SILENCE THERAPEUTICS

Capital Markets Day, 14 November 2017

Welcome

Dr Annalisa Jenkins, MBBS FRCP
Chair of the Board

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 2017

About me

My background

DIMENSION™ THERAPEUTICS	MERCK SERONO	Bristol-Myers Squibb	ROYAL NAVY
Chief Executive Officer	Head of Global R&D	SVP, Head Global Medical Affairs	Surgeon lieutenant commander

Why did I join Silence Therapeutics?

- Excited about the technology
- An opportunity to support a great team
- A passion for making a difference for patients living with serious diseases

© Silence Therapeutics 2017

“The year of RNAi” – The field

- Many years of academic and industry scientific research to date unlocking new opportunities
- Effective delivery now realised in the clinic
- First positive siRNA Phase 3 readout (Patisiran), validating the field
- Several other late-stage clinical candidates making progress in clinical development
- Renewed big pharma interest in leveraging this platform as part of a broader investment in genetic medicines

© Silence Therapeutics 2017

“The year of RNAi” – Silence

Key milestones in 2017

- **Established a competitive GalNAc-siRNA platform technology and advanced our pipeline toward the clinic** (first IND/CTA filing planned in Q4 2018)
- **Licensee** Quark Pharmaceuticals reported **positive Phase 2 results** in Acute Kidney Injury and continued Phase 3 progress in Delayed Graft Function
- We continue to innovate in our labs and have strengthened our patent estate with **European and US patent grants in 2017** and filed multiple patent applications covering additional aspects of our GalNAc-siRNA technology
- In the last 18 months, we have acquired significant industry-leading talent:
  - Chief Financial Officer (David Ellam)
  - Chief Operating Officer (Dr Torsten Hoffmann)
  - Chief Scientific Officer (Dr Dmitry Samarsky)
  - Head of Preclinical Drug Discovery (Dr Ulrich Zuegel)
  - Head of Intellectual Property (Alison Gallafent)
  - Head of Business Development (Michael Mulqueen)
  - Head of Technology Innovation (Dr Marie W Lindholm)

© Silence Therapeutics 2017

SILENCE THERAPEUTICS

Capital Markets Day, 14 November 2017

Introduction and company strategy

Ali Mortazavi
Chief Executive Officer

Our key assets

- Powerful, reproducible and modular platform technology
- Therapeutic pipeline
- Validated foundational Intellectual Property in RNAi, which has been licensed (to Quark Pharmaceuticals) and we believe has potential for future licences
- Business plan and strategy in place to maximise the value of our platform
- Top calibre people to execute our strategy
- Well capitalised to realise our vision

© Silence Therapeutics 2017

We are R&D focused…

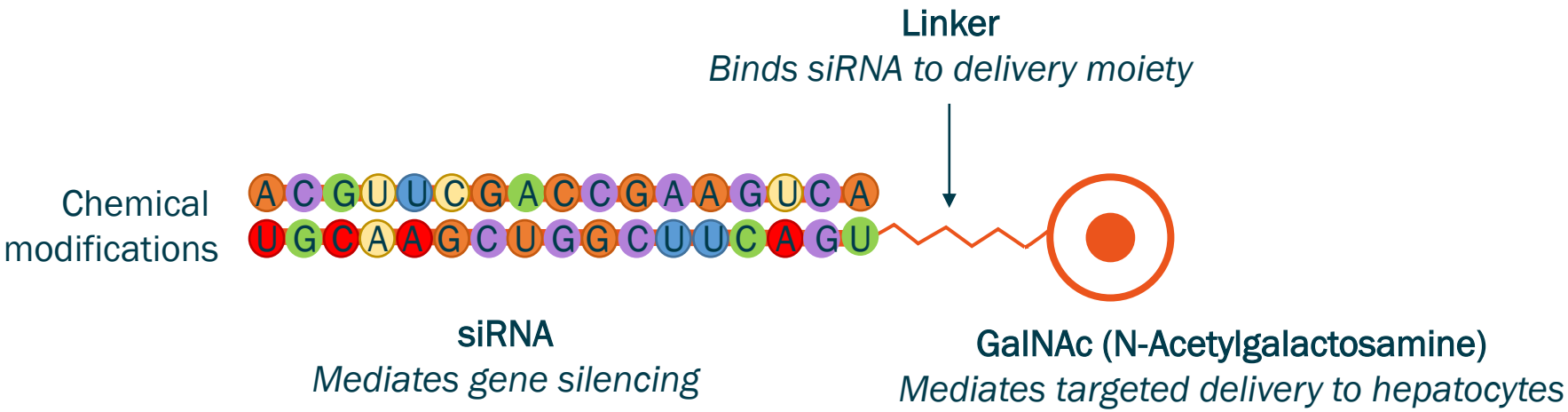


… with the management and support structures in place **to drive execution**

© Silence Therapeutics 2017

GalNAc-siRNA medicines

Schematic structure of our therapeutic molecules:



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

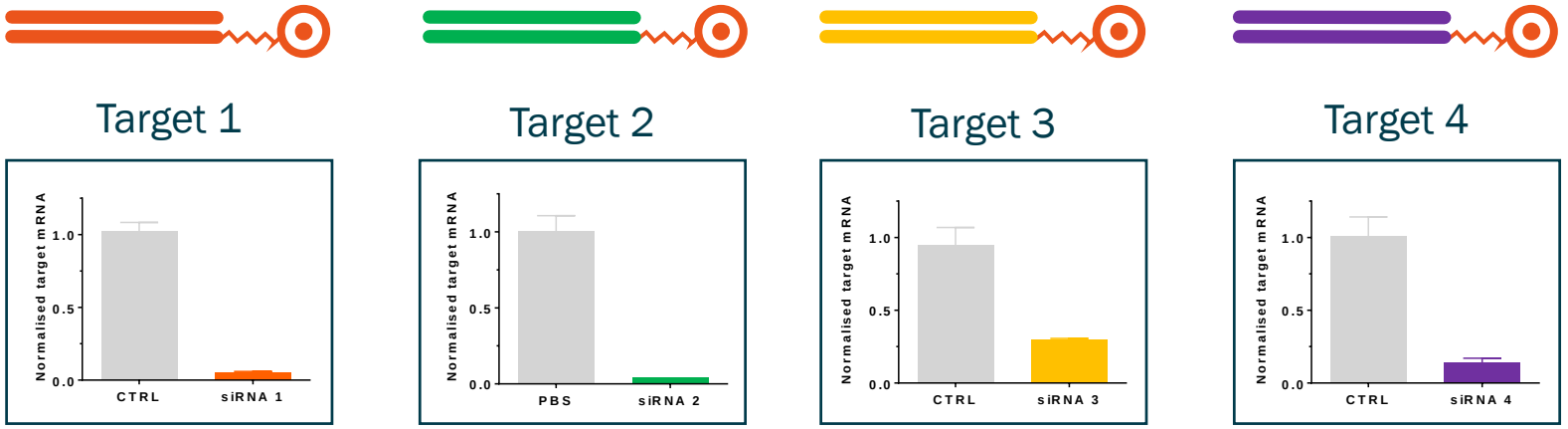
> GalNAc as a targeting ligand per se is free to use
> We have a robust position for our foundational chemical modification technology
> We patent our linker chemistries
> We patent our potent and highly specific siRNA constructs and lead sequences

© Silence Therapeutics 2017

Our core capability

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



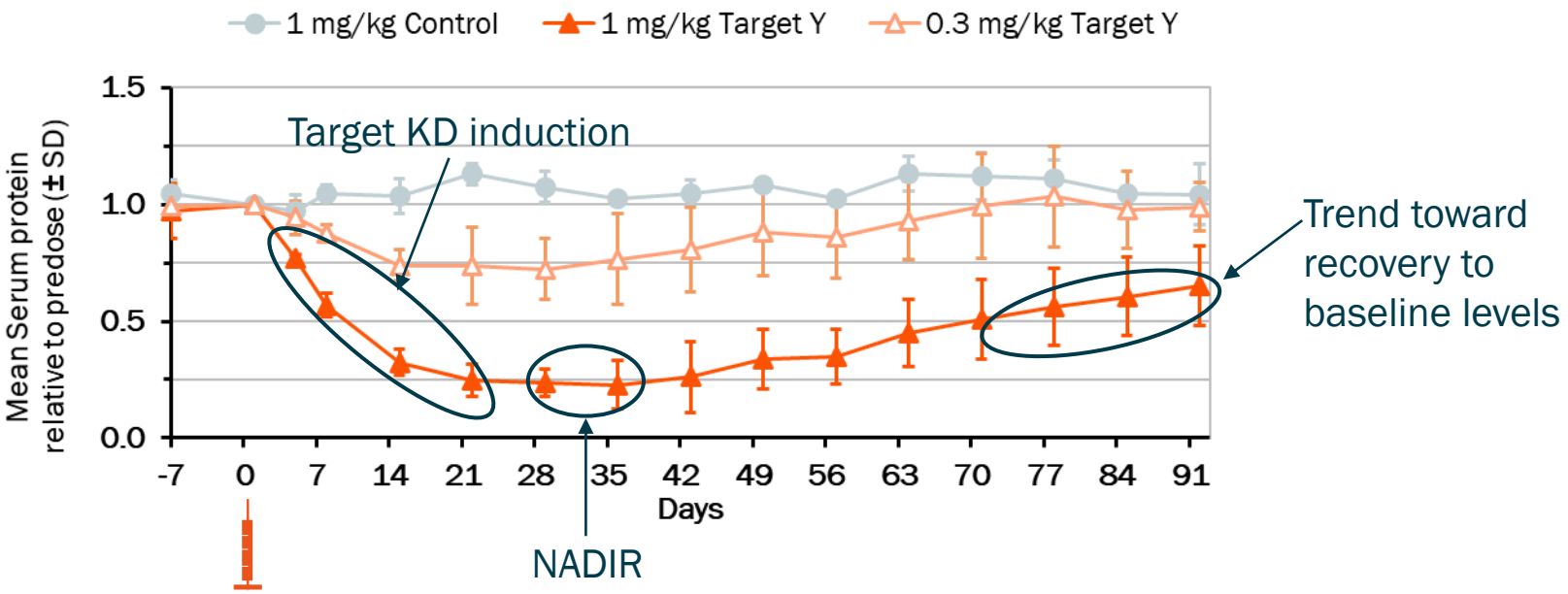
We are able to reproducibly silence disease-causing genes using our platform technology

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

© Silence Therapeutics 2017

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 2017

Intellectual property – Pioneers in siRNA chemical modification technology

We have 13 granted patents and 5 patent applications encompassing our foundational chemical modification technology in US and Europe



Modified siRNA (example)

> **IP validation:** Silence granted a licence in 2005 to Quark Pharmaceuticals, who currently have two late-stage candidates in clinical development using our chemical modification technology

> **We believe third parties need licences under our portfolio and we have:**

- Disclosed some of the relevant **competitor products**
- Served a claim with the **UK High Court** (defendants: Alnylam Pharmaceuticals and The Medicines Company) to determine whether Silence's European patent protection is entitled to a **5-year extension** for the products named in the claim

© Silence Therapeutics 2017

Pipeline strategy

Key criteria

- Hepatocyte expression
- Validated role in disease
- Clinical feasibility
- Commercially viable

Target nomination

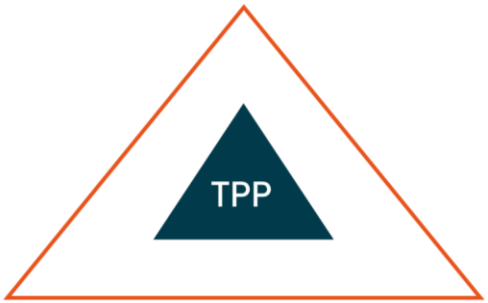
> In-depth analysis and KOL survey

> Defined Target Product Profile (TPP)



Pipeline strategy

Business Development team



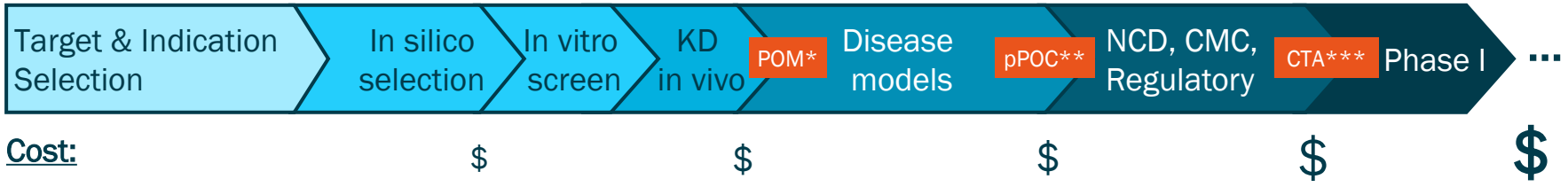
Target Selection team

R&D team

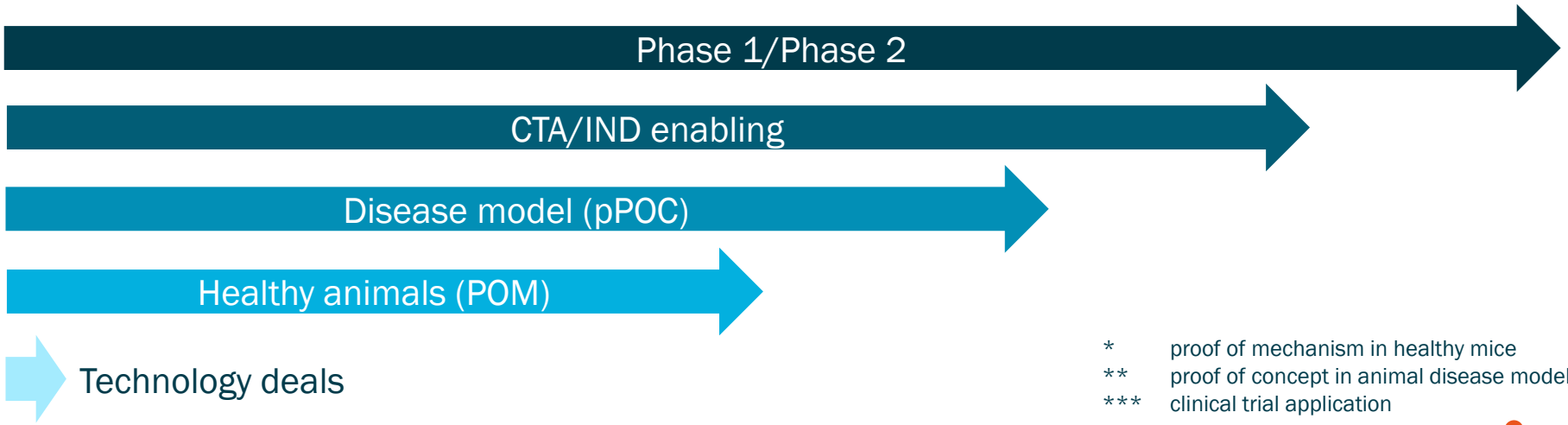
© Silence Therapeutics 2017

Platform strategy

~7,000 accessible gene targets… We have the technology and the team to discover and develop a wide range of therapeutics



