SILENCE THERAPEUTICS

TIDES: Oligonucleotide and Peptide Therapeutics, 07-10 May 2018

Advanced GalNAc-siRNA Platform and Its Therapeutic Applications

Torsten Hoffmann, PhD, Chief Scientific Officer

Forward looking statements

The information contained in this presentation is being supplied and communicated to you on a confidential basis solely for your information and may not be reproduced, further distributed to any other person or published, in whole or in part, for any purpose. In accordance with the prohibition on market abuse contained in Part VIII of the Financial Services and Markets Act 2000 (as amended) (the "Act"): (i) you must not pass this information to any person; and (ii) you must not base any behaviour in relation to any securities or other Qualifying Investments (as that term is defined in the Act) which would amount to market abuse on such information until after it is made generally available.

This presentation is being communicated in the United Kingdom only to (a) persons who have professional experience in matters relating to investments falling within Article 19(1) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005 (the "Order") or (b) high net worth companies and other bodies falling within Article 49(2) of the Order; or (c) persons to whom this presentation may otherwise lawfully be distributed (all such persons being referred to as "relevant persons"). This presentation is only directed at relevant persons, and any investment or investment activity to which this presentation relates is only available to relevant persons or will be engaged in only with relevant persons. Solicitations resulting from this presentation will only be responded to if the person concerned is a relevant person. Other persons should not act upon this presentation or any of its contents.

The distribution of this presentation in certain jurisdictions may be restricted by law, and persons into whose possession this presentation comes should inform themselves about, and observe, any such restrictions. Although reasonable care has been taken to ensure that the facts stated in this presentation are accurate and that the opinions expressed are fair and reasonable, the contents of this presentation have not been verified by Silence Therapeutics plc (the "Company") or any other person. Accordingly no representation or warranty, express or implied, is made as to the fairness, accuracy, completeness or correctness of the information and opinions contained in this presentation and no reliance should be placed on such information or opinions. None of the Company, or any of its respective members, directors, officers or employees nor any other person accepts any liability whatsoever for any loss howsoever arising from any use of such information or opinions or otherwise arising in connection with this presentation. No part of this presentation, or the fact of its distribution, should form the basis of or be relied upon in connection with any contract or commitment or investment decision whatsoever. This presentation does not form part of any offer of securities, or constitute a solicitation of any offer to purchase or subscribe for securities or an inducement to enter into any investment activity. Recipients of this presentation are not to construe its contents, or any prior or subsequent communications from or with the Company or its representatives as investment, legal or tax advice. In addition, this presentation does not purport to be all-inclusive or to contain all of the information that may be required to make a full analysis of any transaction. Further, the information in this presentation is not complete and may be changed. Recipients of this presentation should each make their own independent evaluation of the information and of the relevance and adequacy of the information in this document and should make such other investigations as they deem necessary.

Securities in the Company have not been, and will not be, registered under the United States Securities Act of 1933, as amended (the "Securities Act"), or qualified for sale under the law of any state or other jurisdiction of the United States of America and may not be offered or sold in the United States of America except pursuant to an exemption from, or in a transaction not subject to, the registration requirements of the Securities Act. Neither the United States Securities and Exchange Commission nor any securities regulatory body of any state or other jurisdiction of the United States of America, nor any securities regulatory body of any other country or political subdivision thereof, has approved or disapproved of this presentation or the securities discussed herein or passed on the accuracy or adequacy of the contents of this presentation. Any representation to the contrary is unlawful.

Safe Harbour statement: this presentation may contain forward-looking statements that reflect the Company's current views and expectations regarding future events. In particular certain statements with regard to management's strategic vision, aims and objectives, the conduct of clinical trials, the filing dates for product licence applications and the anticipated launch of specified products in various markets, the Company's ability to find partners for the development and commercialisation of its products as well as the terms for such partnerships, anticipated levels of demand for the Company's products (including in development), the effect of competition, anticipated efficiencies, trends in results of operations, margins, the market and exchange rates, are all forward looking in nature.

Forward-looking statements involve risks and uncertainties that could cause actual results to differ materially from those expressed or implied by the forward looking statements. Although not exhaustive, the following factors could cause actual results to differ materially from those the Company expects: difficulties inherent in the discovery and development of new products and the design and implementation of pre-clinical and clinical studies, trials and investigations, delays in and results from such studies, trials and investigations that are inconsistent with previous results and the Company's expectations, the failure to obtain and maintain required regulatory approvals, product and pricing initiatives by the Company's competitors, inability of the Company to market existing products effectively and the failure of the Company to agree beneficial terms with potential partners for any of its products or the failure of the Company's existing partners to perform their obligations, the ability of the Company to obtain additional financing for its operations and the market conditions affecting the availability and terms of such financing, the successful integration of completed mergers and acquisitions and achievement of expected synergies from such transactions, and the ability of the Company to identify and consummate suitable strategic and business combination transactions and the risks described in our most recent Admission Document.

By participating in this presentation and/or accepting any copies hereof you agree to be bound by the foregoing restrictions and the other terms of this disclaimer.

© Silence Therapeutics 2018

About Silence

© Silence Therapeutics 2018

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*

© Silence Therapeutics 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 organisation

Drug Discovery team restructured

Technology Innovation group created

Experienced management team to execute strategy

© Silence Therapeutics 2018

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



Ali Mortazavi,
Chief Executive Officer



Torsten Hoffmann, Ph.D.
Chief Operating 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



