SILENCE THERAPEUTICS

9th Clinical Trials Innovation Programme, 26 & 27 April 2018

Use of Advanced siRNAs Targeted to Hepatocytes for the Development of Novel Drugs to Treat Liver-related Disorders

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Forward looking statements

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About Silence

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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

> Market cap: £136.5M*

> EV: ~ £104M*

Headcount:

> 42 FTE (27 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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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 organisation

Drug Discovery team restructured

Technology Innovation group created

Experienced management team to execute strategy

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Experienced Leadership Team: Strong background in discovery and development of RNA therapies



Ali Mortazavi,
Chief Executive Officer



Torsten Hoffmann, Ph.D.
Chief Scientific Officer



David Ellam,
Chief Financial Officer



Marie W. Lindholm, Ph.D.
Head of Technology Innovation



Laura Roca-Alonso, Ph.D.
Head of Corporate Development



Michael Mulqueen,
Head of BD & Licensing



Alison Gallafent,
Head of Intellectual Property



Ulrich Zügel, Ph.D.
Head of Pre-Clinical Drug Discovery



Linnea Elrington,
Head of Human Resources

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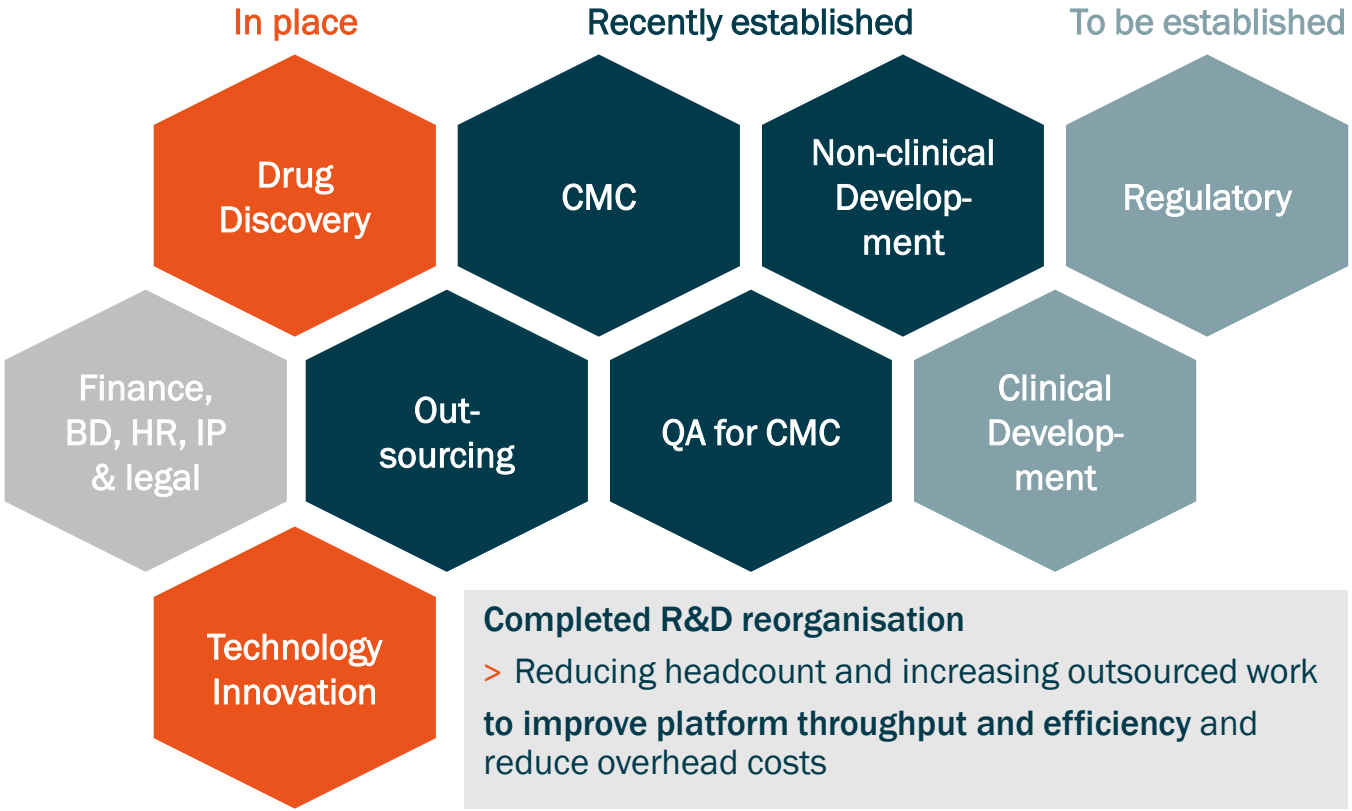
Evolving modular R&D capabilities



Completed R&D reorganisation

> Reducing headcount and increasing outsourced work

to improve platform throughput and efficiency and reduce overhead costs

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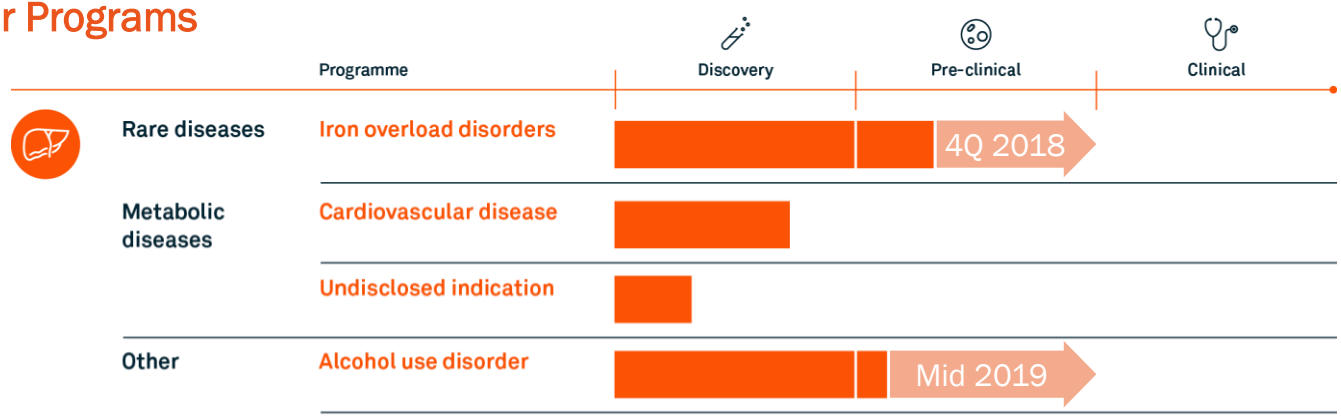
Pipeline