We intend to strategically partner our programmes at different stages to fully unlock the value of our platform – Rapid path to value creation



* proof of mechanism in healthy mice
** proof of concept in animal disease model
*** clinical trial application

© Silence Therapeutics 2017

Summary

We have a powerful drug development platform with a tangible business strategy and the team to execute it

© Silence Therapeutics 2017

Today's agenda

> **Operational and platform technology overview**

Dr Torsten Hoffmann, Chief Operating Officer

> **Pipeline update: selected programmes in preclinical development**

Dr Ulrich Zuegel, Head of Preclinical Drug Discovery

> **Technology innovation**

Dr Dmitry Samarsky, Chief Scientific Officer

> **Panel discussion:**

"The power of genomics, big data and how to harness outcomes with tailored therapies such as RNAi"

© Silence Therapeutics 2017

SILENCE THERAPEUTICS

Capital Markets Day, 14 November 2017

Operational & Technology Overview

Torsten Hoffmann, PhD
Chief Operating Officer

Outline

1 Organisational evolution

2 R&D operational setup

3 GalNAc-siRNA platform technology

4 Accelerating our timelines

© Silence Therapeutics 2017

Organisational evolution

© Silence Therapeutics 2017

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 2017

2017 additions to our experienced team

Dr Annalisa Jenkins, MBBS FCRP **Non-Executive Chair** 10/2017		> Biopharma thought leader, 20 years of industry experience > President and CEO at Dimension Therapeutics since 2014 > Head of global R&D at Merck Serono 2011-14 > Several leadership roles at BMS 1997-2011 > Medical officer with the British Royal Navy
Dr Torsten Hoffmann **Chief Operating Officer** 06/2017		> Over 20 years of international R&D management experience > CSO & Managing Director at Proteros 2015-17 > CSO & Executive VP at Zealand Pharma 2013-15 > Several senior leadership roles at Roche 1999-2015 > Lead inventor of the anti-emetic medicine Netupitant, >25 INDs
Michael Mulqueen **Head of BD & Licensing** 09/2017		> Over 25 years of BD industry experience > VP BD Biotie Therapies 2011-15 > VP Operations & BD Synosia Therapeutics 2006-11 > Global Head of Alliance Management and several senior leadership roles at Roche 1992-2005
Alison Gallafent **Head of Intellectual Property** 01/2017		> European and UK patent attorney, private and industry sector > Senior Associate at Olswang LLP 2016-17 > Director of IP at PLIVA 2006-09 > IP consultant to multi-national pharma 1997-2006, 2009-16 > In-house Counsel at Glaxo Wellcome and Merck 1994-97
Dr Marie W Lindholm **Head of Technology Innovation** 12/2017		> Over 15 years of international R&D management experience > Expert Scientist, Discovery Technology at Roche 2014-17 > Several senior leadership roles at Santaris 2007-14 > Associate/Assistant Professor in Cardiovascular Medicine at Lund University, Sweden 1999-2006

© Silence Therapeutics 2017

R&D operational setup

© Silence Therapeutics 2017

Silence Therapeutics R&D facilities in Berlin

R&D in Berlin



- Lean and agile organisation
- 26 FTEs in R&D
- 1,100 sqm laboratory & office space
- State-of-the-art laboratories for siRNA synthesis, cellular & molecular pharmacology and innovation





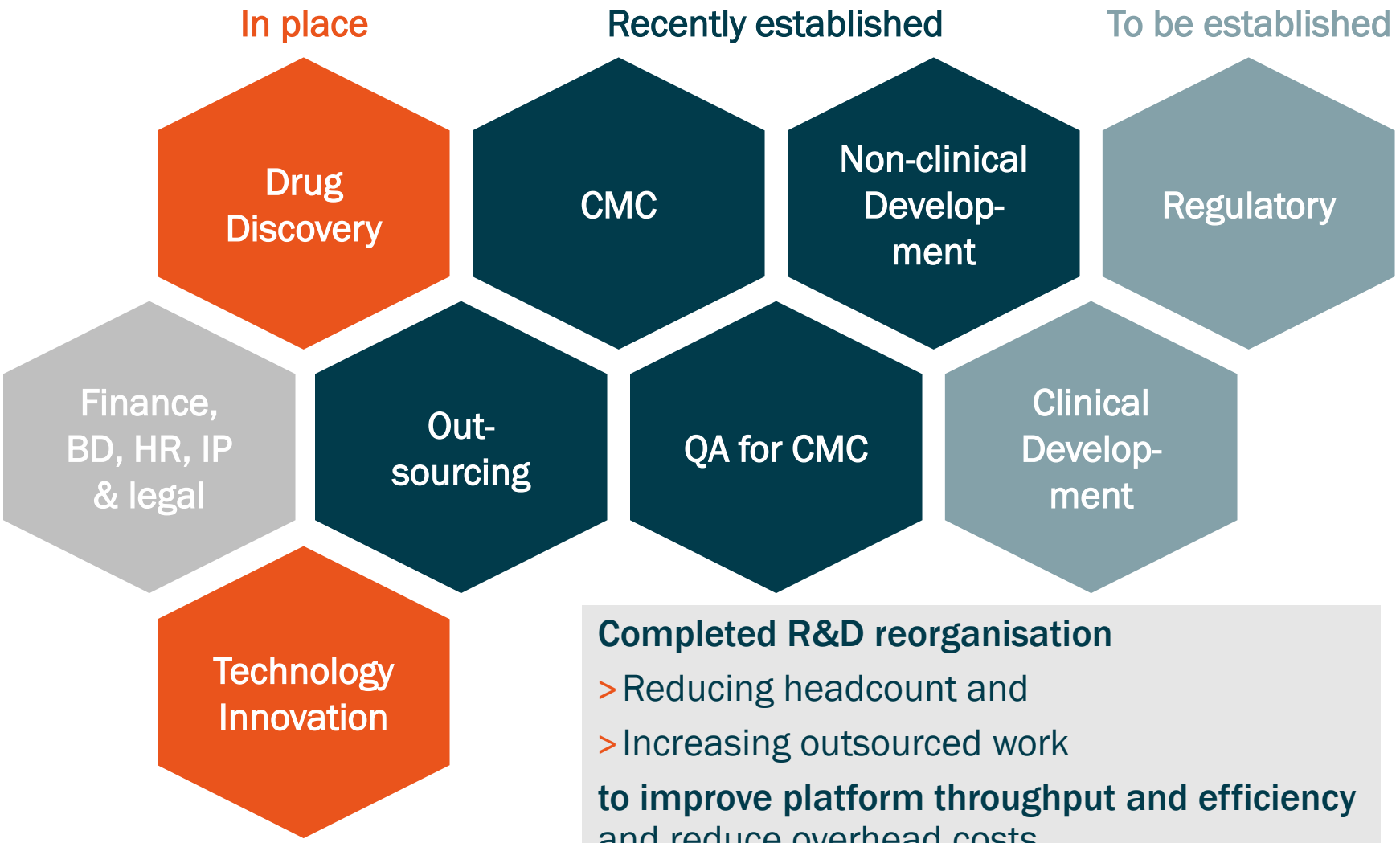






© Silence Therapeutics 2017

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 2017

R&D with focus on portfolio and innovation

Technology Innovation

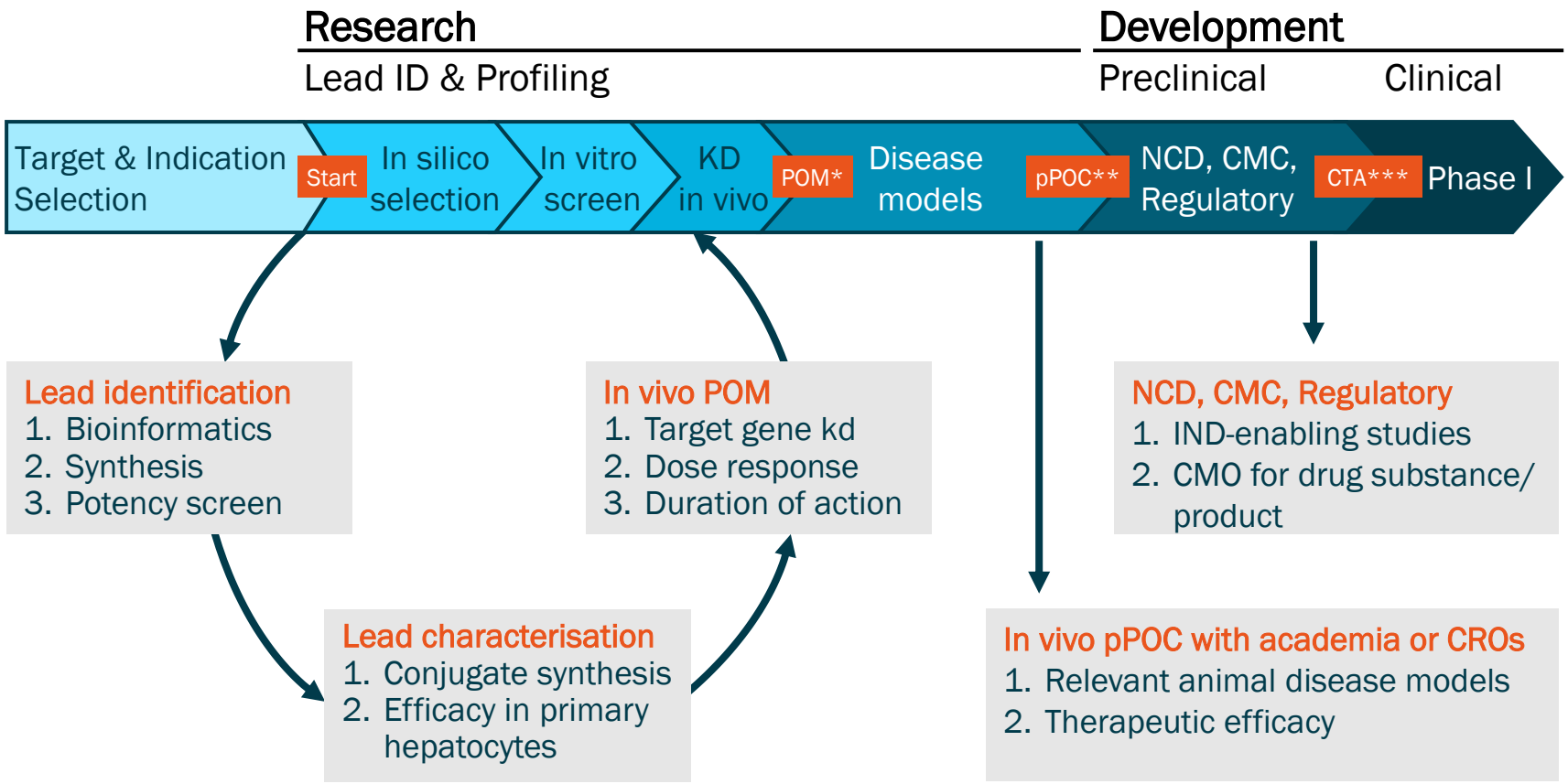
- Improve performance of our GalNAc-siRNA molecules
- Strengthen and broaden IP portfolio
- Expand RNAi horizons beyond hepatocytes
- Apply to therapeutic portfolio upon validation

Drug Discovery & Development

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

© Silence Therapeutics 2017

Outsourcing routine work and disease models



Liberate and focus internal lab resources on IP generation and pharmacology

* proof of mechanism in healthy mice
** proof of concept in disease animal model
*** clinical trial application

© Silence Therapeutics 2017

GalNAc-siRNA platform technology



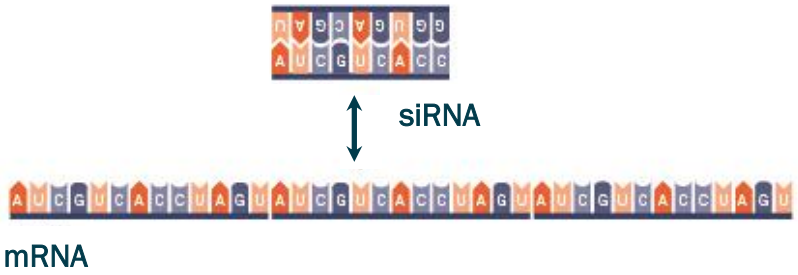
© Silence Therapeutics 2017

How do siRNA medicines work?

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

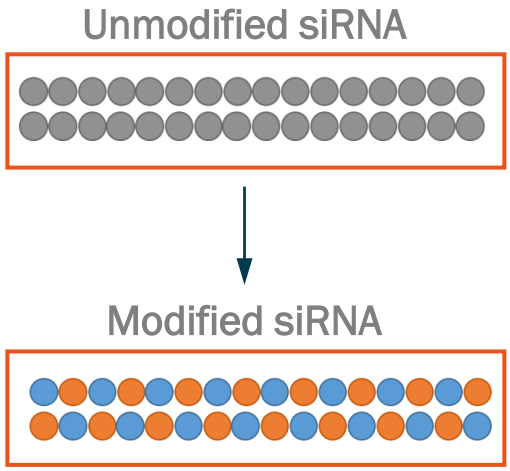
> A natural pathway that can be harnessed to inhibit the expression of disease-causing genes without altering DNA

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

© Silence Therapeutics 2017

Field leading IP position in modified siRNA - importance of siRNA chemical modification

- Chemical modifications of siRNAs are required to
  - Prevent degradation
  - Increase stability and potency
  - Reduce immune stimulation
- Silence has been pioneering advanced chemical modification technology since 2003
- Our proprietary siRNA modification patterns
  - Out-licensed to Quark Pharmaceuticals
  - Excellent clinical safety profile



Example of original siRNA modification pattern (patent filed in 2003)