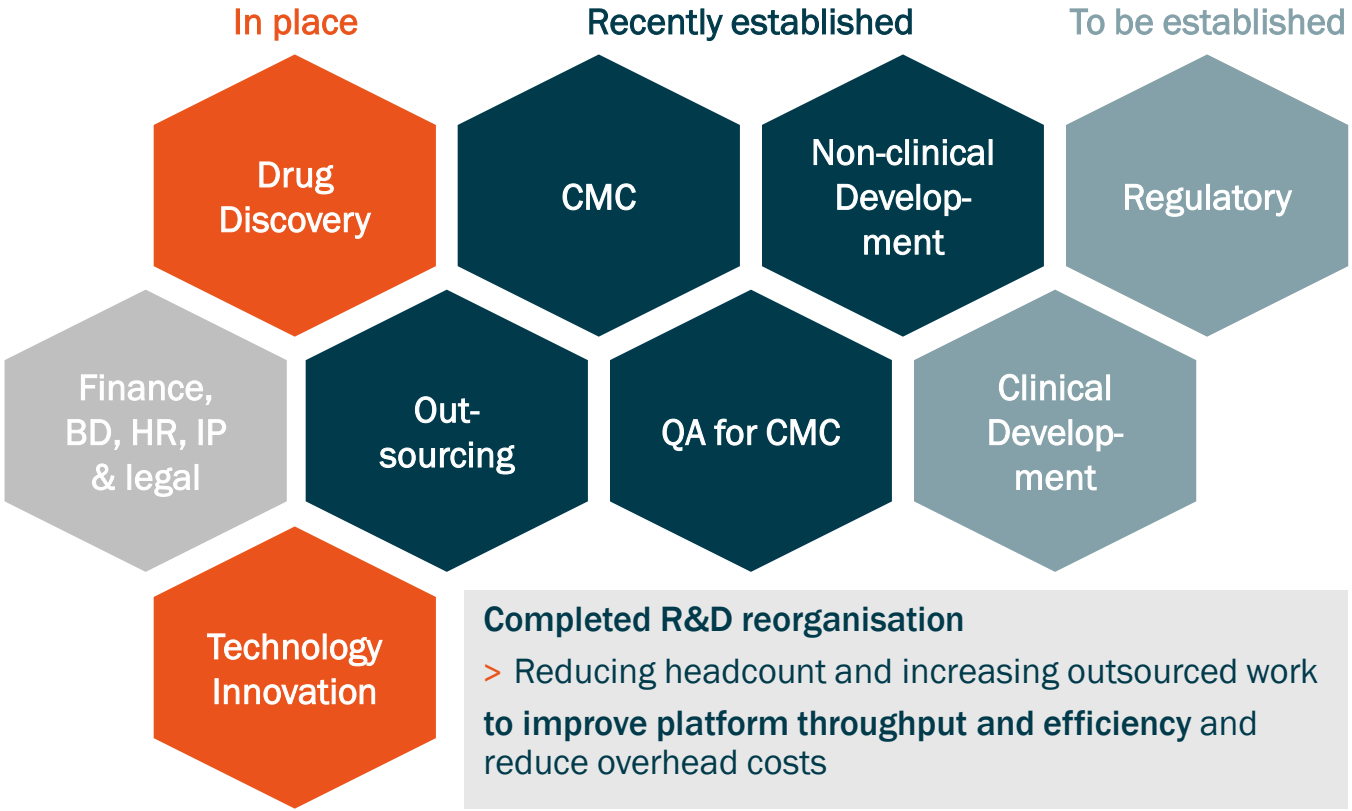
Ulrich Zügel, Ph.D.
Head of Pre-Clinical Drug Discovery



Linnea Elrington,
Head of Human Resources

© Silence Therapeutics 2018

Evolving modular R&D capabilities



Completed R&D reorganisation

> Reducing headcount and increasing outsourced work

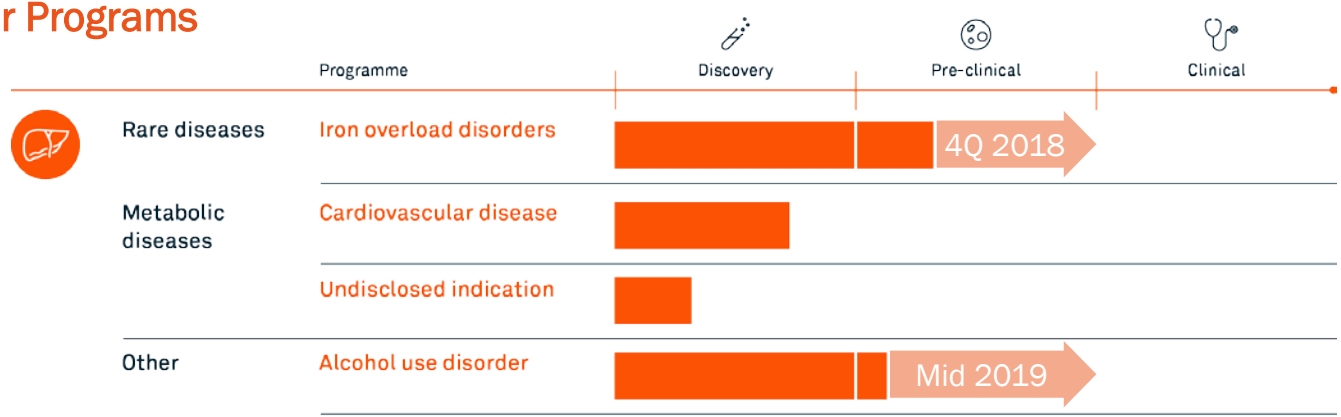
to improve platform throughput and efficiency and reduce overhead costs

© Silence Therapeutics 2018

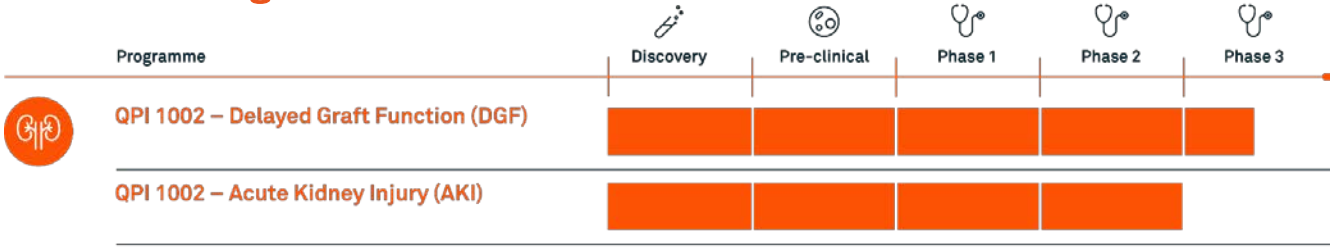
Pipeline

Building a proprietary portfolio, two projects advanced into preclinical development