Building a proprietary portfolio, two projects advanced into preclinical development

Our Programs



Out-Licensed Programs (AtuRNAi™)



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GalNAc conjugated siRNA technology

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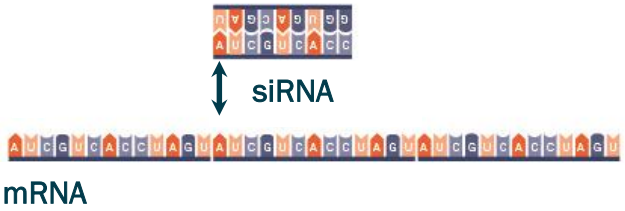
siRNA mechanism of action

1. mRNA sequence for target gene X



2. siRNA designed specifically against target gene X



3. Antisense strand binds to mRNA complementarily



4. mRNA degradation and gene silencing



RNA interference is

> A Nobel prize-winning discovery

> A natural pathway that can be harnessed to inhibit the expression of disease-causing genes without altering DNA

We can specifically target any gene in the genome with our short interfering RNA (siRNA) molecules

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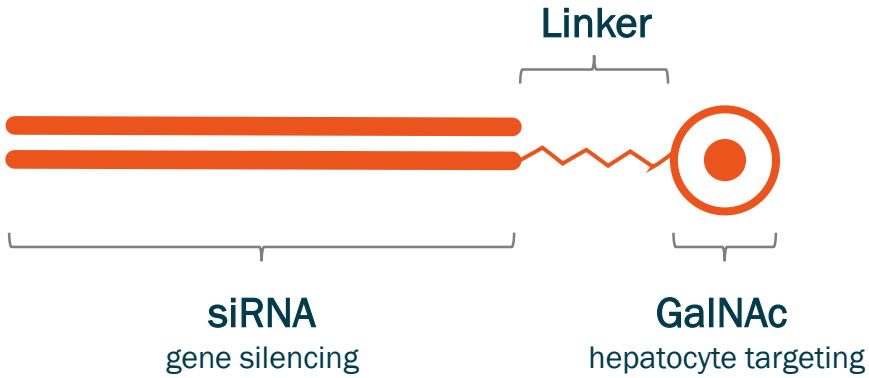
GalNAc-siRNA molecules



Advantages of GalNAc-siRNA technology

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

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

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

> Established **clinically validated technology**

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

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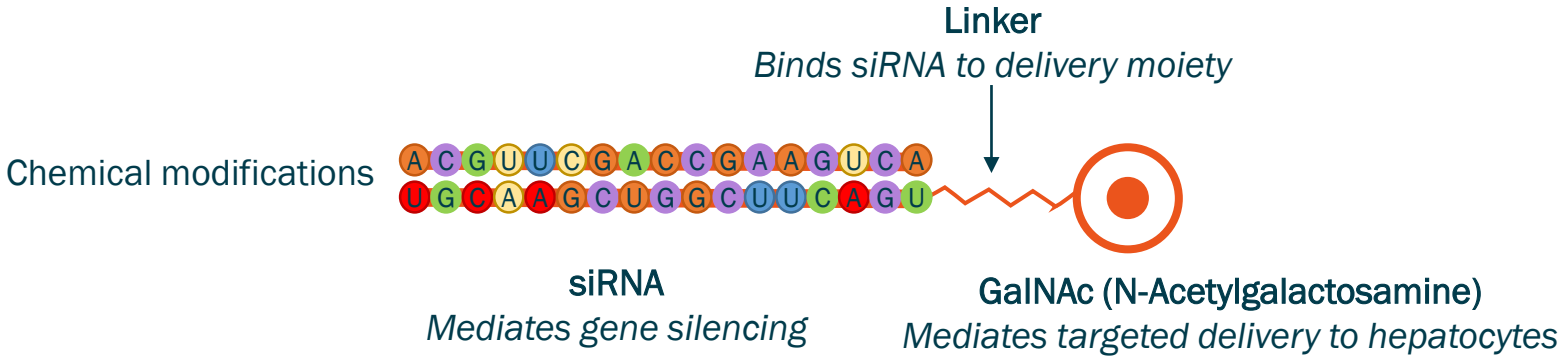
GalNAc-siRNA medicines

Schematic structure of our therapeutic molecules:



How do we ensure that our medicines are protected and free to use?

> GalNAc as a targeting ligand per se is free to use

> We have a robust position for our foundational chemical modification technology

> We patent our linker chemistries

> We patent our potent and highly specific siRNA constructs and lead sequences

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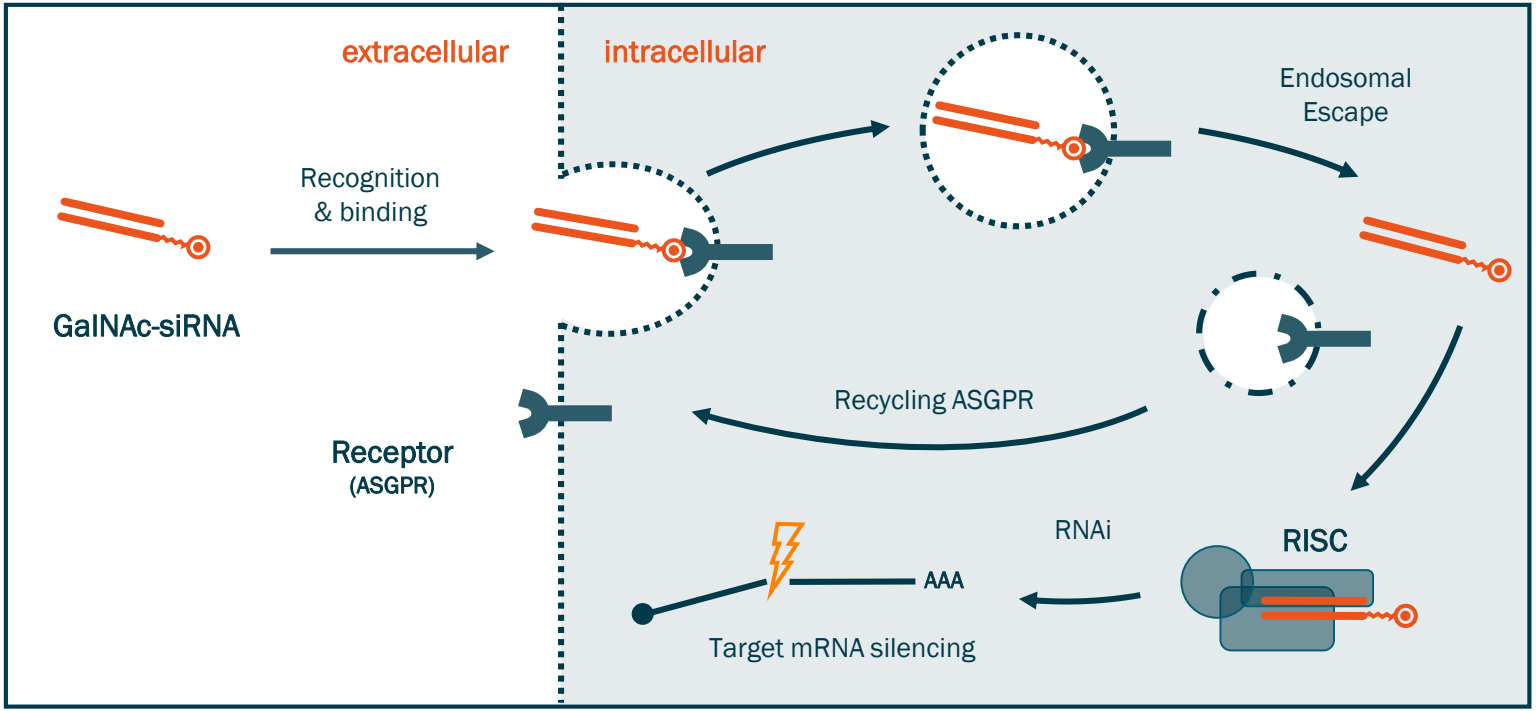
Gene silencing with GalNAc-siRNAs in hepatocytes