Silence patent portfolio protecting our modification technology

Europäisches Patentamt
European Patent Office
Office européen des brevets

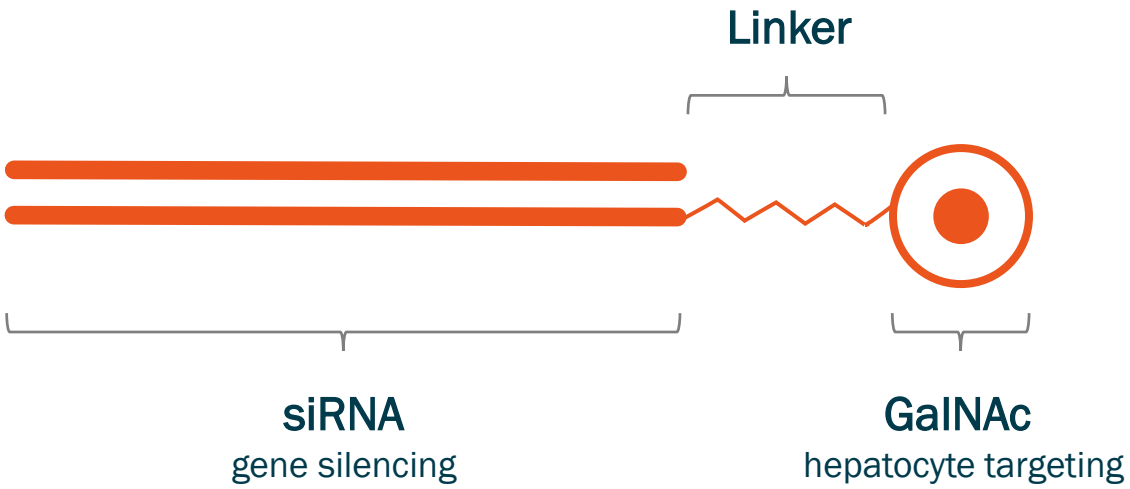
3 granted patents
4 patent applications

10 granted patents
1 patent application

- Similar claims granted and pending in other major countries (including: AU, BR, CA, CN, IL, IN, JP, KR, MX, ZA)

© Silence Therapeutics 2017

GalNAc-siRNA molecules

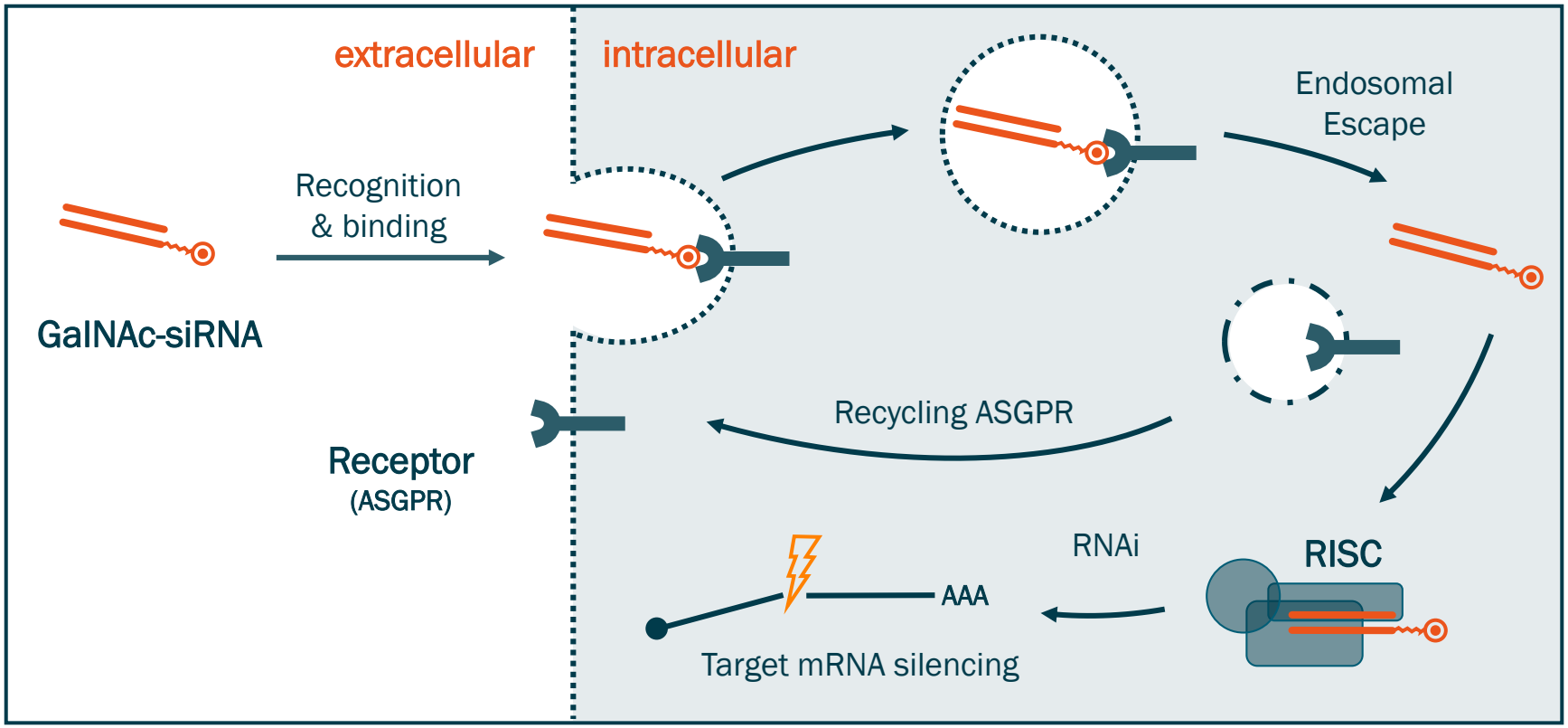


Advantages of GalNAc-siRNA technology

> 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 2017

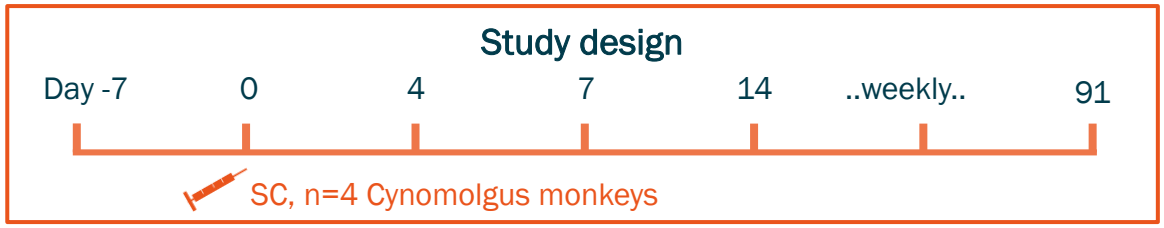
Gene silencing with GalNAc-siRNAs in hepatocytes



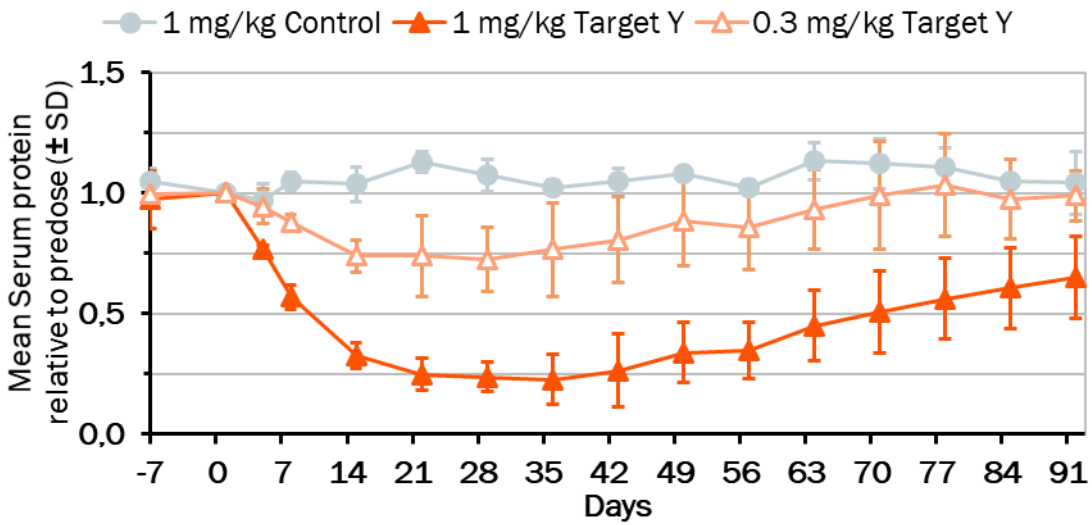
> Intracellular delivery mediated through receptor endocytosis

© Silence Therapeutics 2017

Competitive GalNAc-siRNA performance observed in higher species



Target protein (serum)



> No altered pro-inflammatory cytokines

> No skin reactions

> No behavioural changes

Well tolerated in higher species

> Durable target inhibition achieved safely. Infrequent dosing supported

© Silence Therapeutics 2017

Continued expansion of our IP portfolio

In addition to our patent estate protecting our fundamental chemical modification technology, we strengthened our GalNAc-siRNA IP portfolio by filing the following **patent applications in 2017**:



> Several lead sequences

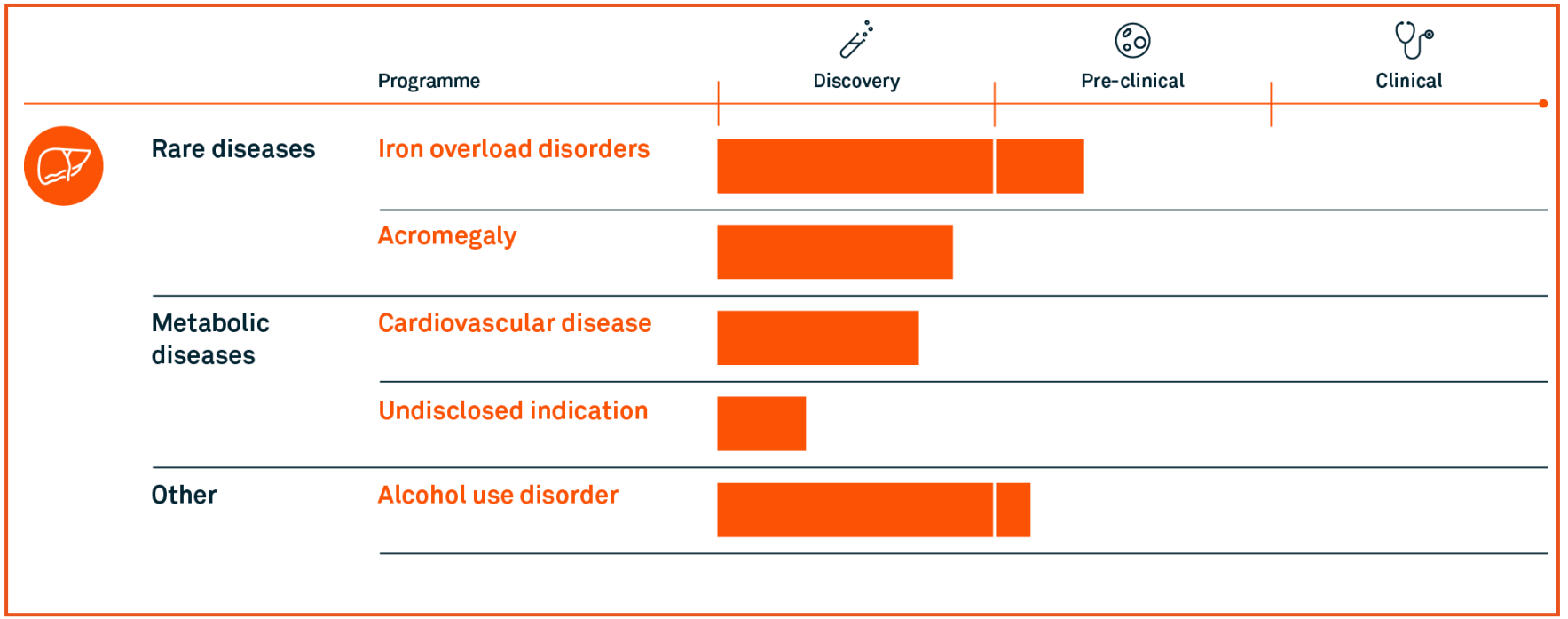
> 2 linker chemistries

> 6 RNAi constructs

> 1 modification rule

© Silence Therapeutics 2017

Current pipeline



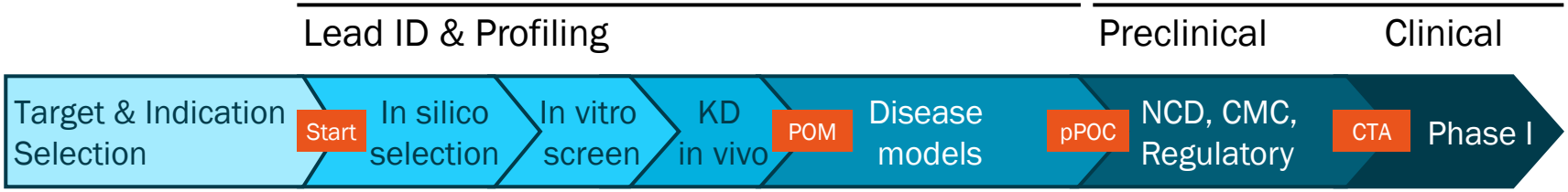
> Building a proprietary portfolio, two projects advanced into preclinical development

© Silence Therapeutics 2017

Accelerating our timelines

© Silence Therapeutics 2017

From target selection to clinical trial initiation



Ways to further accelerate our timelines

> **Bioinformatics:** earlier & faster access to state-of-the-art data bases for target selection and prediction of off-target effects

> **Spheroid cultures** to rapidly select sequences for in vivo pharmacodynamic (PD) studies

> **Human Organ-on-a-chip:** microfluidic in vitro systems to assess therapeutic index, based on efficacy and safety

© Silence Therapeutics 2017

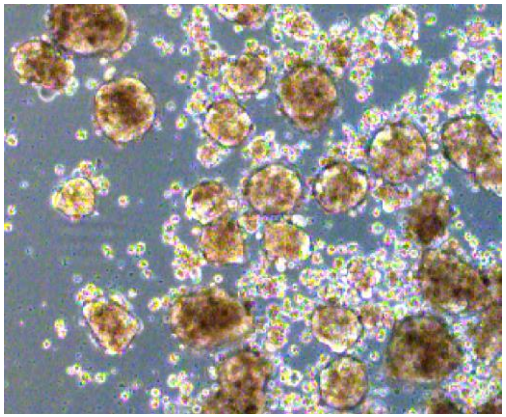
Bridging in vitro to in vivo using human primary hepatocyte spheroid cultures

3D vs 2D hepatocyte culture

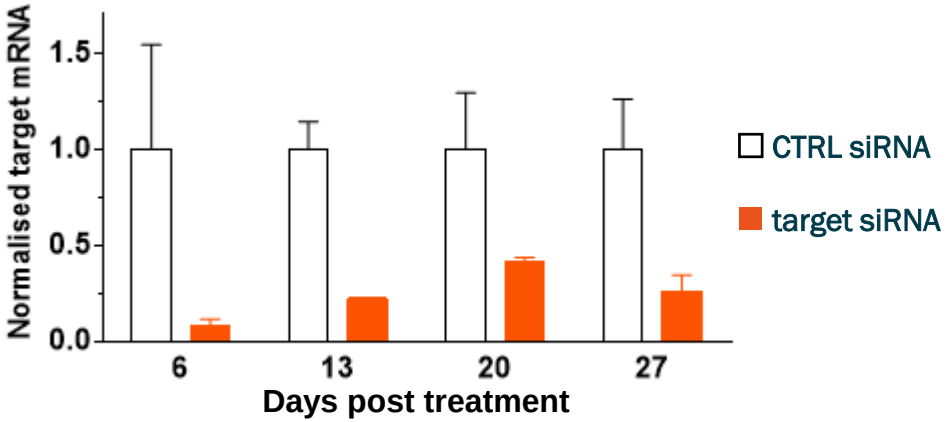
> Liver-specific physiology & gene expression patterns
> Long living organoid structures
> Extended functional ASGPR expression (up to 12 d vs. 4 h)
> Repeated treatments possible