Our Programs



Out-Licensed Programs



Quark

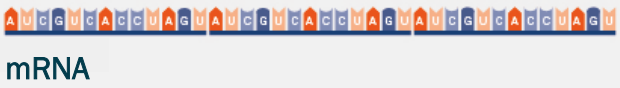
© Silence Therapeutics 2018

GalNAc conjugated siRNA technology

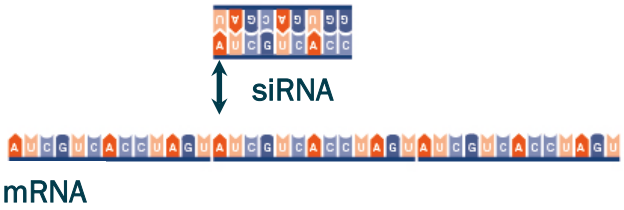
© Silence Therapeutics 2018

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

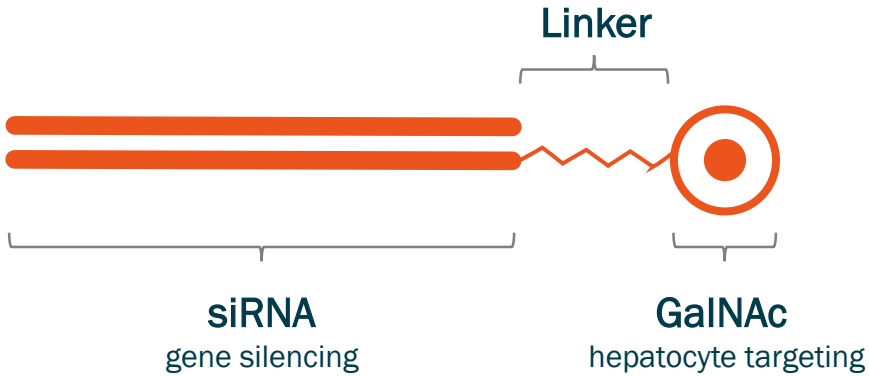
> A Nobel prize-winning discovery

> 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

© Silence Therapeutics 2018

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**

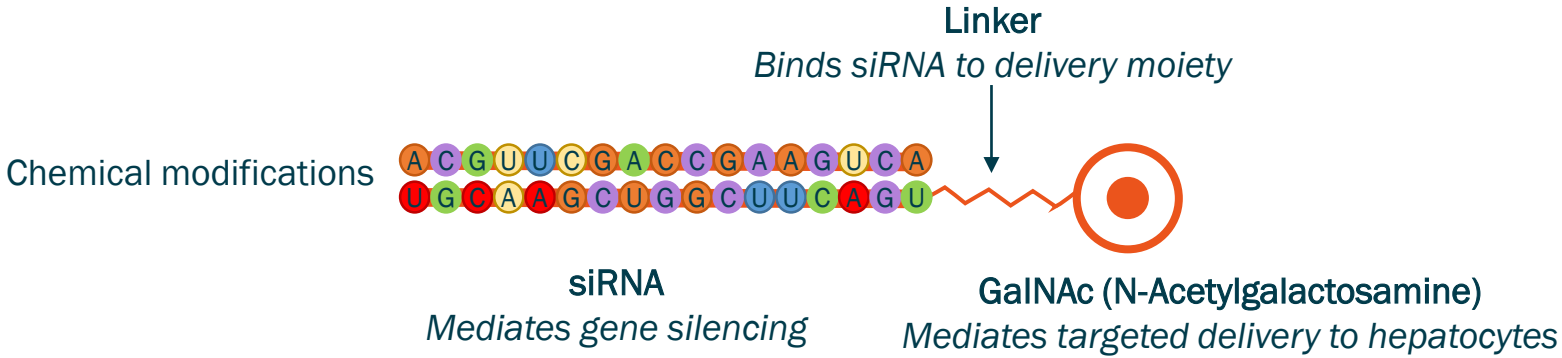
> Established **clinically validated technology**

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

© Silence Therapeutics 2018

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

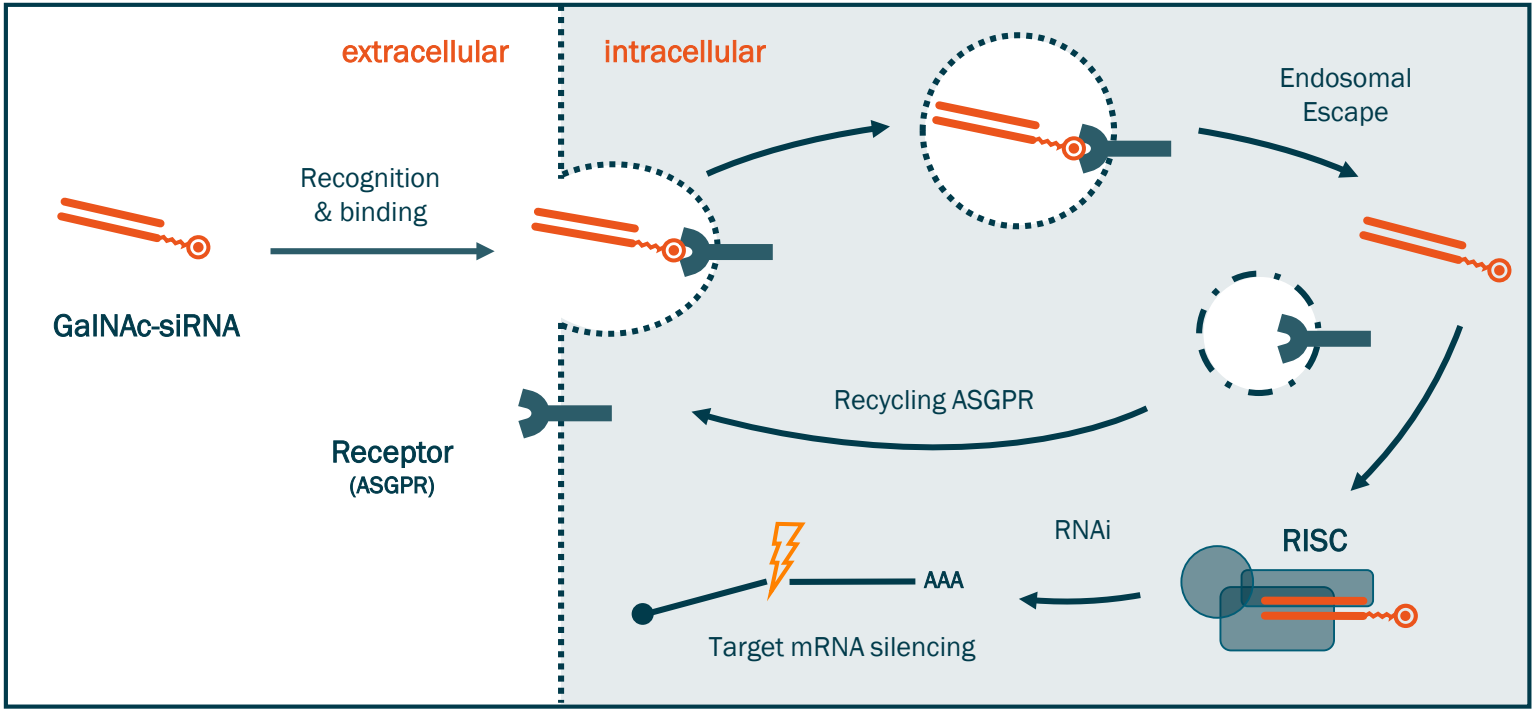
> We have a robust position for our foundational chemical modification technology

> We patent our linker chemistries

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

© Silence Therapeutics 2018

Gene silencing with GalNAc-siRNAs in hepatocytes



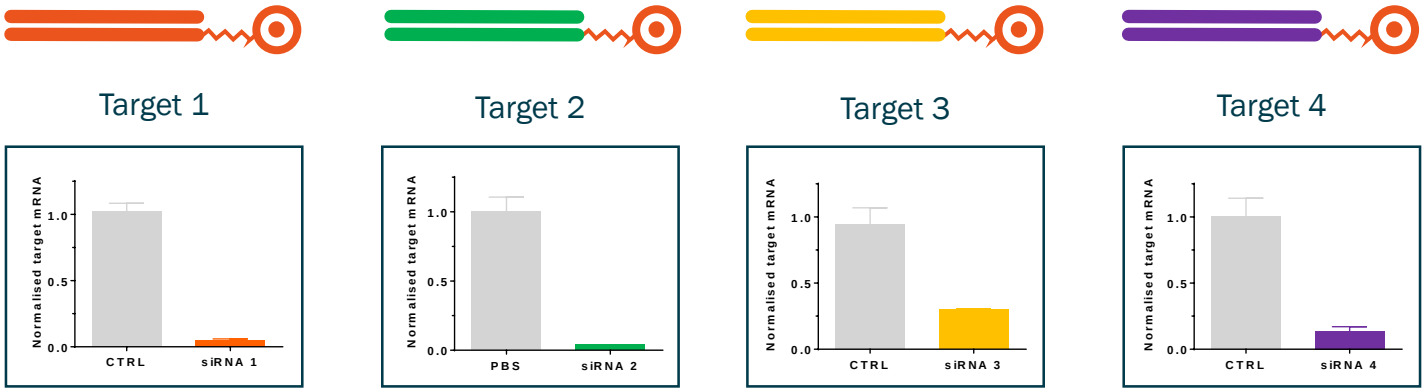
> Intracellular delivery mediated through receptor endocytosis