> Intracellular delivery mediated through receptor endocytosis

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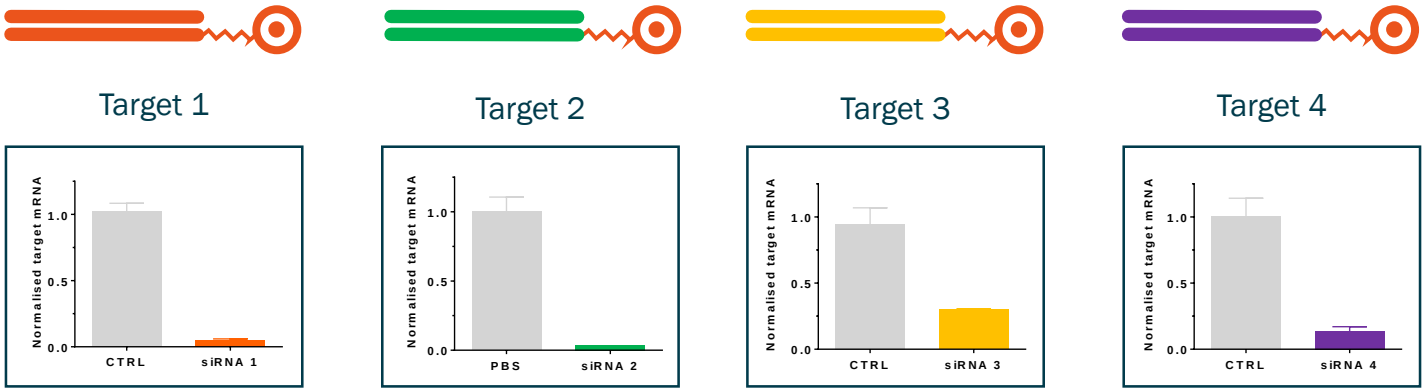
Platform performance

Platform technology: GalNAc-siRNA, able to mediate highly specific gene silencing in hepatocytes (liver) – "Specificity upon specificity"

~7,000 genes operate in the liver. We can target any of them by adapting the siRNA sequence, using the same technology



We are able to reproducibly silence disease-causing genes using our platform technology

Single SC dose of 2-3 mg/kg in healthy mice; analysis after 1-2 weeks

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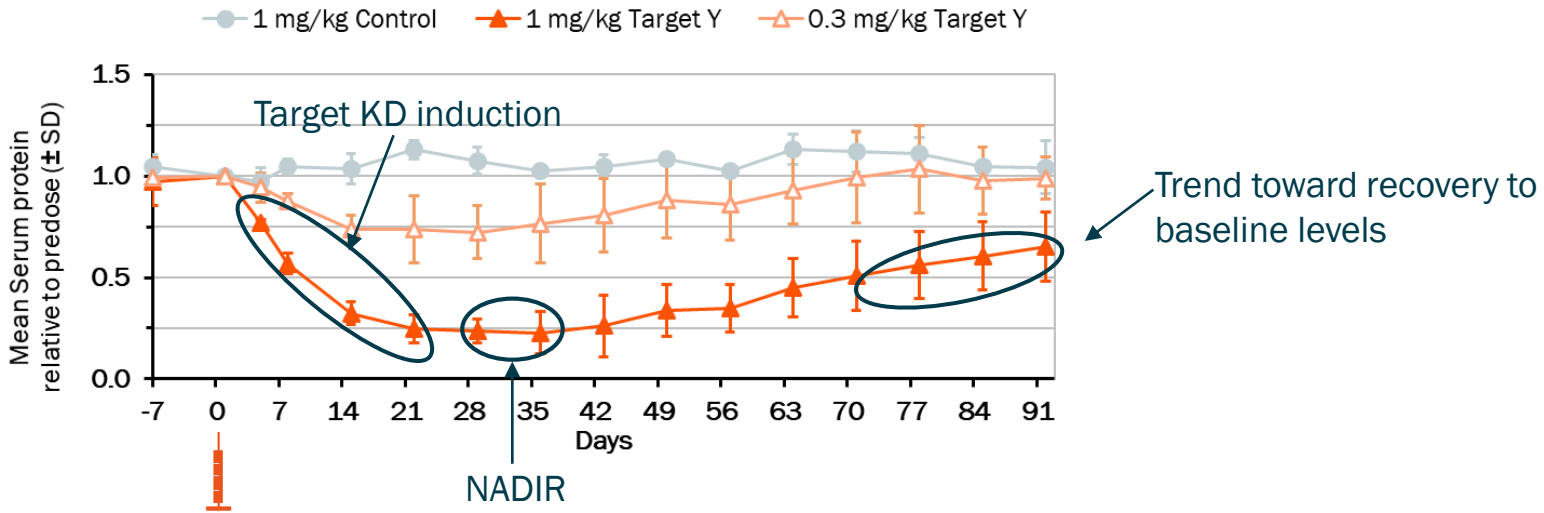
Advantageous properties of our medicines