Spheroid culture



Target mRNA in spheroids

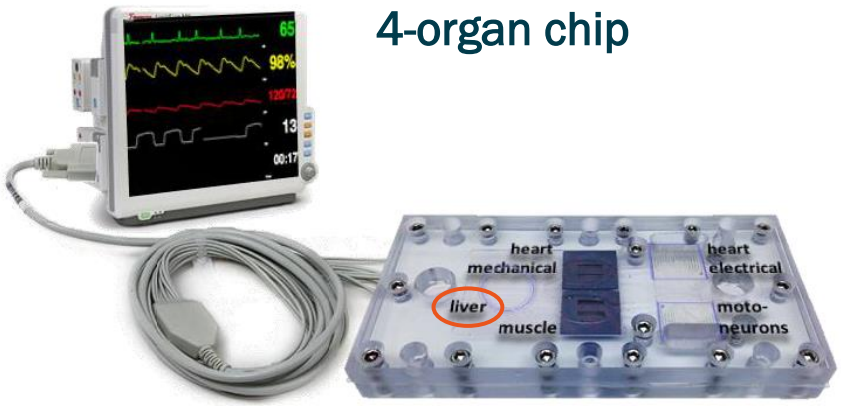


> Efficient target mRNA silencing in 3D hepatocyte spheroids for >3 weeks in culture
> Accelerates sequence selection for subsequent in vivo PD studies

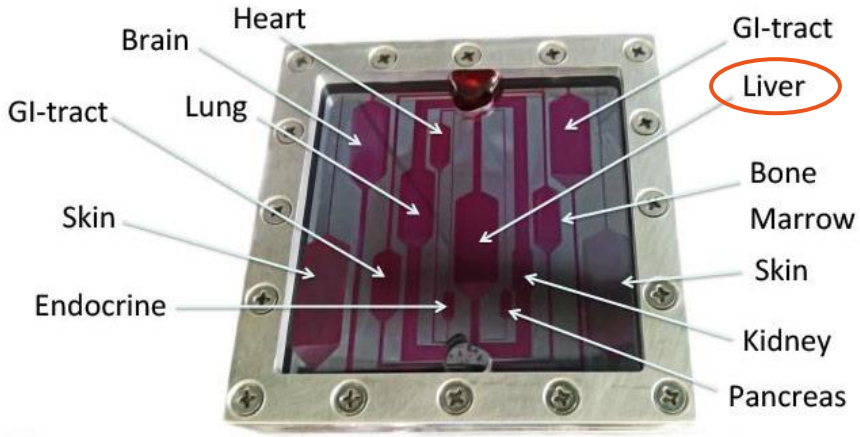
© Silence Therapeutics 2017

Strategic collaboration with Hesperos - Human “Organ-on-a-chip“

4-organ chip



10-organ chip



- > Single microfluidic system in vitro
- > Assessment of therapeutic index in 4-organ chip system
  - Functional mRNA silencing for efficacy
  - On-target and off-target side effect profile
- > Extendable to 10-organ chip system

© Silence Therapeutics 2017

Summary and outlook



- Transitioned from a **technology oriented** company to a focussed GaINAc-siRNA conjugation **therapeutics** company
- Restructured R&D and **outsourced all routine work** to trusted partners
- Consolidated a **Drug Discovery unit** and built a prioritised and competitive **portfolio of therapeutic programmes** with proprietary structures
- Introduced ways to further **accelerate our timelines**
- Established **CMC, QA and NCD functions**
- Created a **Technology Innovation department** to deliver new IP to portfolio
- **Experienced management team** in place to execute strategy

Outlook

- Building clinical **development and regulatory capabilities** to progress portfolio
- Further **expanding our collaboration network** with academia and industry

© Silence Therapeutics 2017

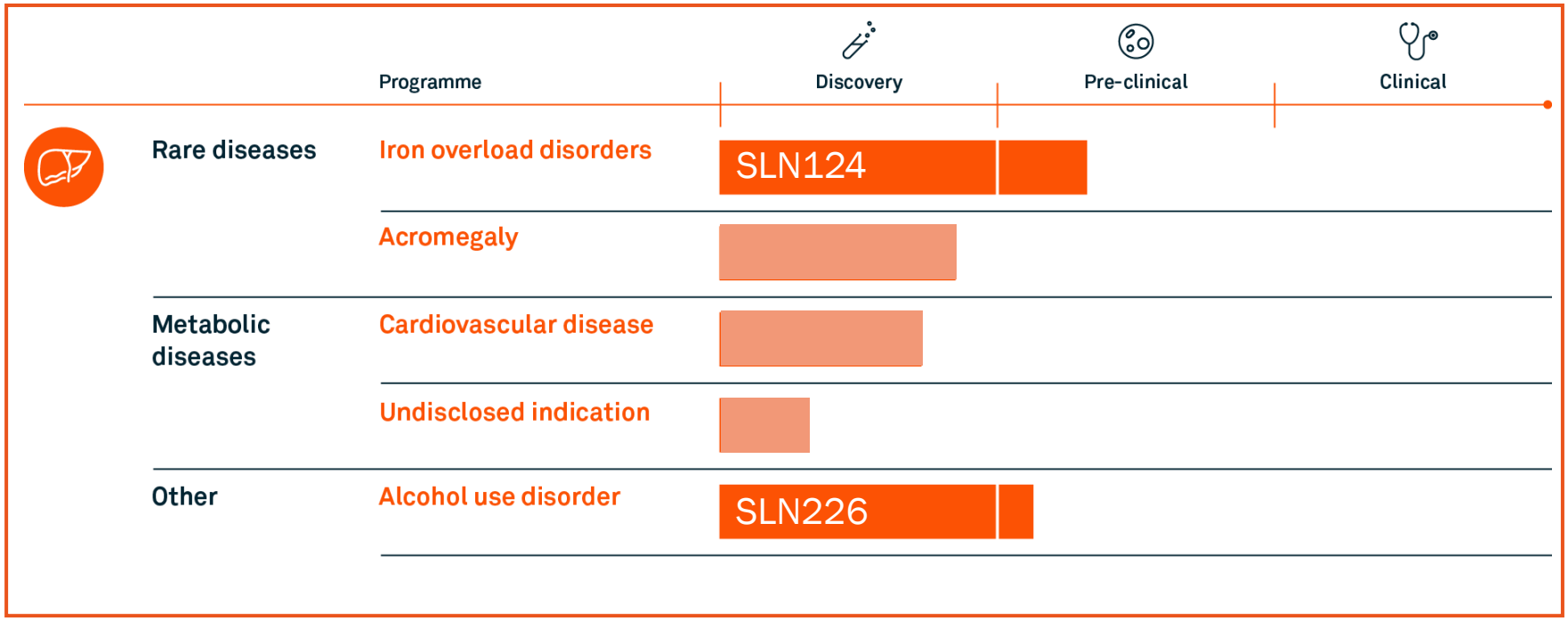
SILENCE THERAPEUTICS

Capital Markets Day, 14 November 2017

Selected programmes in Preclinical Development

Ulrich Zügel, PhD
Head Preclinical Drug Discovery

Programmes presented today



© Silence Therapeutics 2017

SLN124

for the treatment of

Iron overload disorders

© Silence Therapeutics 2017

SLN124 for the treatment of iron overload disorders

Goal:

> Provide an effective & 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:

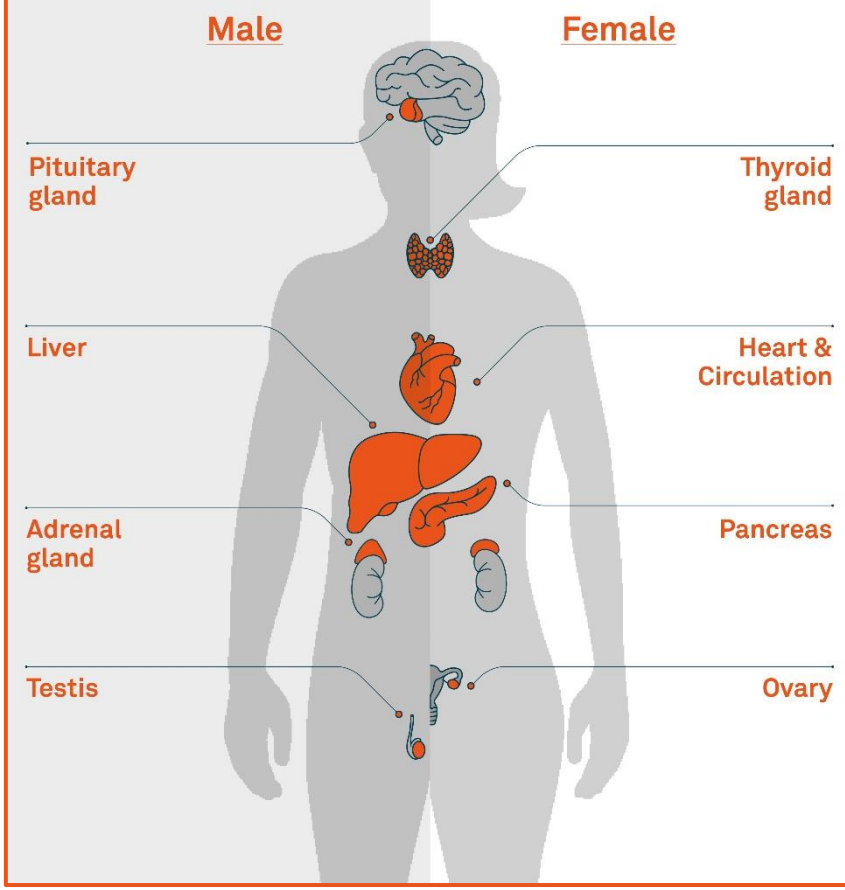
> Preclinical development with plans to enter clinical development in Q4/2018



© Silence Therapeutics 2017

Iron overload disorders

Affected organs by iron overload



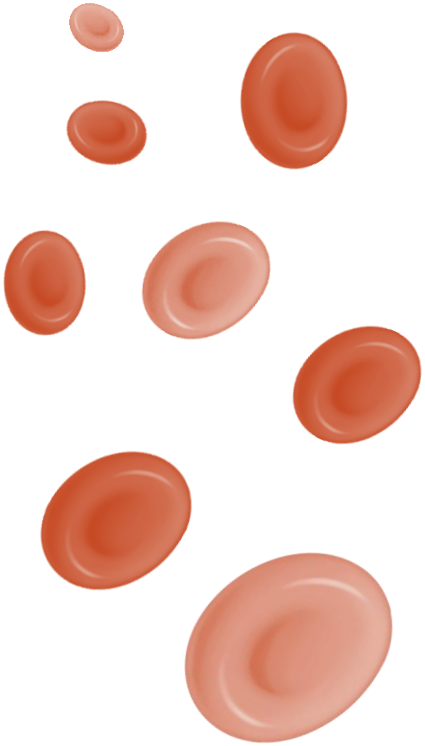
Diseases with iron overload

- 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 !

© Silence Therapeutics 2017

β-Thalassemia facts

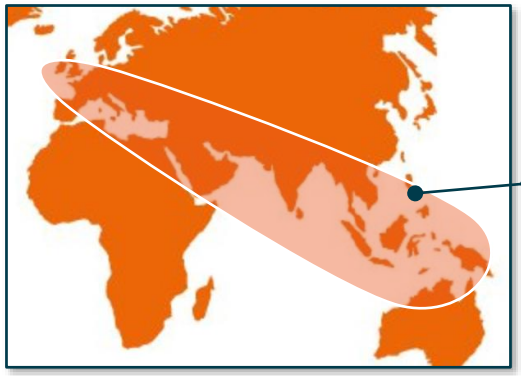


- Rare blood disorder caused by mutations in the **β globin gene**
- Depending on the mutations, patients present **ineffective erythropoiesis** and chronic **haemolytic anaemia**
- Many **β-Thalassemia intermedia** and all **β-Thalassemia major** patients require transfusions to correct anaemia
- **Disturbed 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)

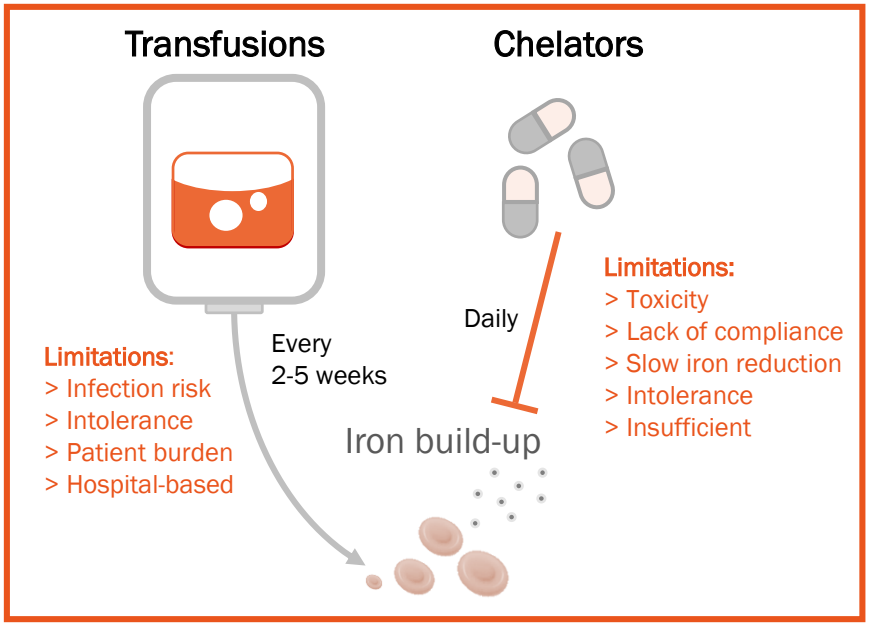


Main β-Thalassemia distribution

© Silence Therapeutics 2017

Medical need in β-Thalassemia

- If untreated, β-Thalassemia major **is lethal** within the first years of life
- β-Thalassemia intermedia & major patients depend on **blood transfusions & lifelong chelation therapy**
- Standard of care therapies with significant **side effects**
- High impact on quality of life



High unmet need for novel effective & safe treatment options

Erythropoiesis	Improve	Transfusion frequency
Patient compliance	Reduce	Demand for iron chelation therapy
Quality of life		Iron overload

© Silence Therapeutics 2017

Market opportunity of SLN124 (US & Europe)