© Silence Therapeutics 2018

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



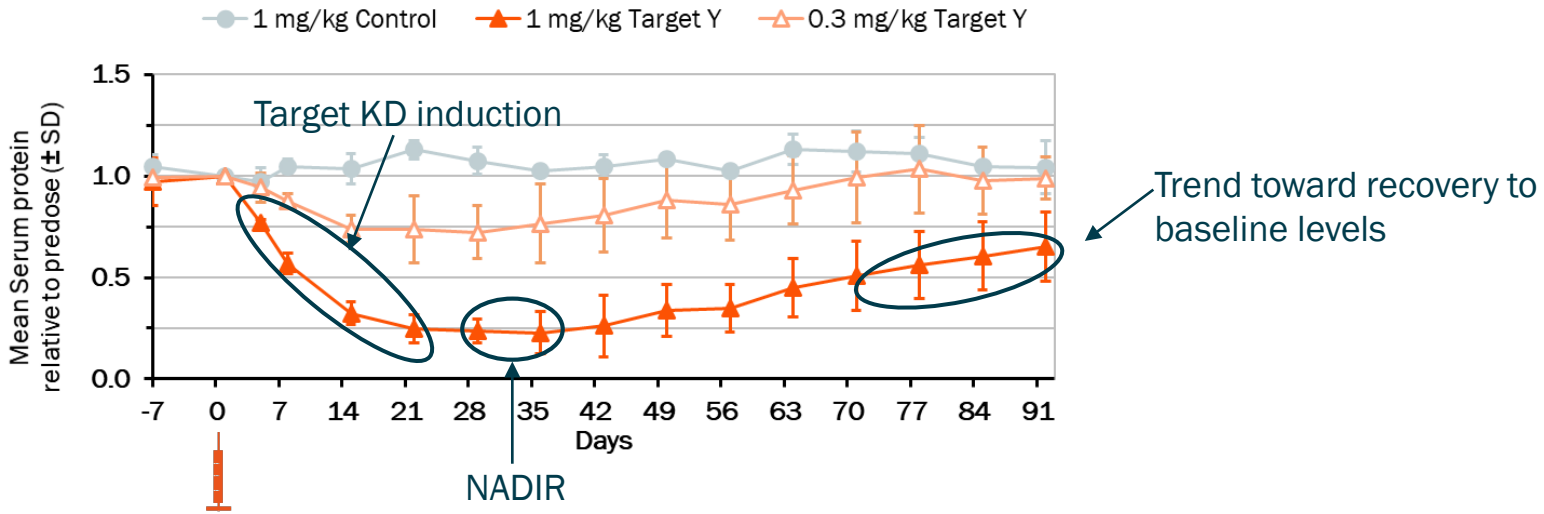
We are able to reproducibly silence disease-causing genes using our platform technology

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

© Silence Therapeutics 2018

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



© Silence Therapeutics 2018

SLN124 for the treatment of iron overload disorders

© Silence Therapeutics 2018

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

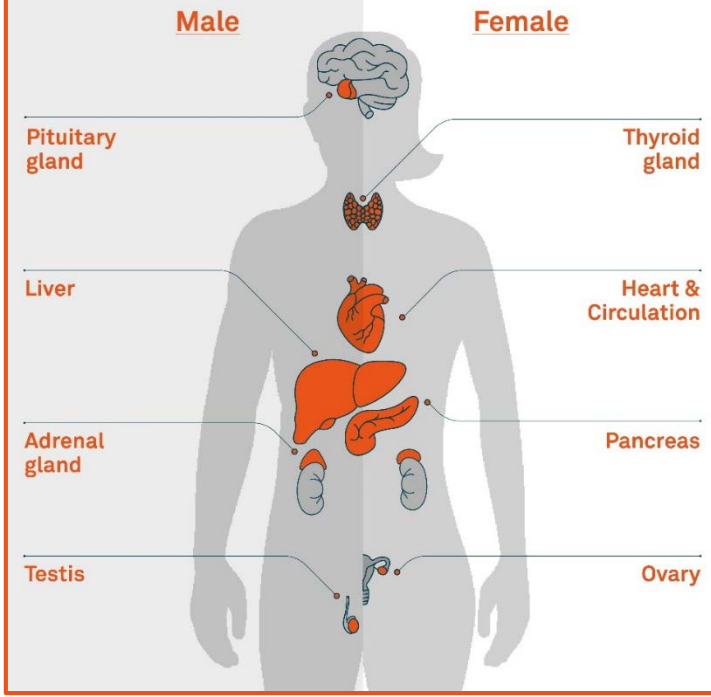
CURRENT STAGE

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

© Silence Therapeutics 2018

Iron Overload Disorders

Affected organs by iron overload



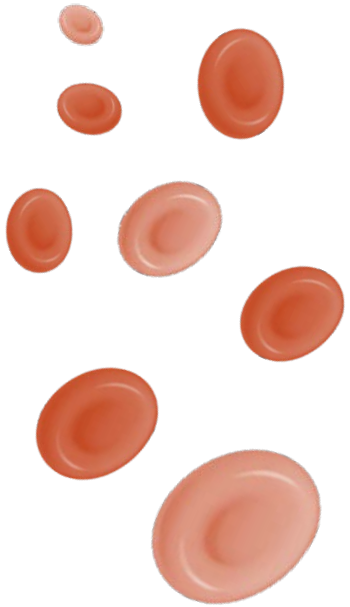
Diseases with iron overload

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

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

© Silence Therapeutics 2018

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

© Silence Therapeutics 2018

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)