- > Subcutaneous administration, patient friendly
- > Long duration of action (variable depending on target gene)
- > Well tolerated
- > Our GalNAc-siRNA medicines are suitable for a wide range of indications



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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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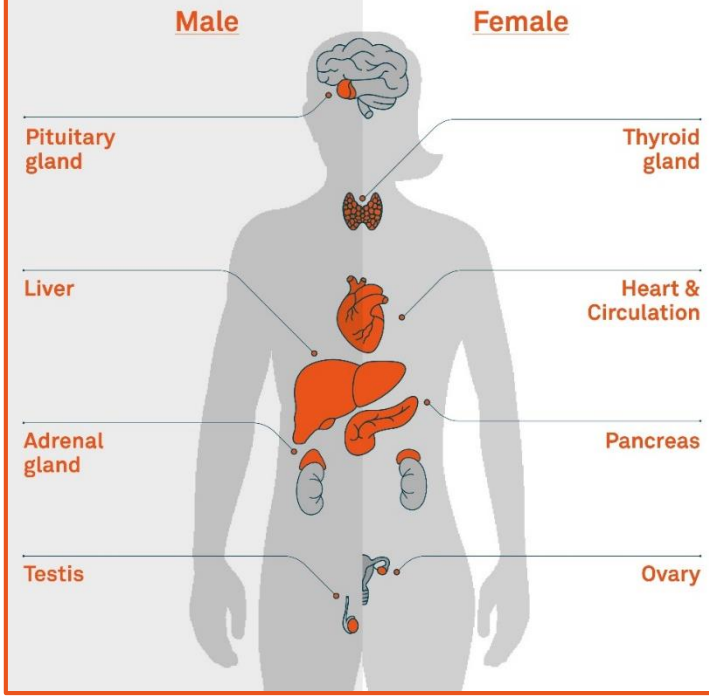
Iron Overload Disorders

Organs affected 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. heart, liver & endocrine organs

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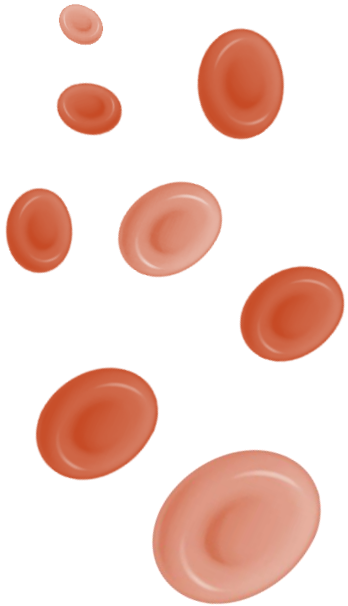
β-Thalassemia facts



- Rare blood disorder caused by mutations in the **β globin gene**
- Patients present with **ineffective erythropoiesis** and chronic **haemolytic anaemia**
- Many **β-Thalassemia intermedia** and all **β-Thalassemia major patients require transfusions to correct anaemia**
- **Ineffective erythropoiesis & blood transfusions** cause **iron overload**
- If untreated leads to severe organ damage, including **cardiac & hepatic failure** early in life

Prevalence

1/100,000 (global); 1/10,000 (Europe)

Up to 30% are genetic carriers (depending on region)



Main β-Thalassemia distribution

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Market opportunity for iron overload disorders



β-Thalassemia intermedia & T. major (TDT)

- >Combination with transfusions & chelators to reduce frequency & dose
- >Improve erythropoiesis and reduce secondary iron overload burden

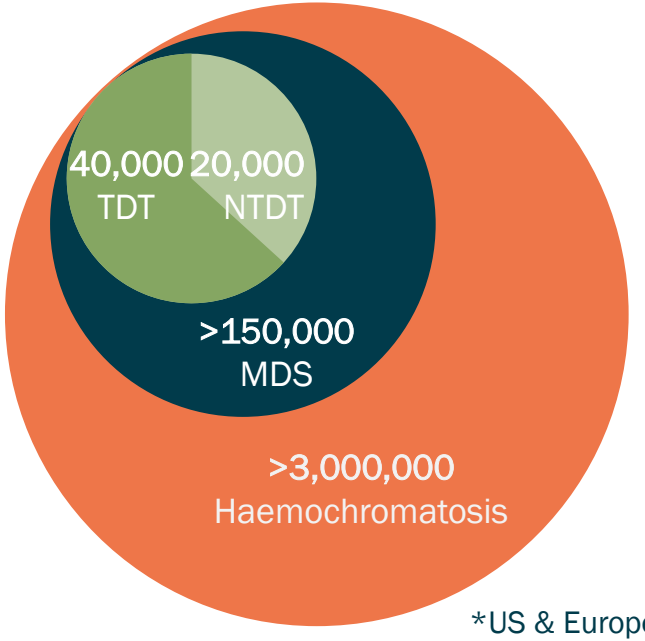
β-Thalassemia intermedia (NTDT)

- >Monotherapy to delay onset of severe symptoms
- >Reduce dietary iron overload & subsequent organ damage

Other iron overload disorders

Myelodysplastic Syndrome (MDS)

Haemochromatosis



*US & Europe

SLN124 for β-Thalassemia with significant upside potential for other iron overload disorders

TDT = transfusion dependent Thalassemia; NTDT = non-transfusion dependent Thalassemia

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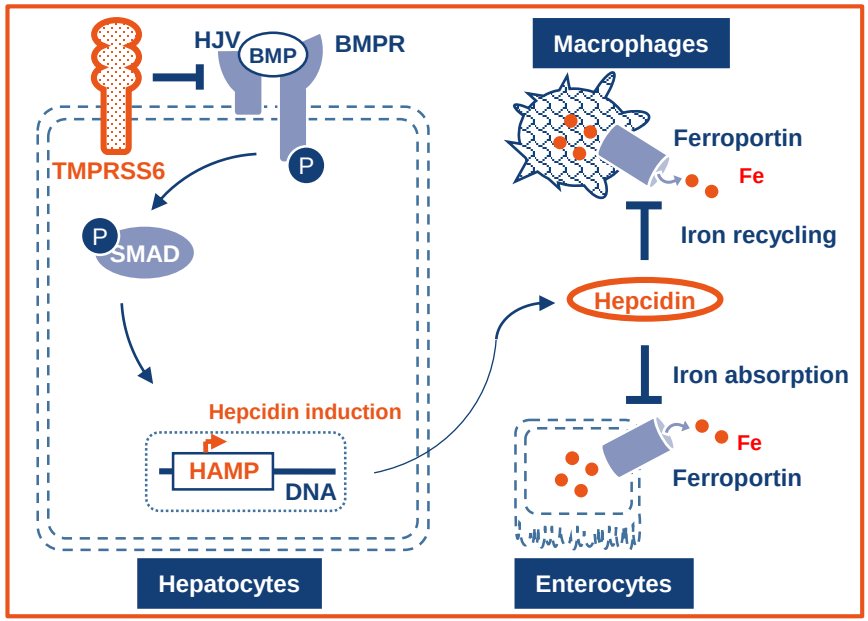
SLN124 mechanism of action