NTDT - β-Thalassemia intermedia

> Monotherapy to delay onset of severe symptoms

> Reduce dietary iron overload & subsequent organ damage

TDT - β-Thalassemia intermedia & major

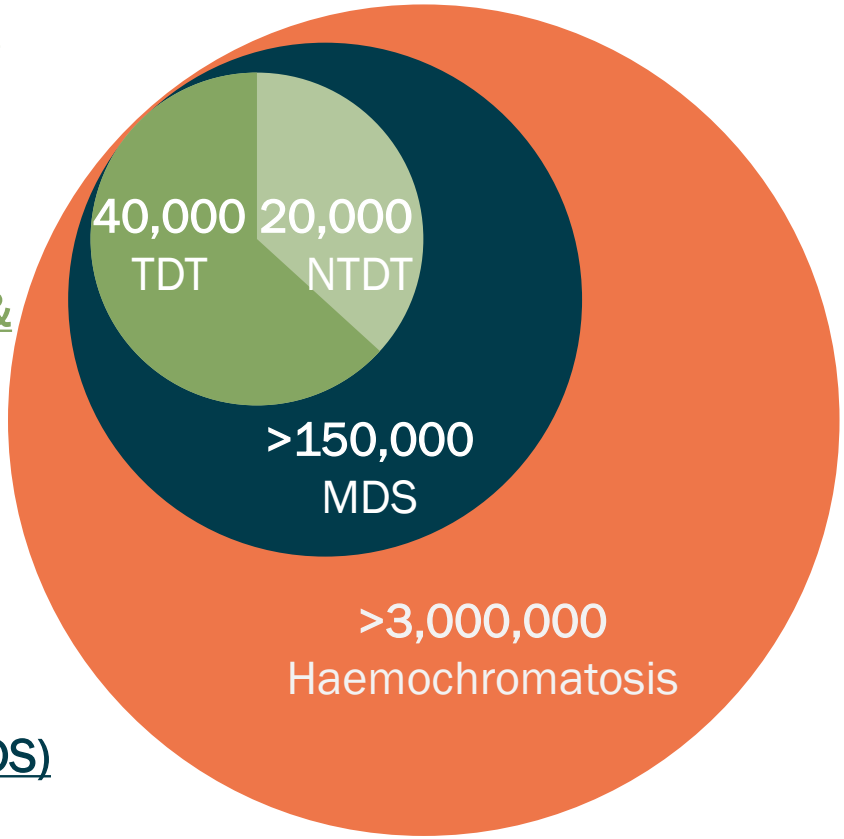
> Combination with transfusions & chelators to reduce frequency & dose

> Improve erythropoiesis and reduce secondary iron overload burden

Other iron overload disorders

Myelodysplastic Syndrome (MDS)

Haemochromatosis



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

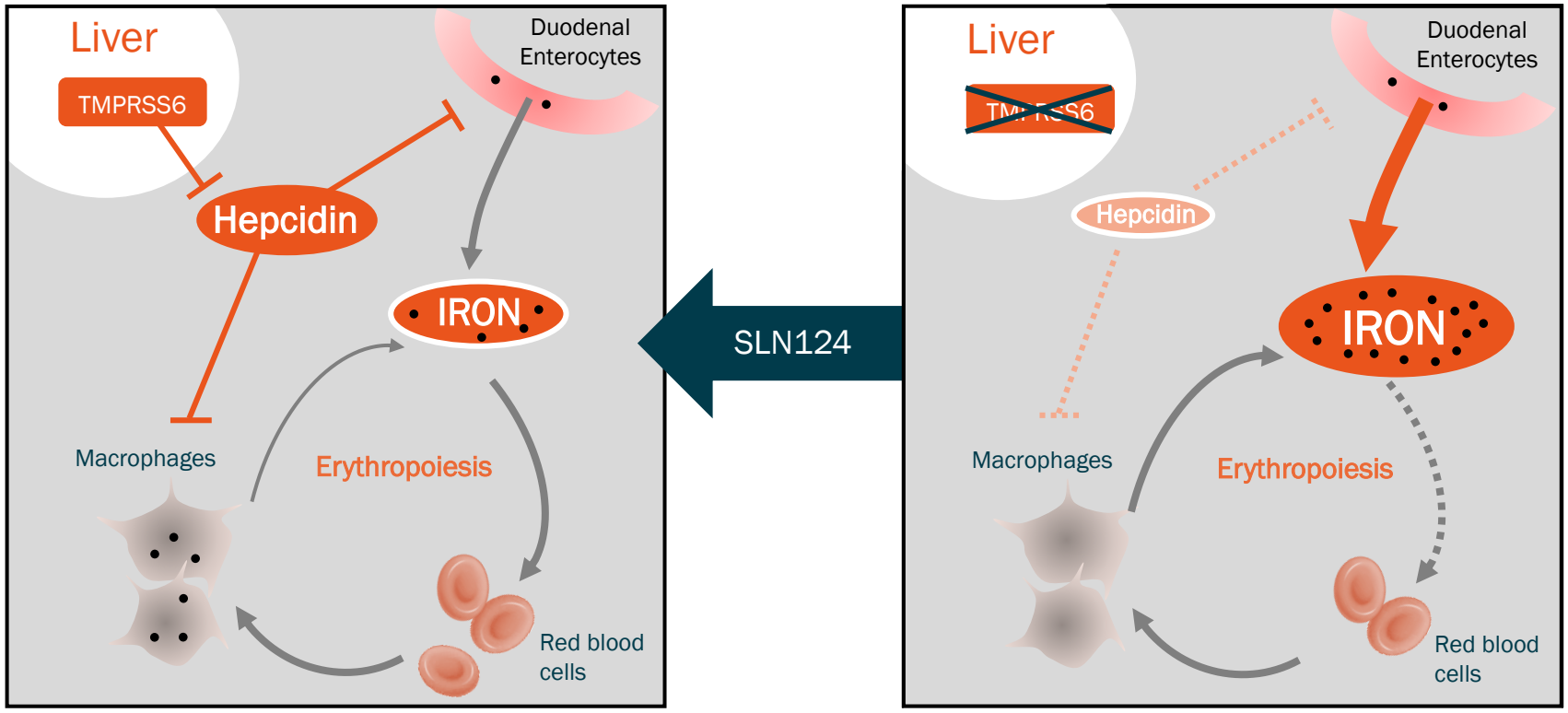
TDT = transfusion dependent Thalassemia; NTDT = non-transfusion dependent Thalassemia

© Silence Therapeutics 2017

TMPRSS6 is a negative regulator of hepcidin and plays a key role in iron homeostasis

Normal hepcidin levels control iron release from cellular stores & intestinal uptake

Low hepcidin levels, as in **β-Thalassemia result in high iron levels** & overload in organs



Silencing TMPRSS6

1. Increases hepcidin levels
2. Reduces iron levels
3. Improves erythropoiesis
4. Reduces organ iron overload

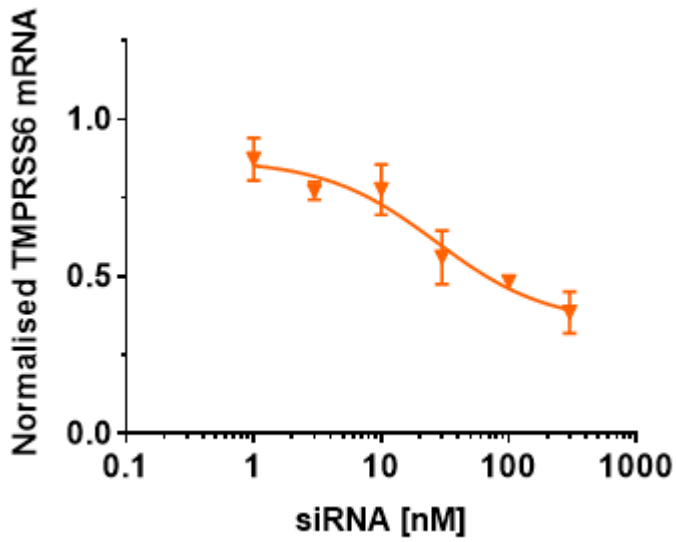
TMPRSS6 = Transmembrane Protease, Serine 6

© Silence Therapeutics 2017

Effective TMPRSS6 mRNA knockdown in primary hepatocytes

- Bioinformatic-based selection of siRNA sequences by proprietary algorithm and screen for functional activity
- Various sequences identified which potently inhibit TMPRSS6 mRNA expression in target cells

Human primary hepatocytes

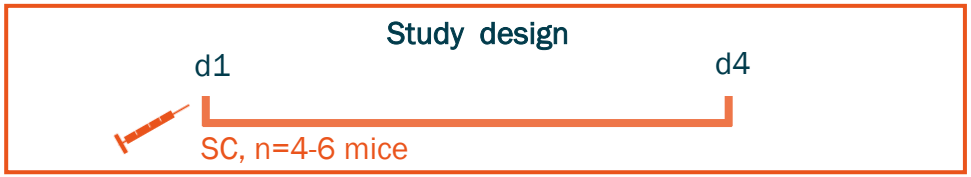




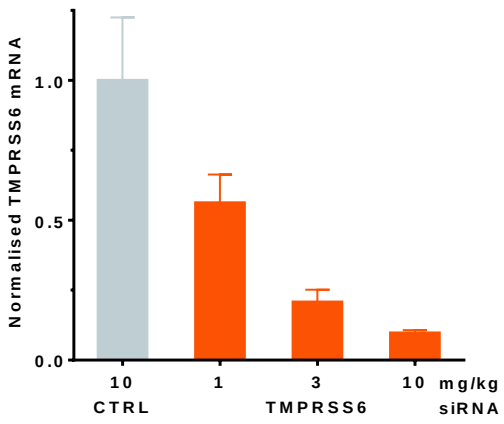
- Receptor mediated uptake & potent activity in the nM range
- Efficacy in primary hepatocytes (mouse, cynomolgus, human)

© Silence Therapeutics 2017

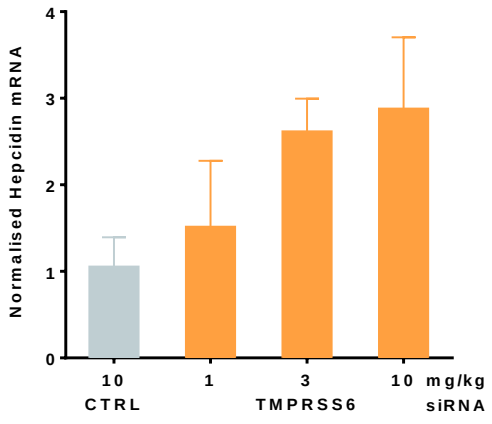
Silencing TMPRSS6 lowers serum iron levels in mice



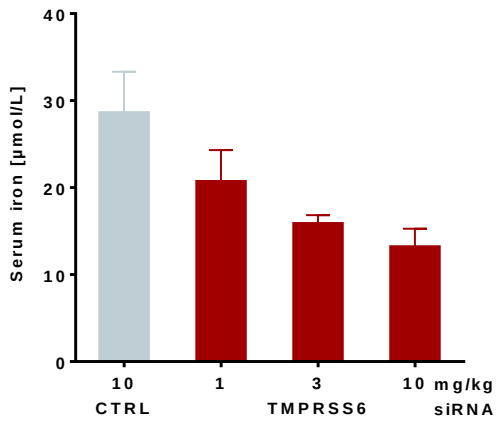
TMPRSS6 mRNA (liver)



Hepcidin mRNA (liver)



Iron (serum)



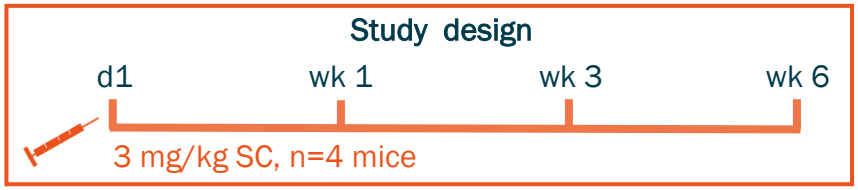
> Single administration results in specific silencing of TMPRSS6

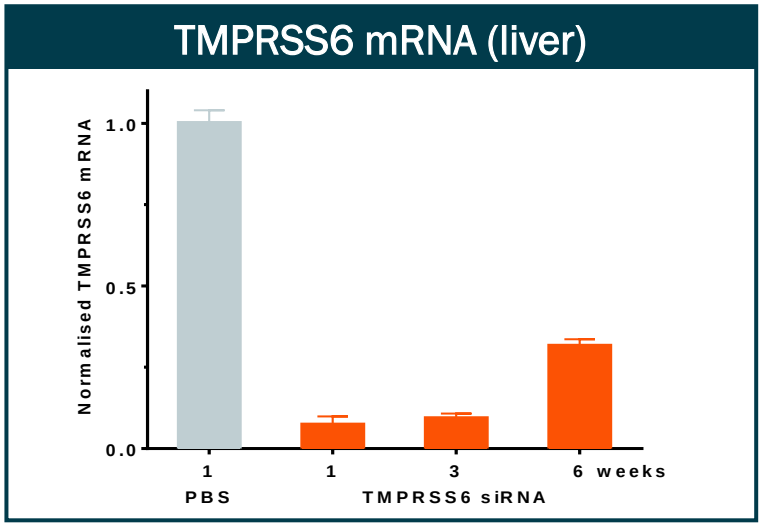
> Upregulated Hepcidin causes reduction of blood iron levels

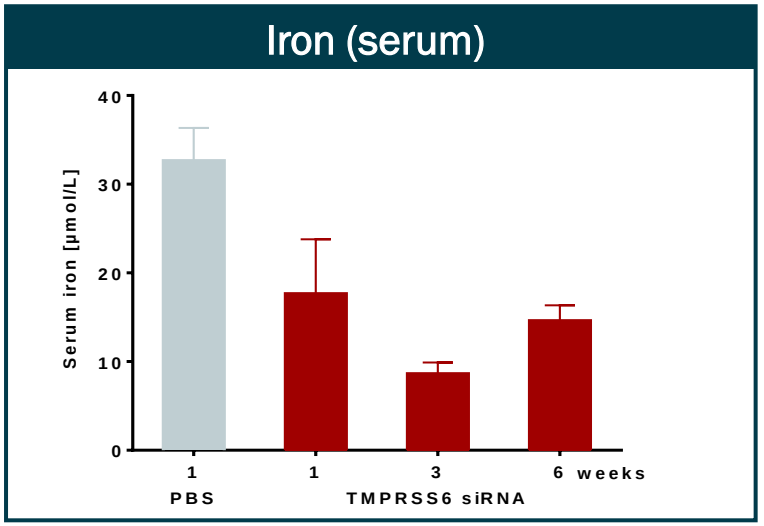
> **Proof of mechanism demonstrated**

© Silence Therapeutics 2017

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







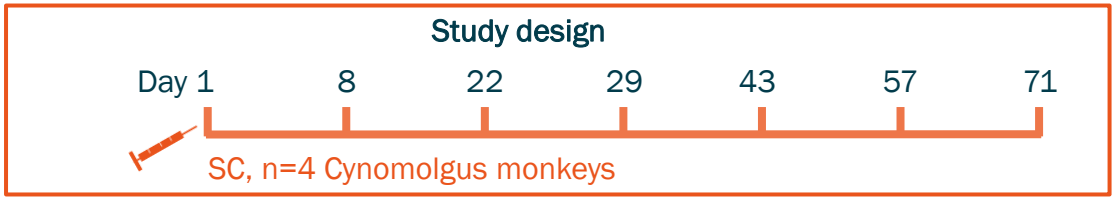
> Long-lasting functional TMPRSS6 mRNA silencing in liver