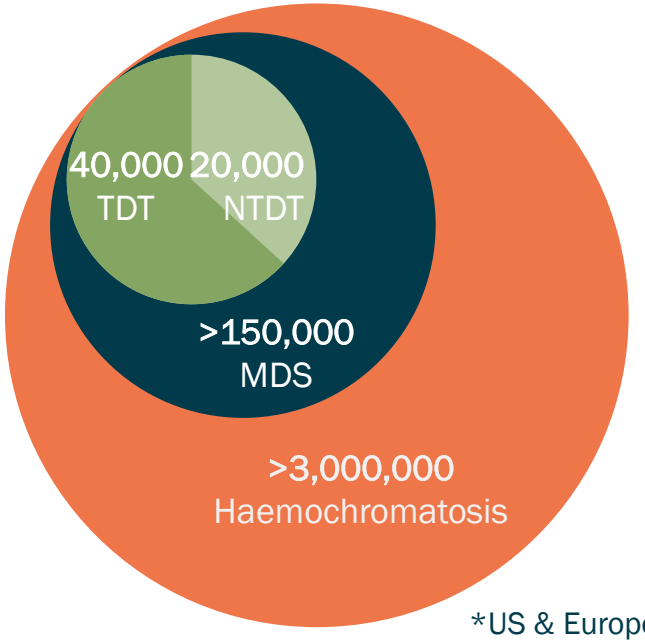
> Monotherapy to delay onset of severe symptoms

> Reduce dietary iron overload & subsequent organ damage

Other iron overload disorders

Myelodysplastic Syndrome (MDS)

Haemochromatosis



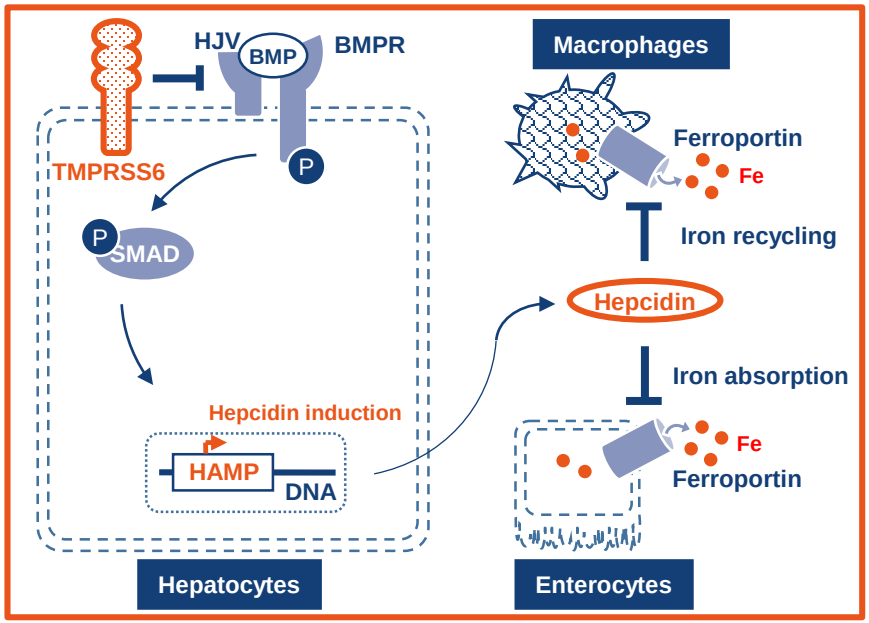
*US & Europe

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

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

© Silence Therapeutics 2018

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

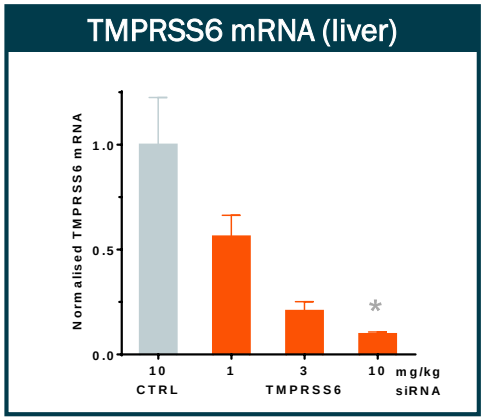
Silencing TMPRSS6

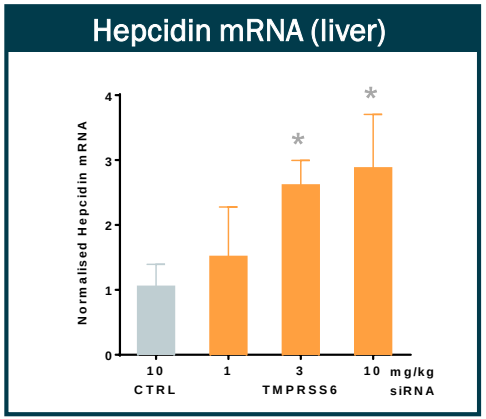
1. Increases Hepcidin levels
2. Reduces iron levels
3. Improves erythropoiesis
4. Reduces anaemia & iron overload

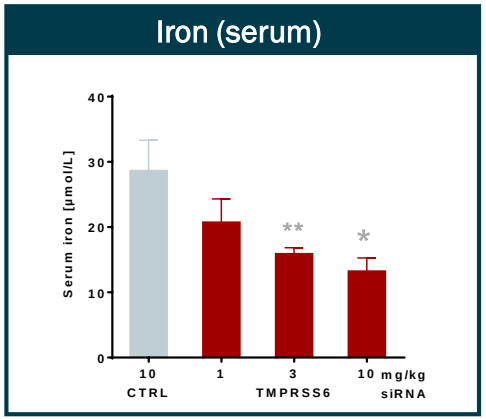
© Silence Therapeutics 2018

Silencing TMPRSS6 lowers serum iron levels in mice









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

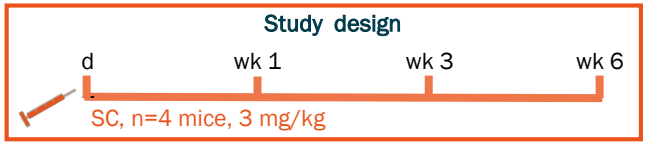
> Single subcutaneous administration reduces TMPRSS6 expression

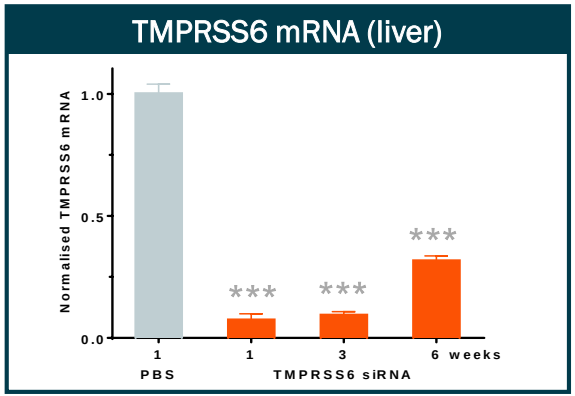
> Induction of Hepcidin causes reduction of blood iron levels

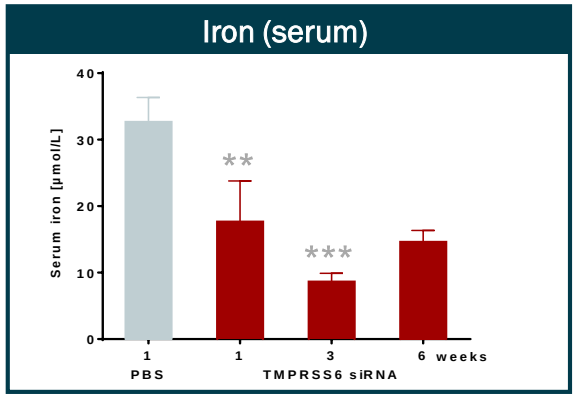
> **Proof of mechanism demonstrated**

© Silence Therapeutics 2018

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)