> **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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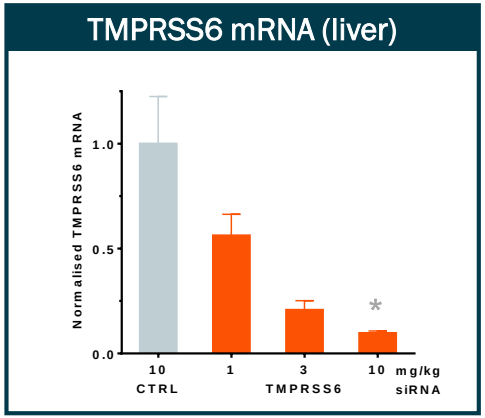
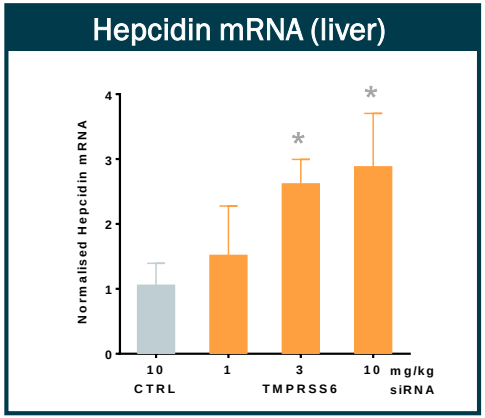
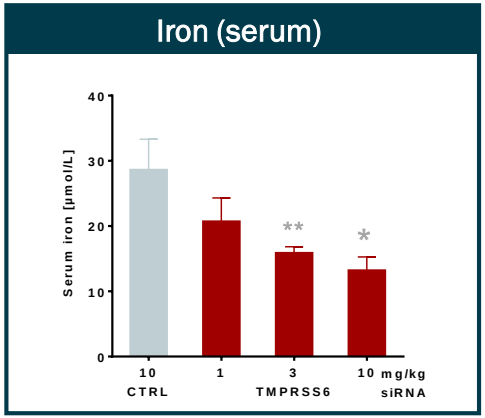
Silencing TMPRSS6 lowers serum iron levels in mice









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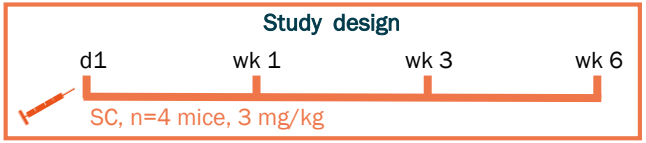
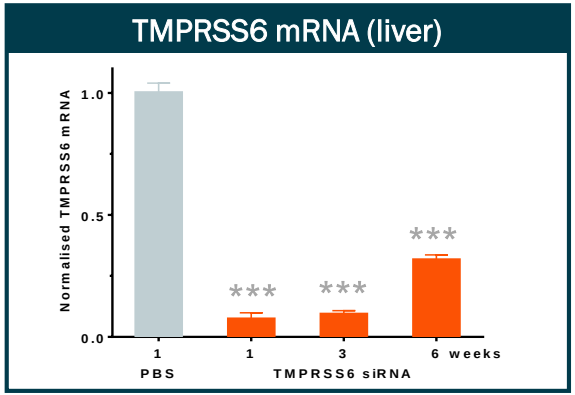
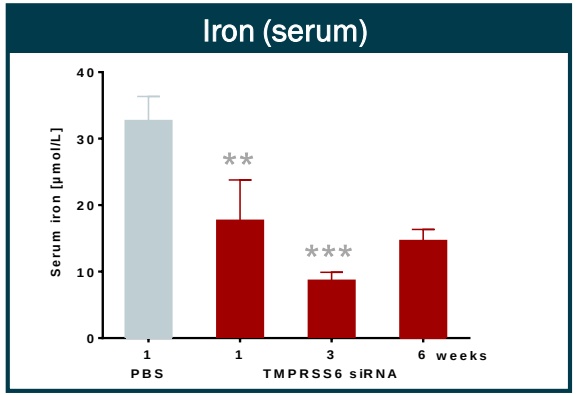
SLN124 lowers iron levels for at least 6 weeks after single administration in mice







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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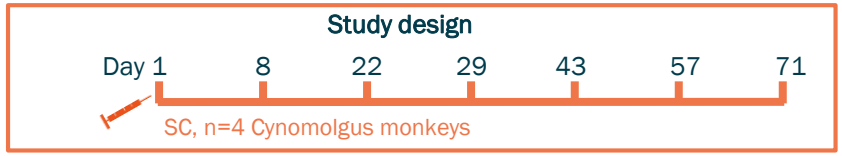
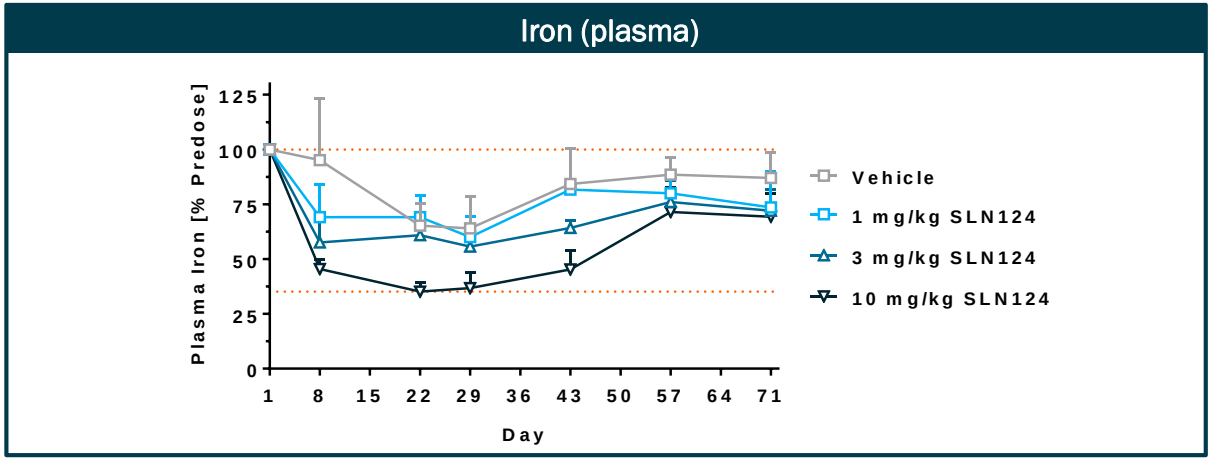
Sustained reduction of circulating iron levels after single administration in non-human primates