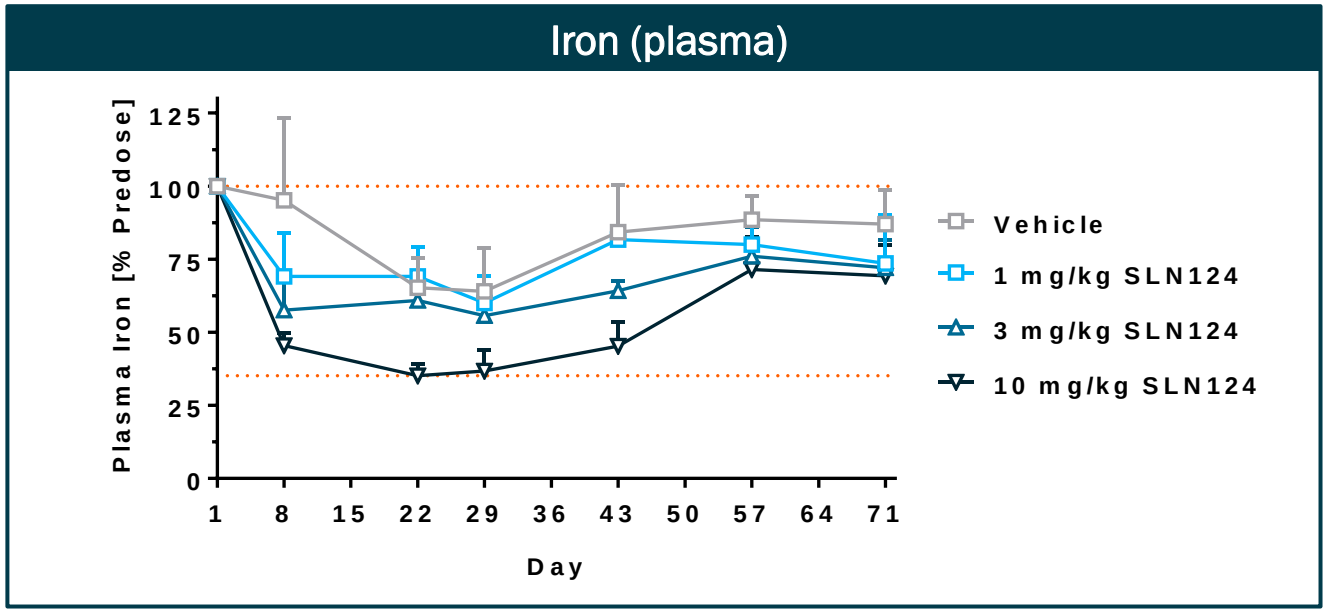
> Reduction of serum iron levels for at least 6 weeks

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

© Silence Therapeutics 2017

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





> Durable plasma iron reduction for up to 6 weeks

> Well tolerated with long duration of action

© Silence Therapeutics 2017

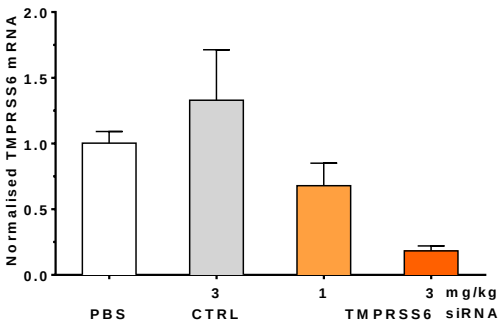
Therapeutic activity of SLN124 in an iron overload model (HFE -/- mice) - 1/2

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

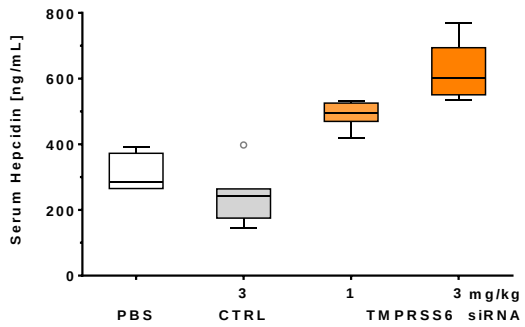
Study design



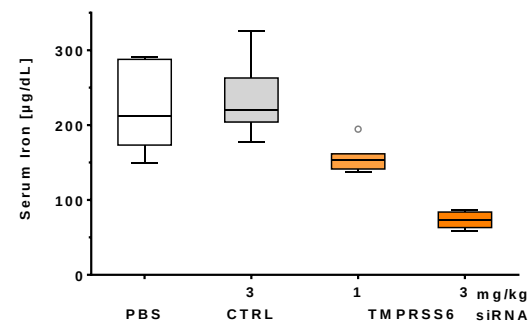
TMPRSS6 mRNA (liver)



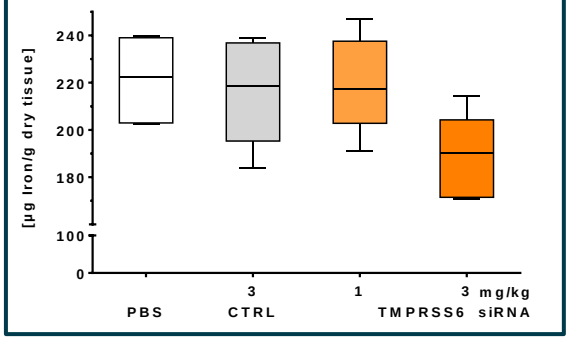
Hepcidin (serum)



Iron (serum)



Iron (kidney)



> Dose-dependent and robust silencing of TMPRSS6 mRNA in the liver

> Increased serum hepcidin levels

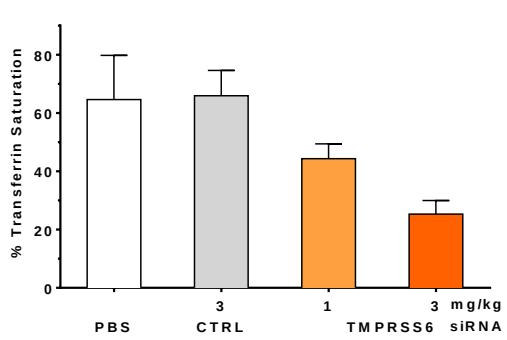
> Normalisation of serum and kidney iron levels

© Silence Therapeutics 2017

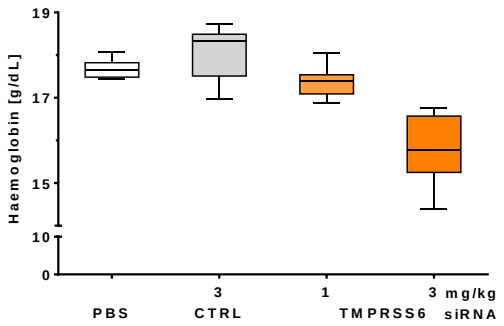
Therapeutic activity of SLN124 in an iron overload model (HFE -/- mice) - 2/2

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

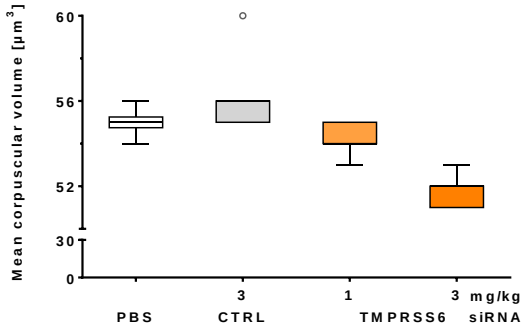
Transferrin saturation



Haemoglobin



Mean corpuscular volume



> Normalisation of transferrin saturation

> Normalisation of haematological parameters

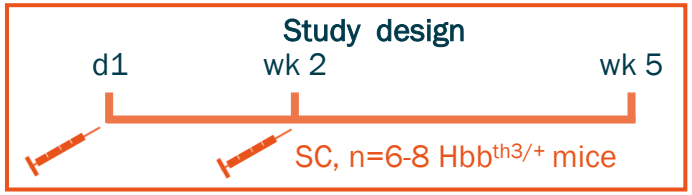
> Therapeutically active in HFE -/- mice after single administration, proof of concept achieved

© Silence Therapeutics 2017

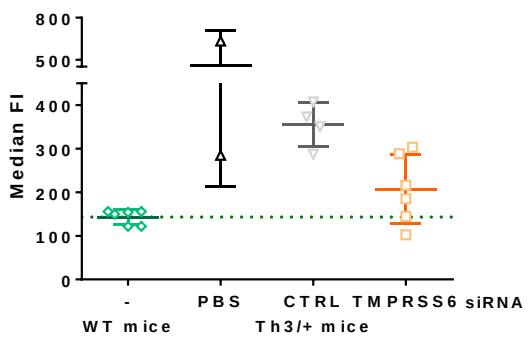
SLN124 normalizes ROS species & improves RBC parameters in β-Thalassemia disease model

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

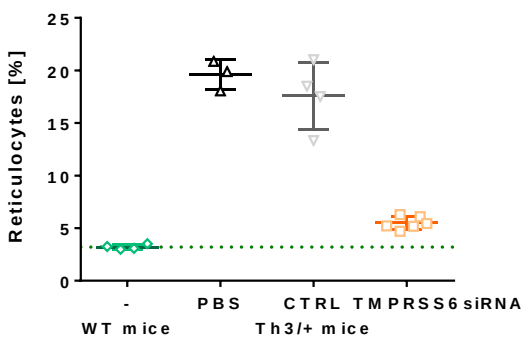
HUDSON INSTITUTE OF MEDICAL RESEARCH



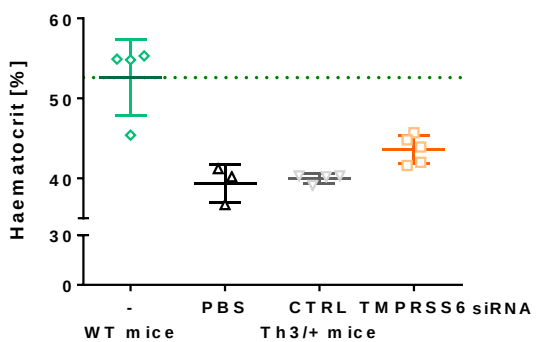
Reactive oxygen species (ROS)



Reticulocyte proportion



Haematocrit



> Normalisation of ROS to levels in healthy mice

> Normalisation of reticulocyte proportion and improvement of haematocrit

> SLN124 significantly improves erythropoiesis in animal model for β-Thalassemia intermedia

ROS = reactive oxygen species; RBC = red blood cells

© Silence Therapeutics 2017

Feedback by key opinion leaders on SLN124

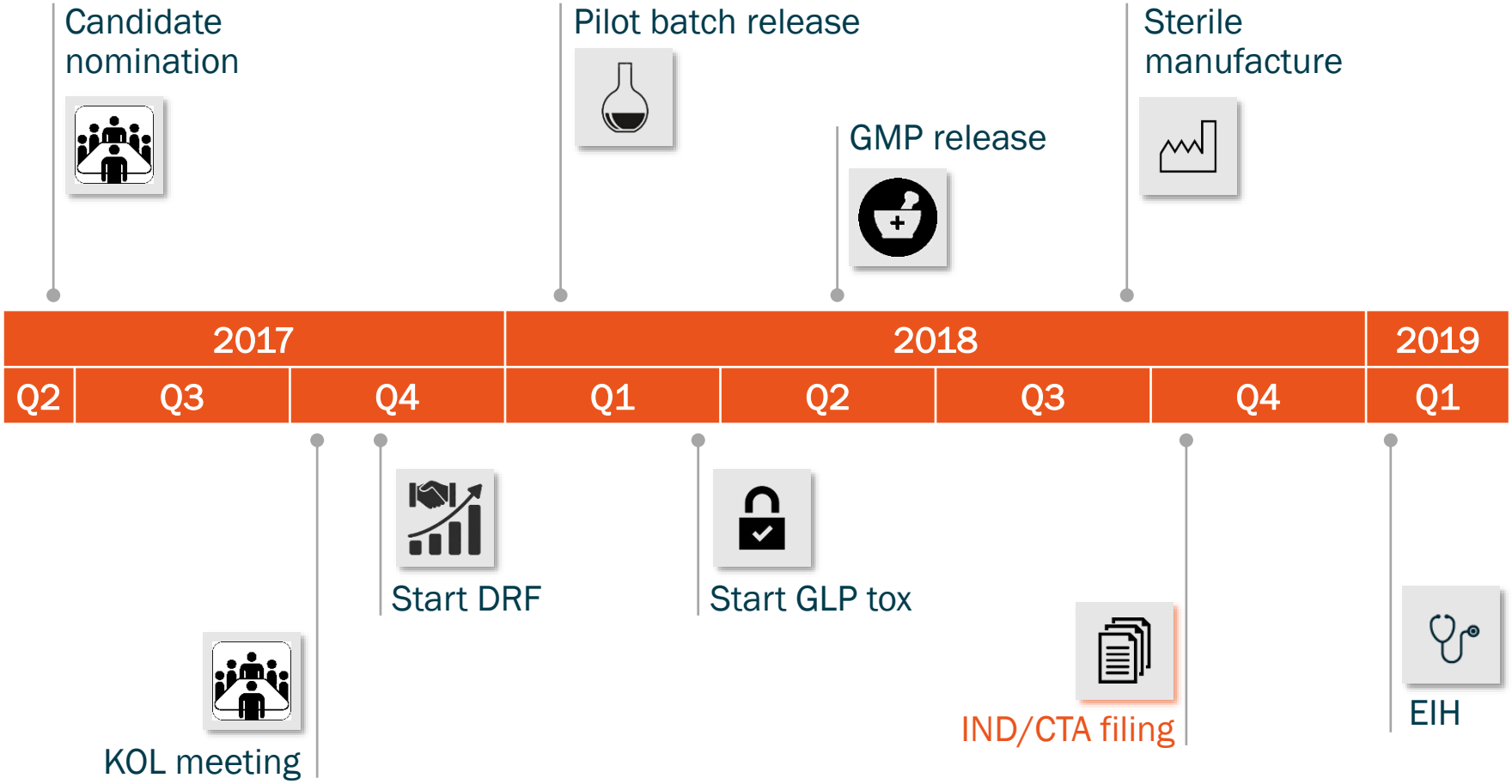
International KOL workshop with clinical and regulatory experts in the field of iron overload disorders

