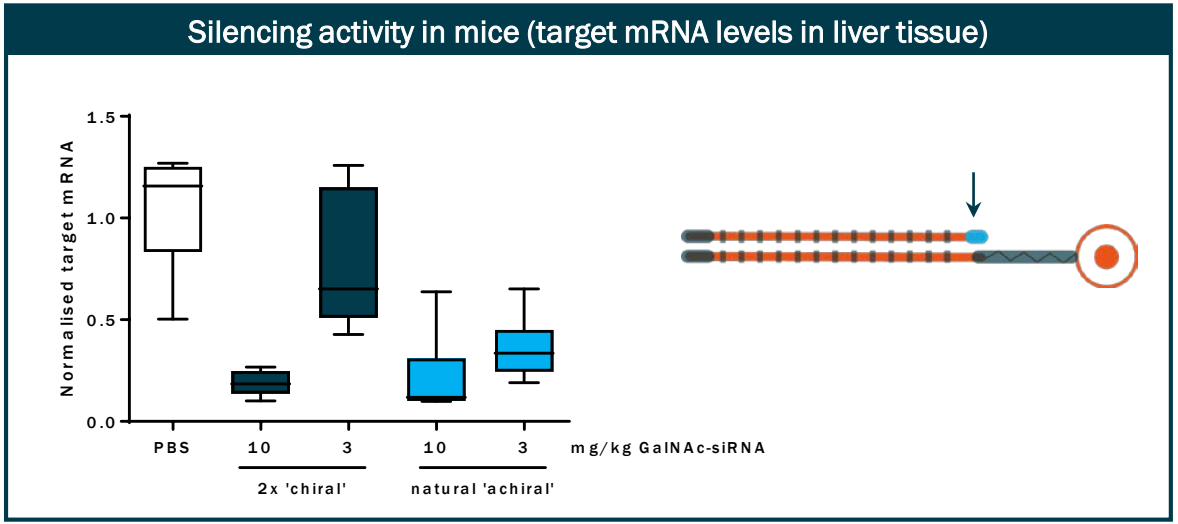


Silencing activity in primary hepatocytes



Engagement of single naturally occurring ‘achiral’ end-protecting moieties yields increased stability and robust gene silencing activity

In vivo activity of GalNAc-conjugated siRNA with natural achiral end-protecting moieties



GalNAc-siRNA molecules with naturally occurring single ‘achiral’ end-protecting moieties are highly potent in vivo

Summary – End modifications for exonuclease protection

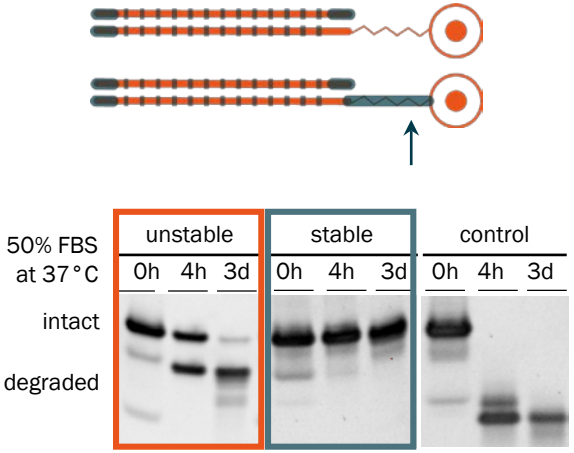
Identified end-protecting moieties, which

- Are naturally occurring and do not add stereogenic complexity ('achiral')
- Yield increased nuclease stability
- Show excellent activity in vitro and in vivo
- Can be applied to **any siRNA** sequence