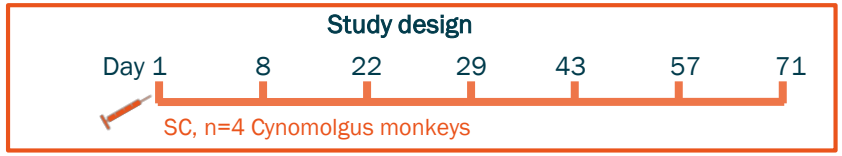
> Long-lasting functional mRNA KD in liver

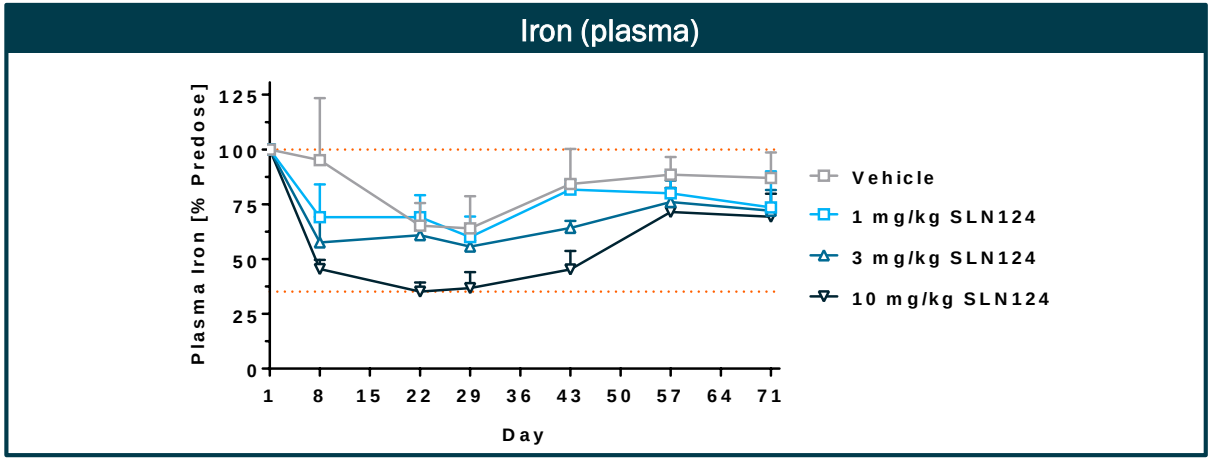
> Reduction of serum iron levels for at least 6 weeks

> Well tolerated with long duration of action in mice

© Silence Therapeutics 2018

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

© Silence Therapeutics 2018

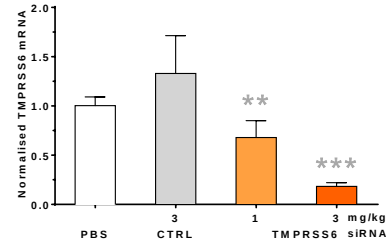
Therapeutic activity of SLN124 in a disease model for hereditary haemochromatosis ($HFE^{-/-}$ mice) - 1/2

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

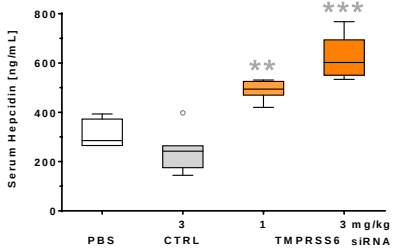
Study design



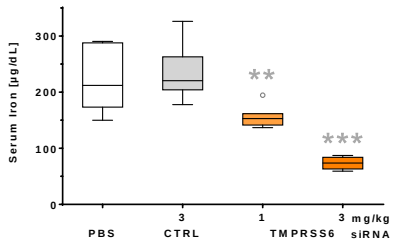
TMPRSS6 mRNA (liver)



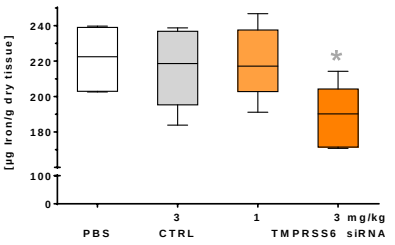
Hepcidin (serum)



Iron (serum)



Iron (kidney)



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

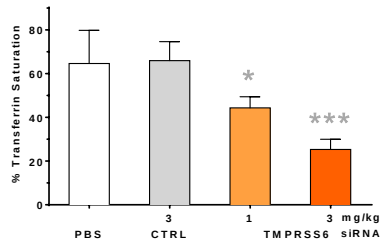
- Dose-dependent and robust silencing of TMPRSS6 mRNA in the liver
- Increase in serum hepcidin levels
- Reduction of serum and kidney iron levels to physiological values

© Silence Therapeutics 2018

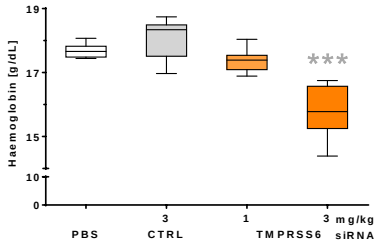
Therapeutic activity of SLN124 in a disease model for hereditary haemochromatosis ($HFE^{-/-}$ mice) - 2/2

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

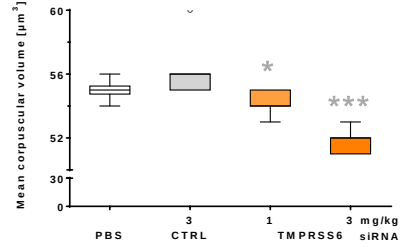
Transferrin Saturation



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

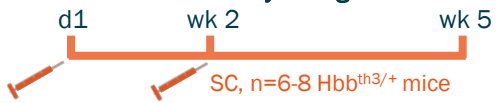
© Silence Therapeutics 2018

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

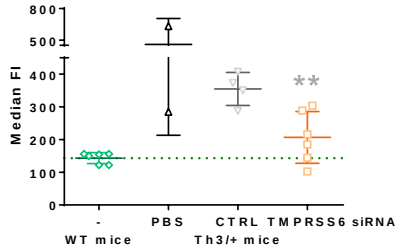
Collaboration with
Prof. J. Vadolas & Dr. Grigoriadis
Monash Medical Centre/Melbourne, Australia

HUDSON INSTITUTE OF MEDICAL RESEARCH

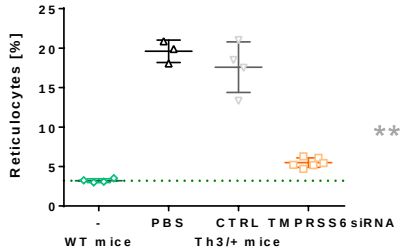
Study design



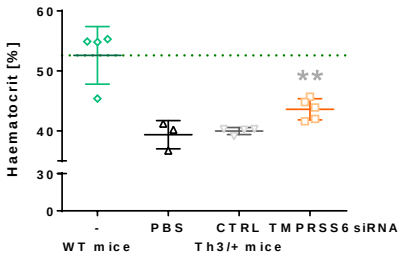
Reactive oxygen species (ROS)