- High medical need to reduce iron overload and number of transfusions in patients
  - Not met by currently available therapies
- SLN124 has the potential to
  - Reduce systemic iron
  - Prevent organ iron overload
  - Enhance erythropoiesis

... providing a significantly improved therapeutic option and better quality of life for patients living with iron overload conditions, such as β-Thalassemia

© Silence Therapeutics 2017

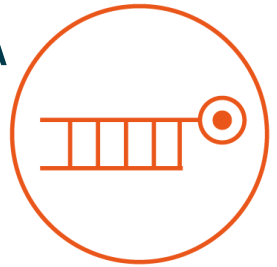
SLN124 development timelines – key milestones



On track for CTA filing 15 months after candidate selection

© Silence Therapeutics 2017

Summary SLN124



- Highly potent, selective and long acting GalNAc-siRNA
- Efficacious in lowering blood iron and well tolerated in healthy mice & 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 2017

SLN226

for the treatment of

Alcohol use disorder

© Silence Therapeutics 2017

SLN226 for the treatment of alcohol use disorder

Project Goal:

> Provide an effective & safe novel treatment option for patients with alcohol use disorder (AUD)

Rationale:

> Target ALDH2, a validated target for alcohol aversion therapy, with a GalNAc-siRNA molecule providing a **highly specific, effective & safe option** through inhibition of the ALDH2 gene expressed in hepatocytes

Project Phase:

> Preclinical development with plans to enter clinical development in Q2/2019*

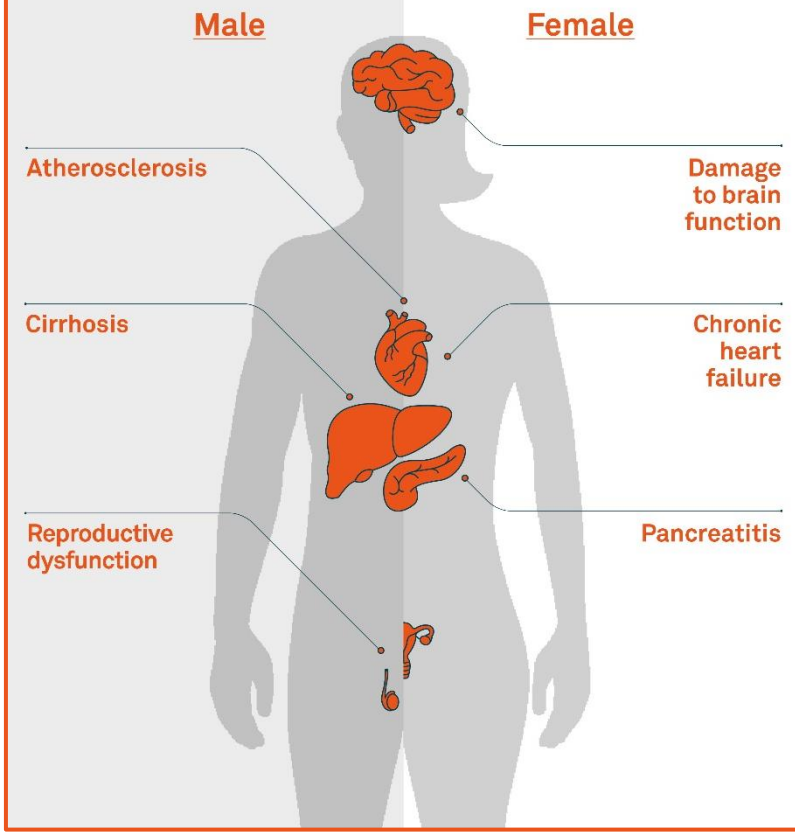


*potentially with partner

© Silence Therapeutics 2017

Alcohol use disorder facts - 1/2

Long term effects of alcohol abuse



Consequences of alcohol abuse

- Liver damage
- Cardiovascular complications
- Gastrointestinal damage
- Central & peripheral neurological symptoms
- Anxiety, depression, suicidal tendencies
- Negative impact on social life

Alcohol abuse & physiological dependence on alcohol is a global problem with tremendous impact on health, society and economics !

© Silence Therapeutics 2017

Alcohol use disorder facts - 2/2

- Chronic alcohol abuse leads to **alcoholic liver disease (ALD)** – spectrum of conditions including **hepatitis** and **cirrhosis** which may eventually require **liver transplantation**
- One third of all liver transplants due to ALD (~4,000 per year); 6-month abstinence rule while waiting for liver transplant

Abstinence is the key requirement for successful resolution of alcohol use disorder, especially for ALD patients awaiting a liver transplant and for the long-term success of the transplant

- Primarily managed by **psychotherapy** but around **70% of patients relapse** after therapy
- **Disulfiram** is often included as co-therapy but use is limited due to significant **safety** and **compliance issues**

High medical need for effective & safe treatment options to improve compliance and alcohol abstinence

© Silence Therapeutics 2017

Market opportunity of SLN226 (US & Europe)



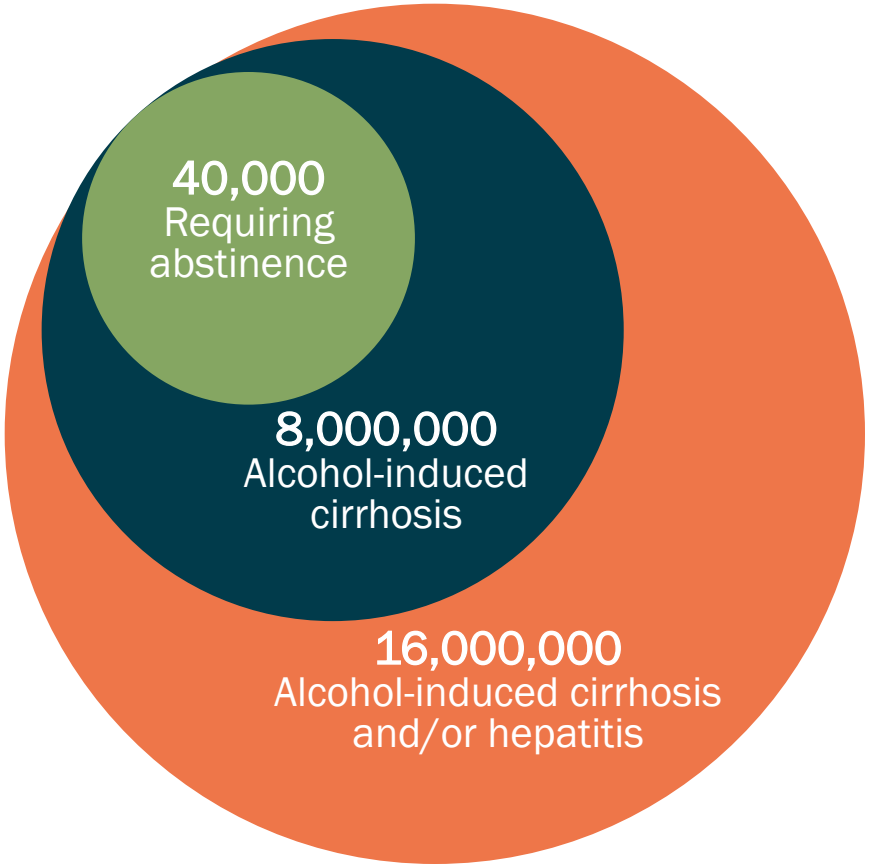
Patients urgently requiring abstinence

- 20-33% liver transplants due to alcohol abuse alone or in combination with viral infection
- Potentially a similar number of patients on the waiting list needing abstinence support
- Expansion to patients with alcohol use disorder strongly committed to abstinence

ALD related disorders

Alcohol-induced cirrhosis

Alcohol-induced hepatitis



- SLN226 has significant potential to aid abstinence in alcohol dependent patients on psychotherapy

ALD – Alcoholic Liver Disease

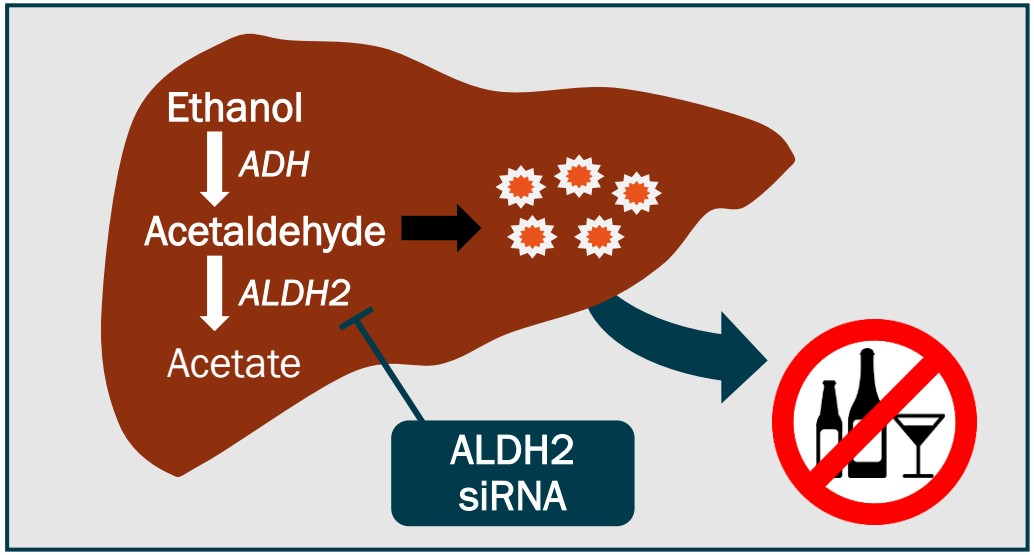
© Silence Therapeutics 2017

Aldehyde dehydrogenase 2 (ALDH2) is the key alcohol metabolising enzyme

>ALDH2 is ubiquitously expressed

>Liver is the key organ for ethanol detoxification by ALDH2

>ALDH2 is rate limiting enzyme in the ethanol metabolic pathway



Validated target

> Clinically: ALDH inhibitors e.g. Disulfiram

> Genetically in human subpopulations: alcohol flushing reaction

Silencing ALDH2

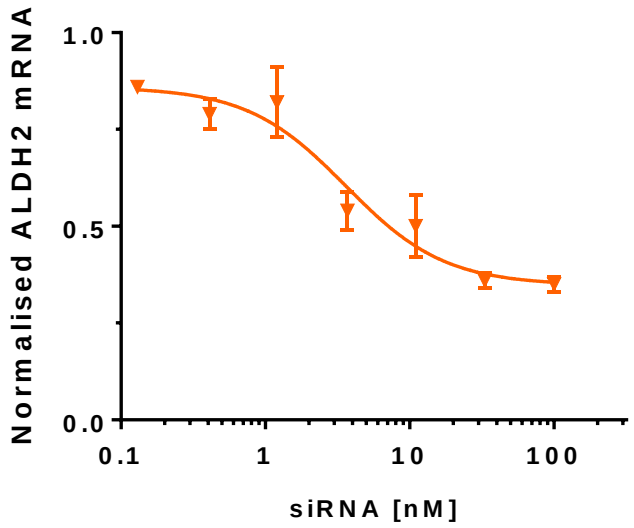
1. Acetaldehyde accumulation <u>upon alcohol consumption</u>
2. Unpleasant physiological effects
3. Disrupt addictive cycle & alcohol seeking behaviour
4. Abstinence

© Silence Therapeutics 2017

Robust ALDH2 mRNA knockdown in primary hepatocytes

- Bioinformatic-based selection of siRNA sequences by proprietary algorithm and screen for functional activity
- Several sequences identified which potently inhibit ALDH2 mRNA expression in target cells

Human primary hepatocytes





- Receptor mediated uptake & is highly potent in the nM range
- Efficacy in primary hepatocytes (mouse, cynomolgus, human)

© Silence Therapeutics 2017

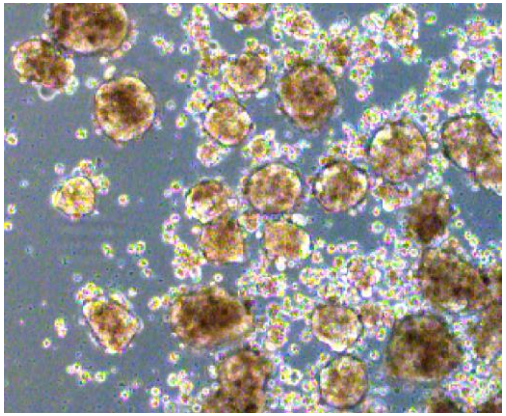
Efficient ALDH2 mRNA reduction in human primary hepatocyte spheroid cultures

3D vs 2D hepatocyte culture

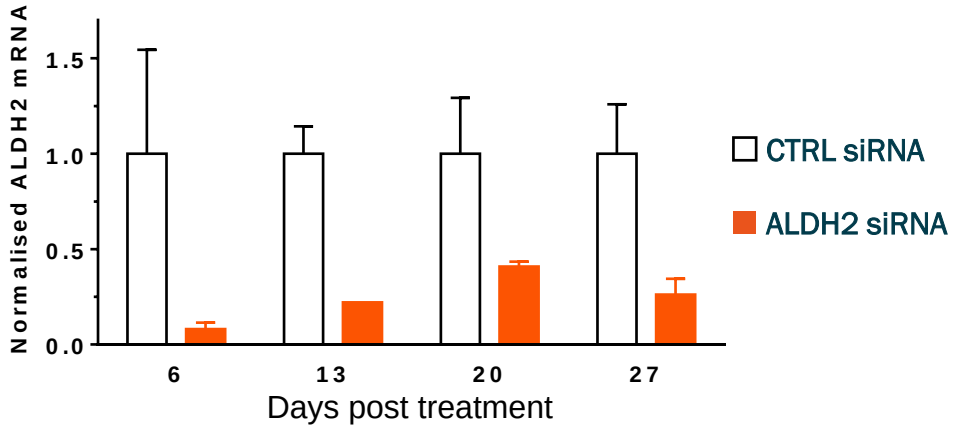
> Liver-specific physiology & gene expression patterns
> Long living organoid structures
> Extended functional ASGPR expression (up to 12 d vs. 4 h)
> Repeated treatments possible



Spheroid culture



ALDH2 mRNA in spheroids



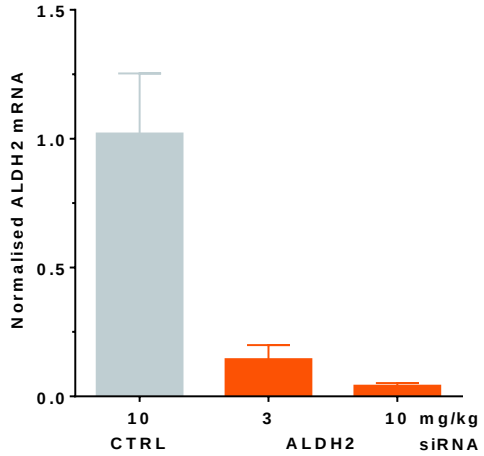
> Efficient ALDH2 mRNA silencing in 3D hepatocyte spheroids for >3 weeks in culture
> Accelerates sequence selection for subsequent in vivo PD studies