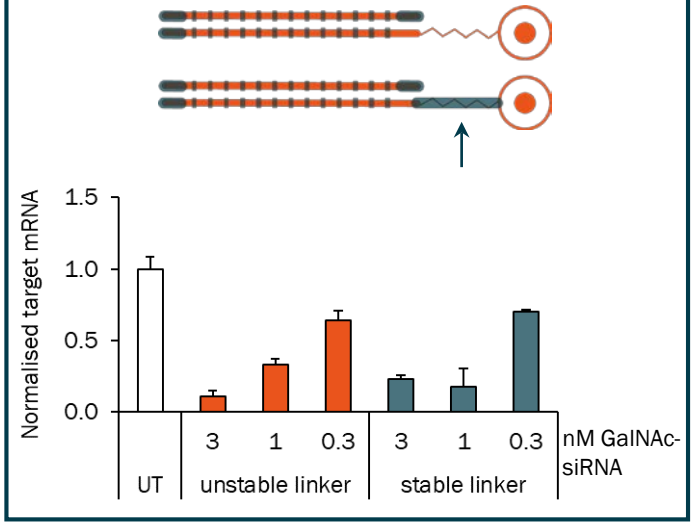
Stabilization of the linker

Performance of GalNAc-conjugated siRNA with stabilized linker

Serum stability

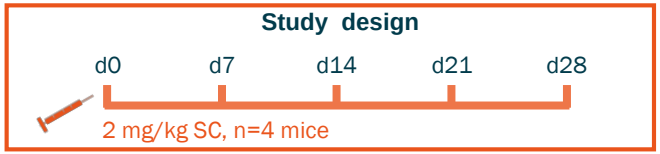


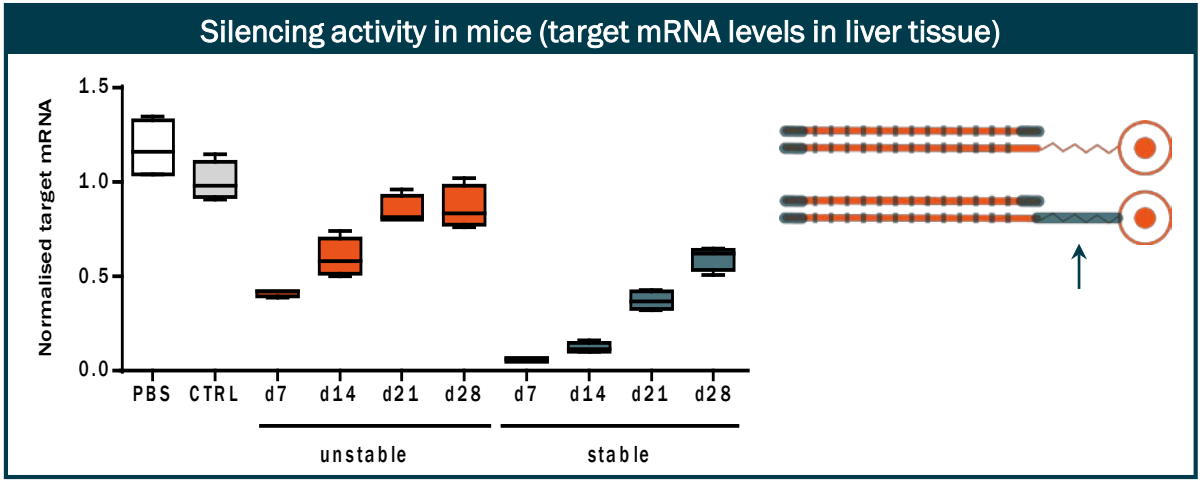
Silencing activity in primary hepatocytes



GalNAc-conjugated siRNA with stabilized linker produces robust silencing activity in primary hepatocytes

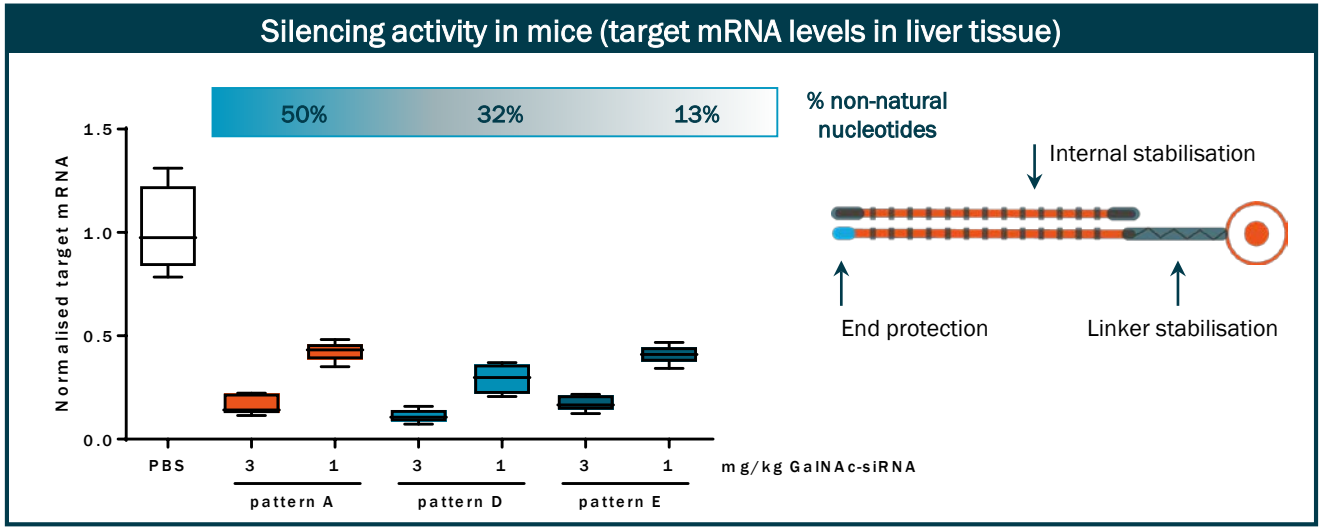
In vivo activity of GalNAc-conjugated siRNA with stabilized linker





GalNAc-conjugated siRNA with stabilized linker yields stronger and prolonged target silencing *in vivo*

Combining GalNAc-conjugated siRNA nucleobase modifications, end protection, and linker stabilization



Incorporation of novel chemical modification patterns, end-protecting and linker-stabilising moieties yields robust GalNAc-siRNA silencing in vivo

Summary – GalNAc-conjugated siRNA innovation

- Designed highly stable and potent GalNAc-siRNA molecules
- Reduced non-natural nucleotide content and “unpredicted chiral’ end-protecting modifications by up to 85%
- Internal and end-protecting patterns can be applied to any siRNA sequence, accelerating lead optimisation
- Established a more robust and easier to control synthesis
- Supported by fundamental IP, granted in US and Europe
- 10+ additional patent applications filed 2017

Acknowledgements

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Silence Preclinical Drug Discovery Team:
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