> Dose dependent, durable plasma iron reduction up to 6 weeks

> Well tolerated with long duration of action

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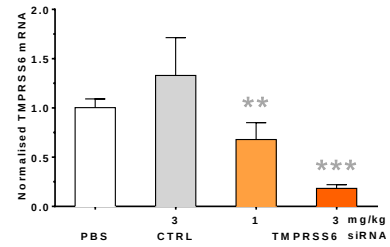
Therapeutic activity of SLN124 in a disease model for hereditary haemochromatosis ($HFE^{-/-}$ mice) - 1/2

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

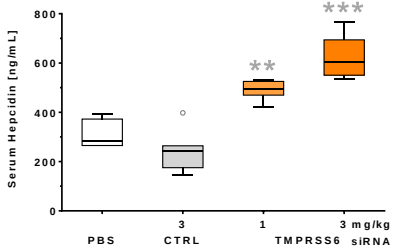
Study design



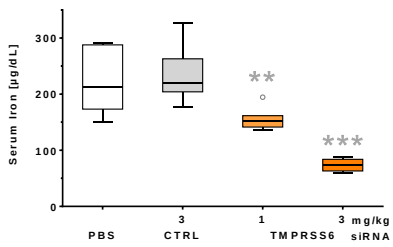
TMPRSS6 mRNA (liver)



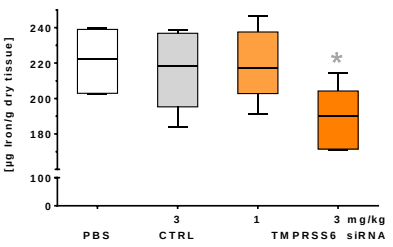
Hepcidin (serum)



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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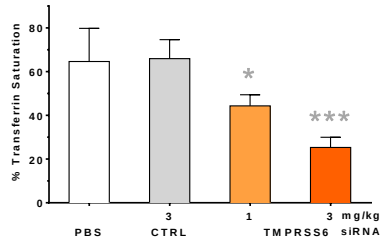
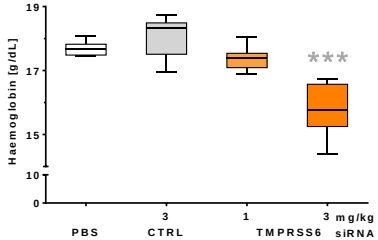
Therapeutic activity of SLN124 in a disease model for hereditary haemochromatosis ($HFE^{-/-}$ mice) - 2/2

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

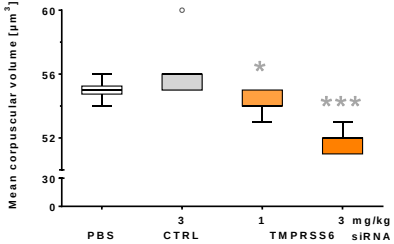
Transferrin Saturation



Haemoglobin



Mean corpuscular volume



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

> Reduction of transferrin saturation to physiological values

> Normalization of haematological parameters

> Therapeutically active in $HFE^{-/-}$ mice after single administration

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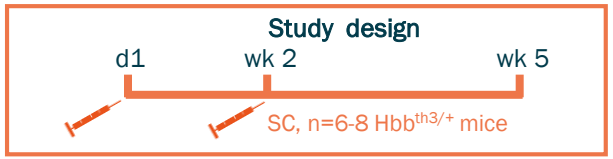
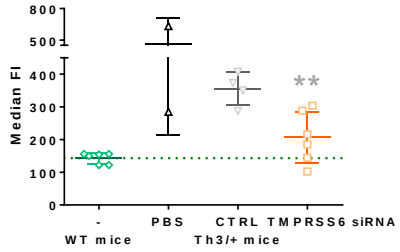
SLN124 normalizes ROS species & improves RBC parameters in β-Thalassemia disease model

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

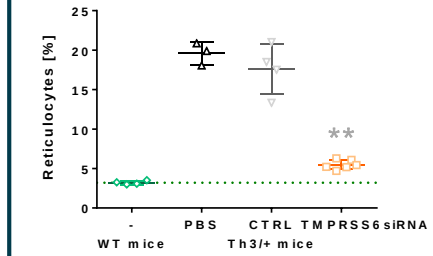
HUDSON INSTITUTE OF MEDICAL RESEARCH



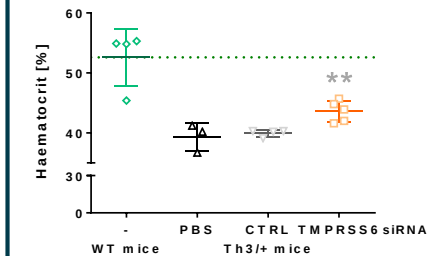
Reactive oxygen species (ROS)



Reticulocyte proportion



Haematocrit



Unpaired t test with Welch´s correction against non-targeting control CTRL

> Normalisation of ROS to levels towards values in healthy mice

> Normalisation of reticulocyte proportion and improvement of haematocrit

> SLN124 ameliorates erythropoiesis in animal model for β-Thalassemia intermedia

ROS = reactive oxygen species; RBC = red blood cells

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Why we are excited about SLN124?

Science

What does the Mode of action bring?

2018: Gene silencing via siRNA is a proven concept

SLN124 has proven to increase hepcidin and **reduce iron plasma levels**, thus restoring iron homeostasis

The GalNAc conjugate **targets hepatocytes** in the liver, acting specifically at hepcidin's predominant synthesis site

SLN124 is **highly specific** targeting a single gene

Indication

How does the science connect to the diseases?

beta-Thalassemia
Myelodysplastic Syndromes
Potential for Haemochromatosis

Central role of hepcidin enables lowering of iron plasma levels, **optimising erythropoiesis**

Mechanistic claim – treatment of iron overload disorders

SLN124: a treatment in the mono- or combination therapy setting as **new SoC**

Patient

What is the patient benefit?