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

© Silence Therapeutics 2018

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)

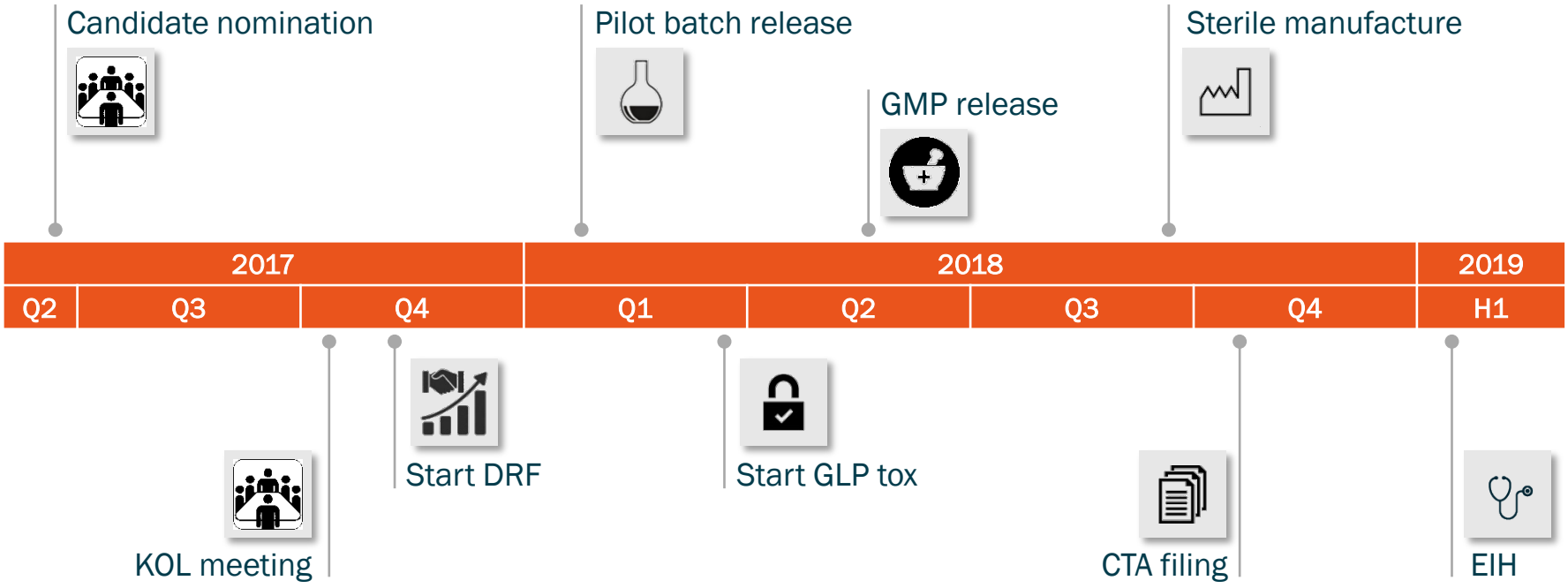
Launch would be expected by 2024/25 via an Orphan designation

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

We are seeking **commercialisation partnerships**

© Silence Therapeutics 2018

SLN124 development timelines – key milestones



On track for CTA filing 15 months after candidate selection

© Silence Therapeutics 2018

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

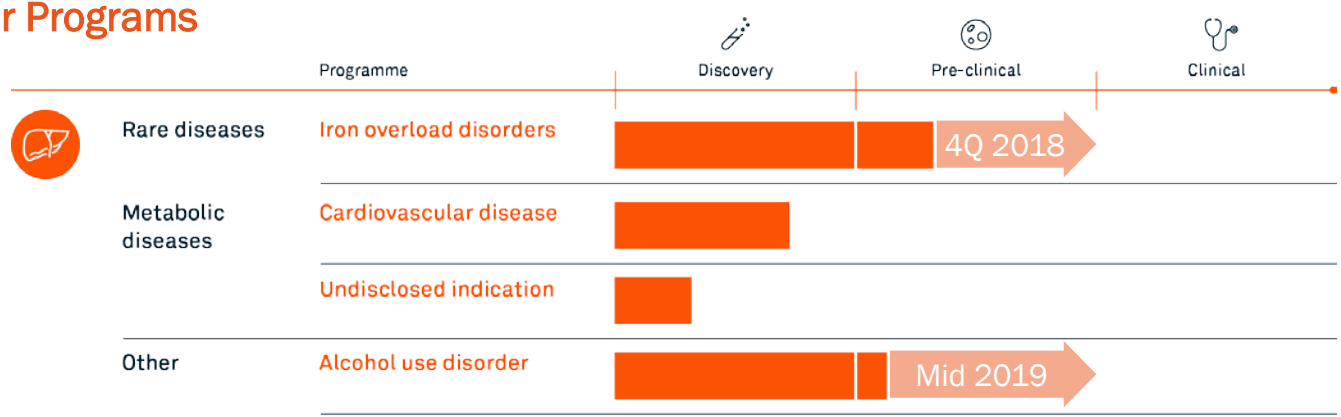
SLN124 represents a highly valuable therapeutic candidate for patients with iron overload disorders, such as β-Thalassemia

© Silence Therapeutics 2018

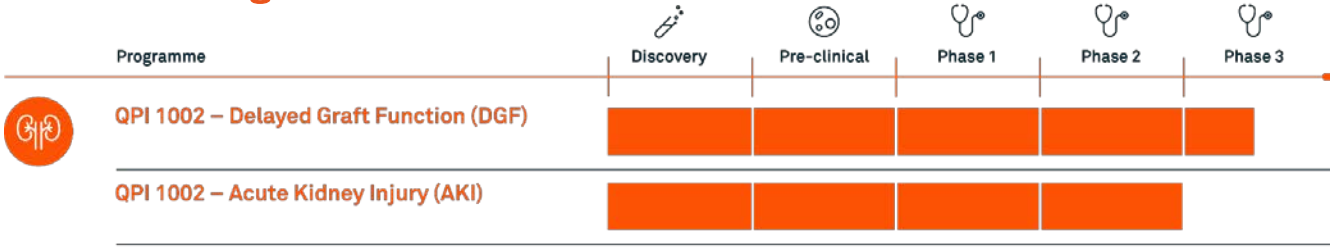
Pipeline

Building a proprietary portfolio, two projects advanced into preclinical development