SLN124 has the potential to become an **essential component of the future SoC**

QoL parameters will be improved such as transfusion frequency and drug burden of chelators

Enables an early treatment option for the **prevention of iron deposition in organs**

Pediatrics and adults will be treated

We will work with patient organisations in 2018

Market

When and where do we want to market it?

First In Class in iron overload

High value product with peak sales of $600 million (BT) and $3 billion (MDS)

Launch would be expected by 2024/25 via an Orphan designation

A corporate strategy is required to access geographies in the **middle and far east**

We are seeking **commercialisation partnerships**

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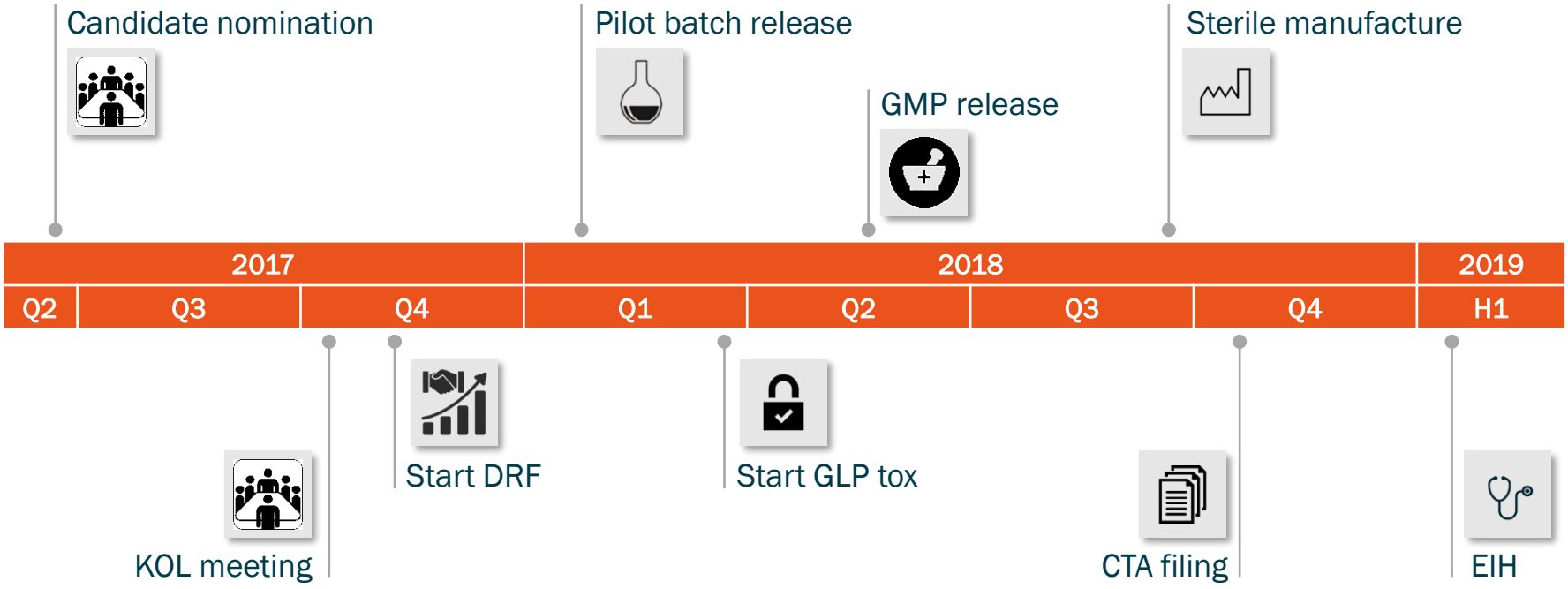
SLN124 development timelines – key milestones



On track for CTA filing 15 months after candidate selection

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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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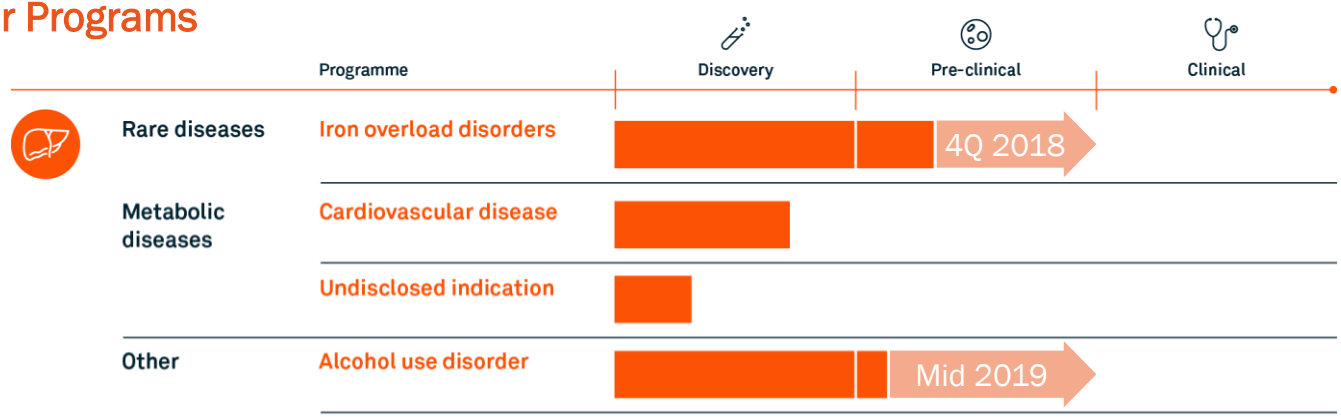
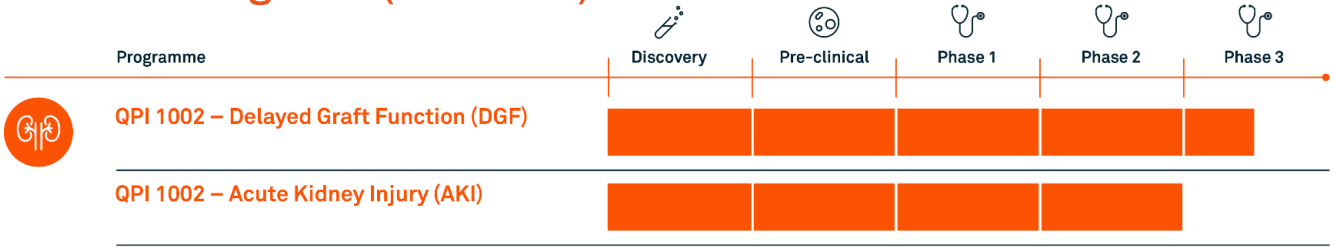
Pipeline

Building a proprietary portfolio, two projects advanced into preclinical development

Our Programs



Out-Licensed Programs (AtuRNAi™)



Quark

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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 horizons beyond hepatocytes
- Apply to therapeutic portfolio upon validation



Marie W. Lindholm, Ph.D.
Head of Technology Innovation
Roche
santaris pharma a/s

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



Ulrich Zügel, Ph.D.
Head of Pre-Clinical Drug Discovery
BAYER
SCHERING

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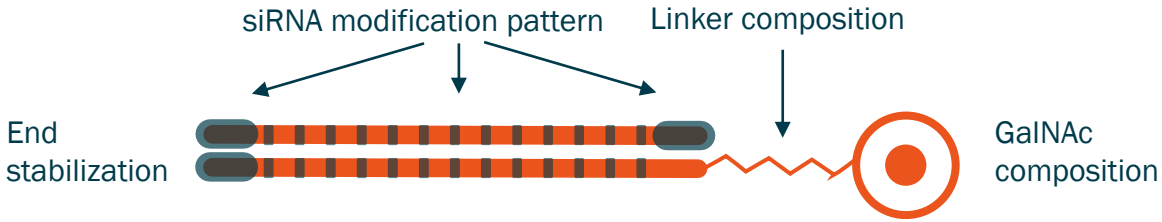
Fine-tuning molecular design to enhance performance



Focus areas for fine-tuning:

> Modification pattern: reduced number of non-natural modifications resulting in retained or improved activity

> End stabilisation: increased circulation half-life, increased activity and duration of action

> Linker: simplified and flexible synthesis, increased activity, and option to control circulation and intracellular half-life

> GalNAc: optimization of number and location of GalNAc units for increased activity and duration of action with a reduced dose vs. “traditional design”

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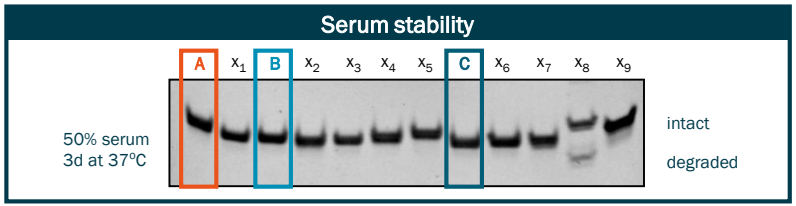
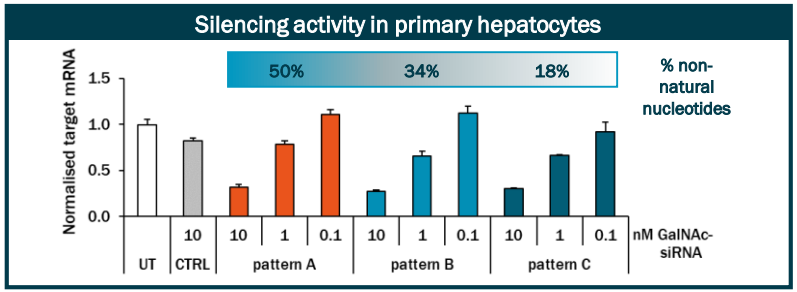
Example A: reducing number of non-natural modifications

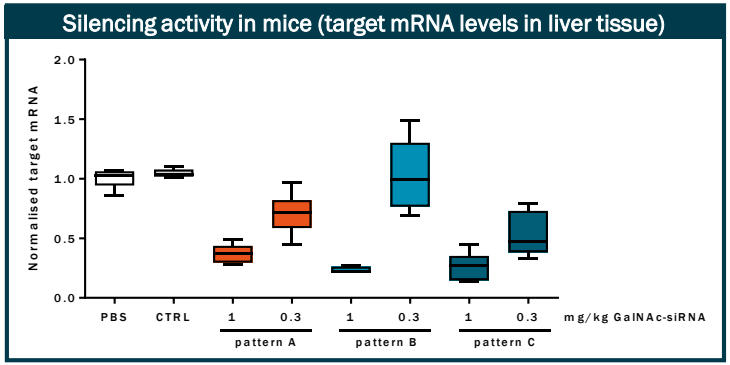
Serum stability and *in vitro* activity





In vivo activity





> Non-natural siRNA modifications can be dramatically reduced with retained nuclease resistance, 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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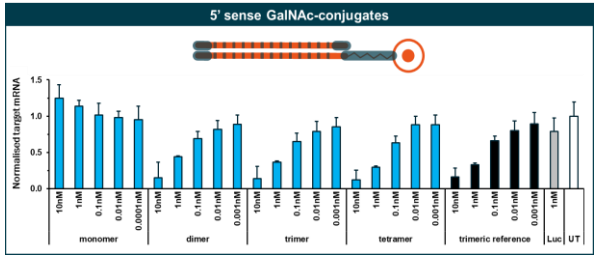
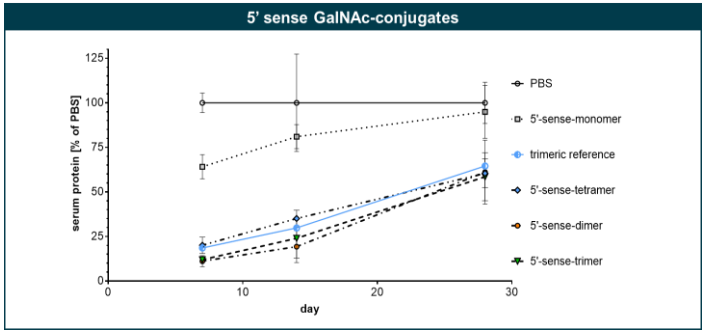
Example B: optimising number/location of GalNAc units

In vitro activity of 5’ sense and 3‘ anti-sense conjugates



In vivo activity of 5’ sense conjugates





> siRNA conjugated to GalNAc clusters of 2-4, but not 1, units are all similarly potent *in vitro*

> *In vitro* activity is similar for 2-4 GalNAcs located at 5’end of sense as at 3’end of antisense strand

> *In vivo* activity and duration of action is similar for clusters of 2-4 GalNAc 5’sense strand conjugates, only the single unit GalNAc conjugate lost activity compared to the other variants

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