Our Programs



Out-Licensed Programs



Quark

© Silence Therapeutics 2018

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

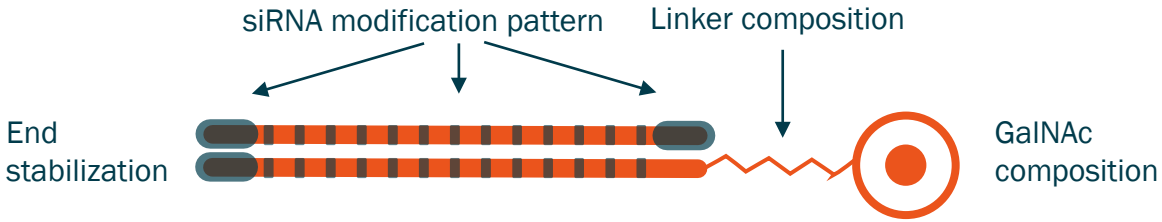
- Build a proprietary therapeutic portfolio by applying validated siRNA technologies
- Partner programs in a strategic manner
- Add new programs in a risk-diversified manner



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

© Silence Therapeutics 2018

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

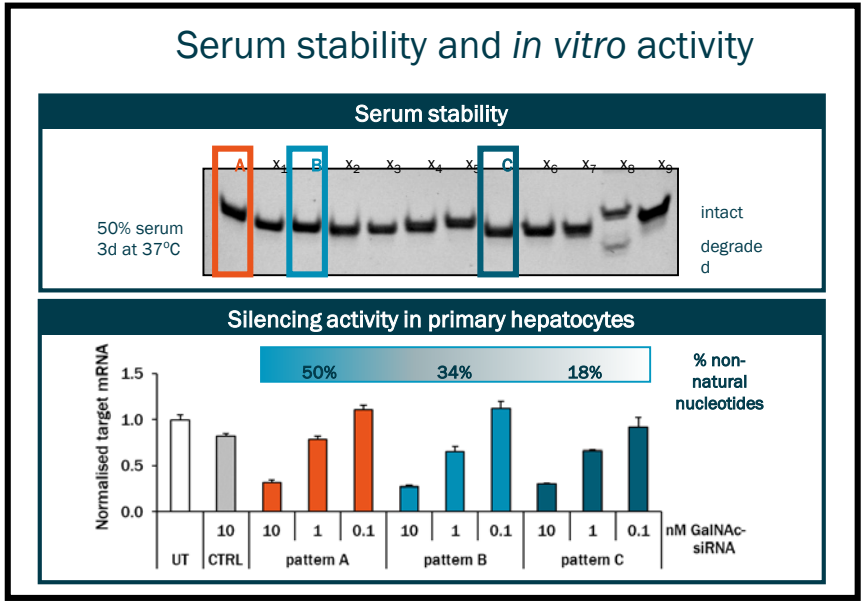
> End stabilisation: increased circulation half-life, increased activity and duration of action

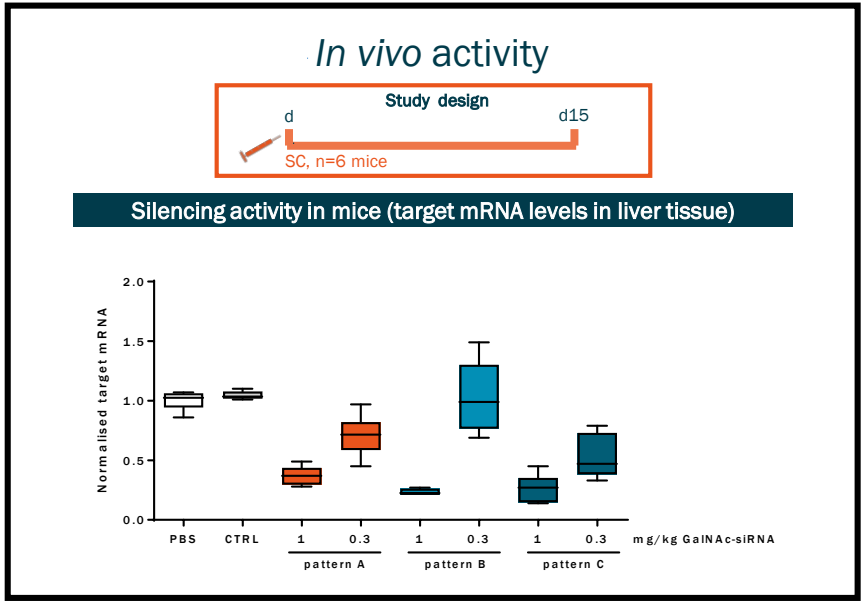
> Linker: simplified and flexible synthesis, increased activity, and option to control circulation and intracellular half-life

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

© Silence Therapeutics 2018

Example A: reducing number non-natural modifications



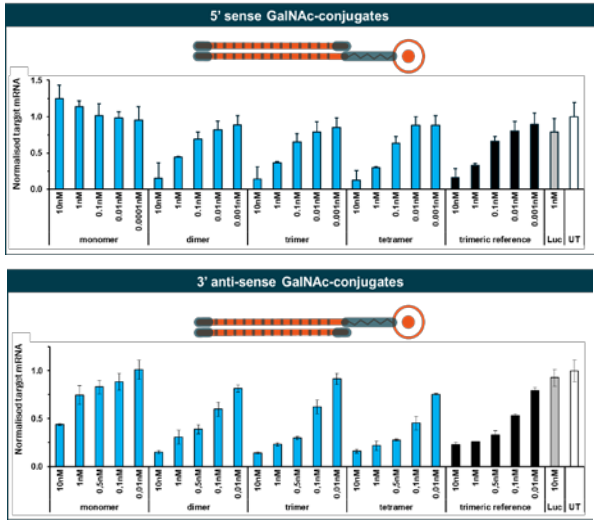


> Non-natural siRNA modifications can be dramatically reduced with retained nuclease resistance, and activity in primary hepatocytes, compared to molecules with 50% non-natural modifications

> 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)

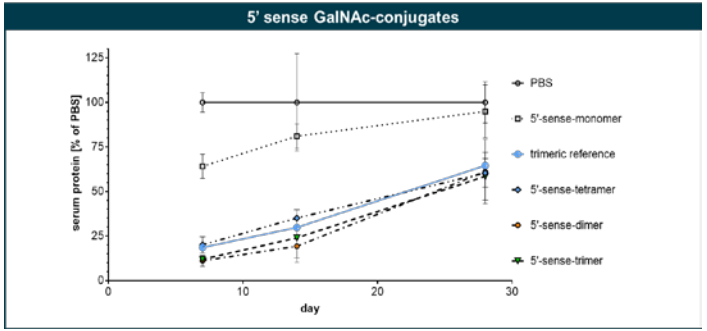
Example B: optimising number/location of GalNAc units

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

© Silence Therapeutics 2017

Acknowledgements

Silence Drug Development Team
Manuela Aleku, Christian Frauendorf & Jens-Uwe Künstler

Silence Preclinical Drug Discovery Team
Ute Schaeper, Steffen Schubert & Ulrich Zügel

Silence Technology Innovation Team
Marie W. Lindholm & Dmitry Samarsky

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

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

© Silence Therapeutics 2018