© Silence Therapeutics 2017

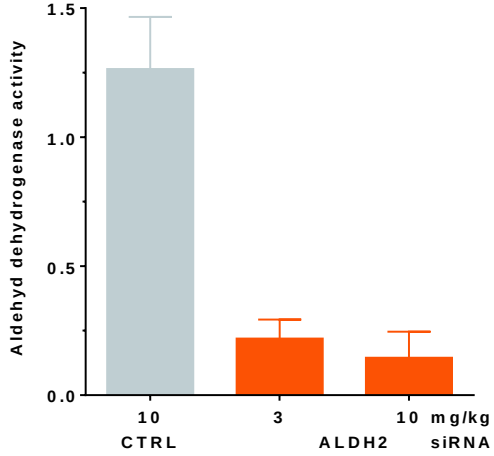
ALDH2 GalNAc-siRNA treatment induces hepatic acetaldehyde accumulation in mice



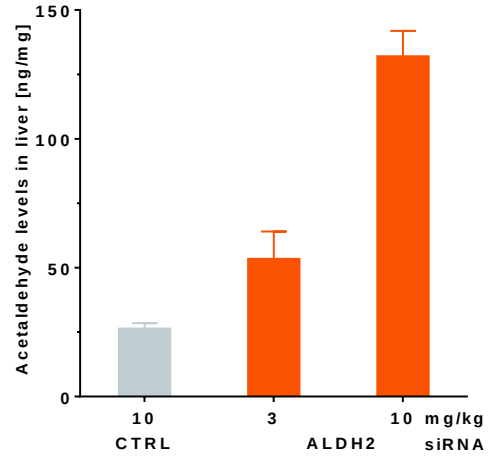
ALDH2 mRNA (liver)



ALDH enzymatic activity (liver)



Acetaldehyde (liver)



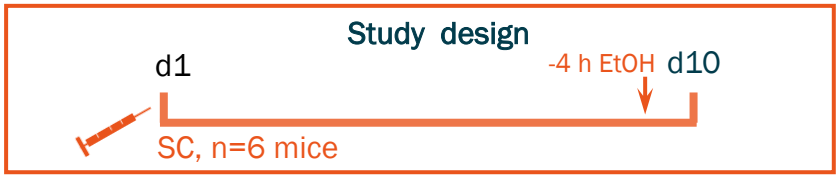
> Single administration results in specific ALDH2 mRNA silencing

> Silencing ALDH2 reduces the capacity of mouse liver to metabolise acetaldehyde

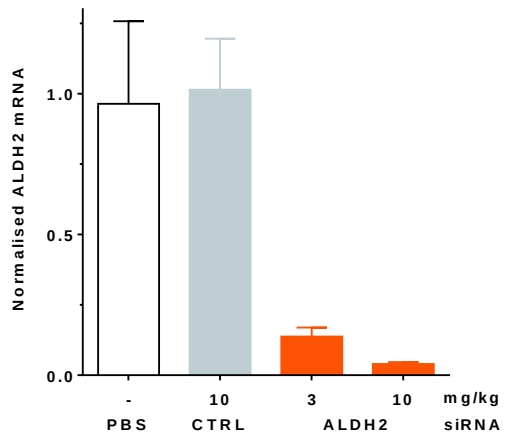
> **Proof of mechanism demonstrated**

© Silence Therapeutics 2017

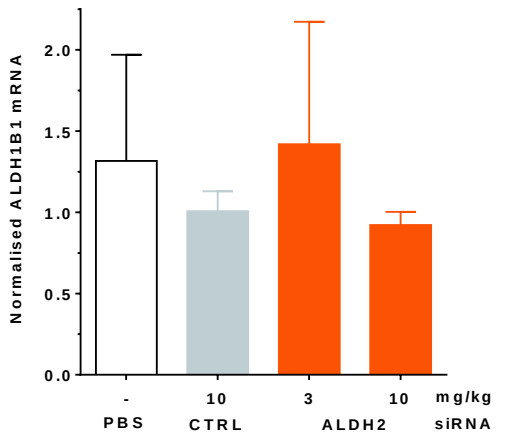
Liver expression of ALDH1 isoenzymes upon ALDH2 silencing in mice



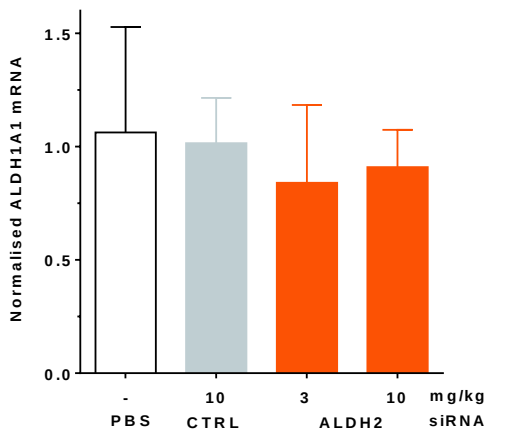
ALDH2 mRNA (liver)



ALDH1B1 mRNA (liver)



ALDH1A1 mRNA (liver)

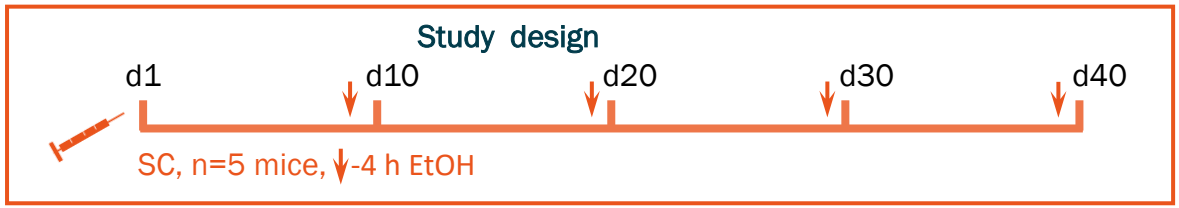


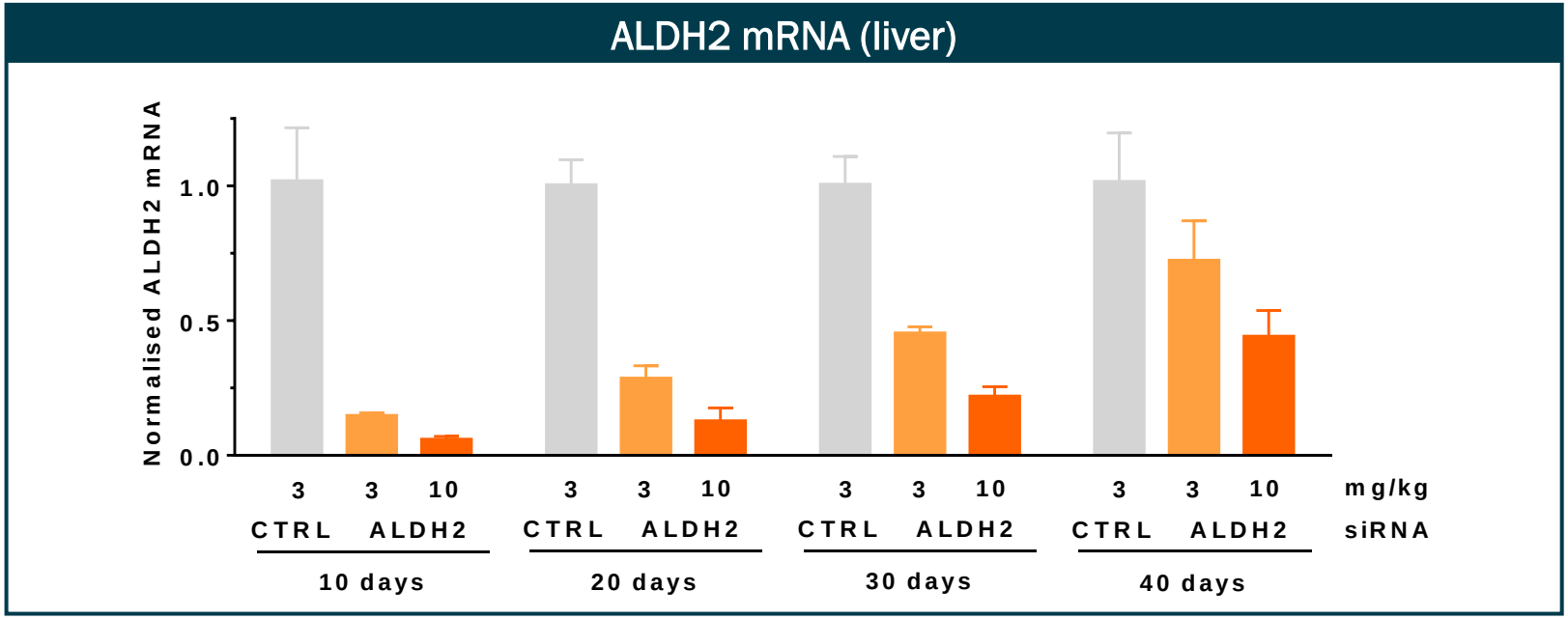
> No impact observed on expression levels of alternative isoenzymes, which are capable of metabolising acetaldehyde in mice

> No compensatory mechanism by ALDH1 isoenzymes

© Silence Therapeutics 2017

SLN226 reduces ALDH2 mRNA in liver for at least 6 weeks after single administration in mice





> Robust mRNA reduction up to 6 weeks by single administration of 10 mg/kg

> Well tolerated with long duration of action in mice

© Silence Therapeutics 2017

Further characterisation of SLN226

Ethanol consumption mouse model

> Assess effect of SLN226 in alcohol seeking behaviour in high alcohol preferring (HAP) mice

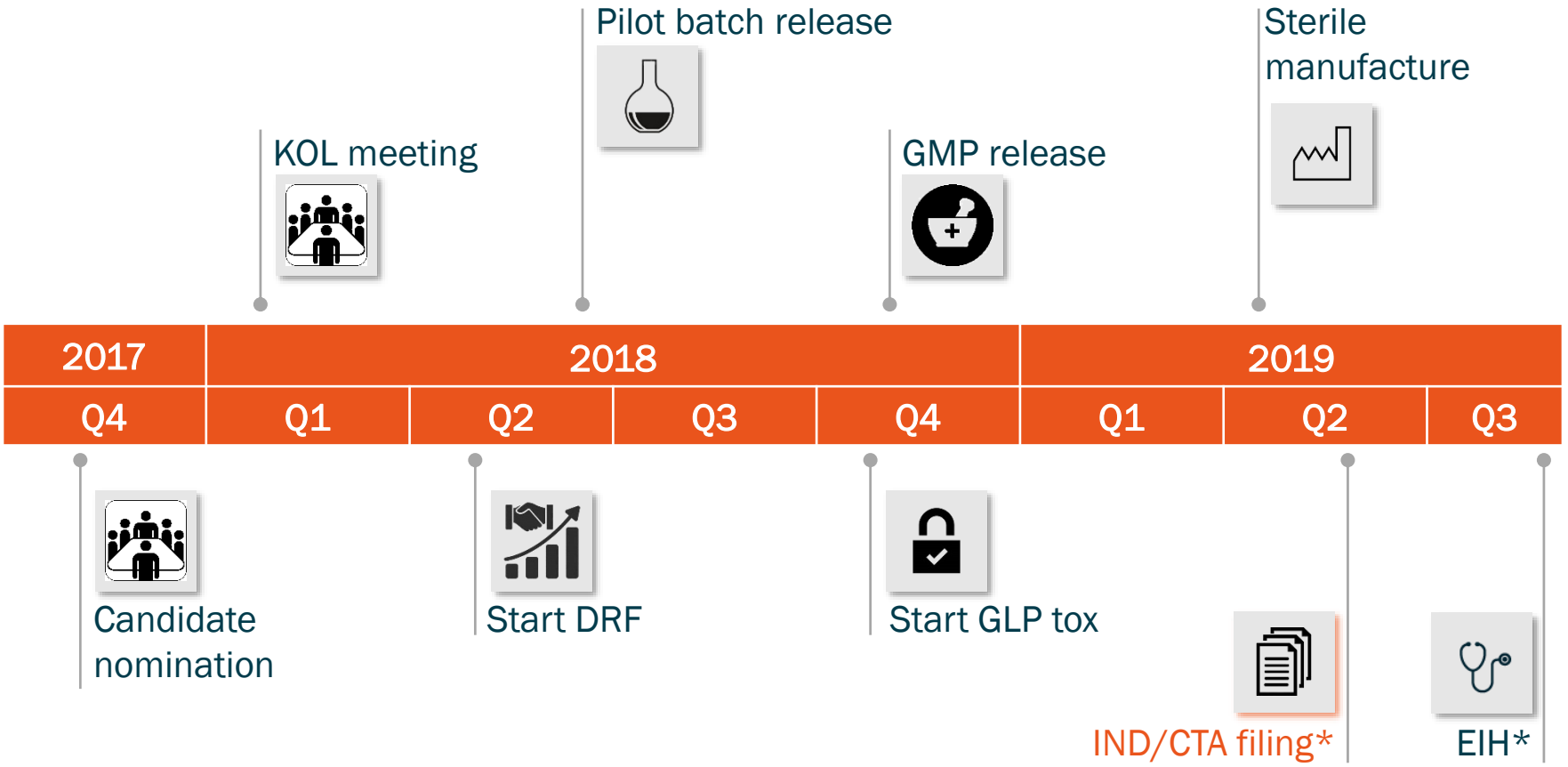
> State of the art animal model which resembles patients' free choice drinking and its physiological consequences

Efficacy of SLN226 in higher species

> Study pharmacodynamics/-kinetics of SLN226 in alcohol challenged animals

© Silence Therapeutics 2017

SLN226 development timelines – key milestones

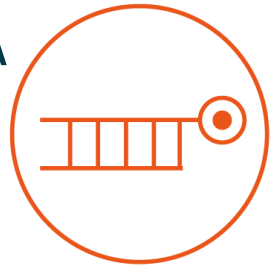


On track for IND/CTA filing in Q2 / 2019

*potentially with partner

© Silence Therapeutics 2017

Summary SLN226



- Highly potent, selective and long acting GalNAc-siRNA
- Induces acetaldehyde accumulation in mice after single subcutaneous administration
- Currently in preclinical development with plans to enter clinical development in Q2 2019*
- Studies initiated to show therapeutic efficacy in a clinically relevant animal disease model and in higher species

SLN226 represents a highly valuable therapeutic candidate for patients with AUD to maintain alcohol abstinence

*potentially with partner

© Silence Therapeutics 2017

SILENCE THERAPEUTICS

Capital Markets Day, 14 November 2017

Technology Innovation

Dmitry Samarsky, PhD
Chief Scientific Officer

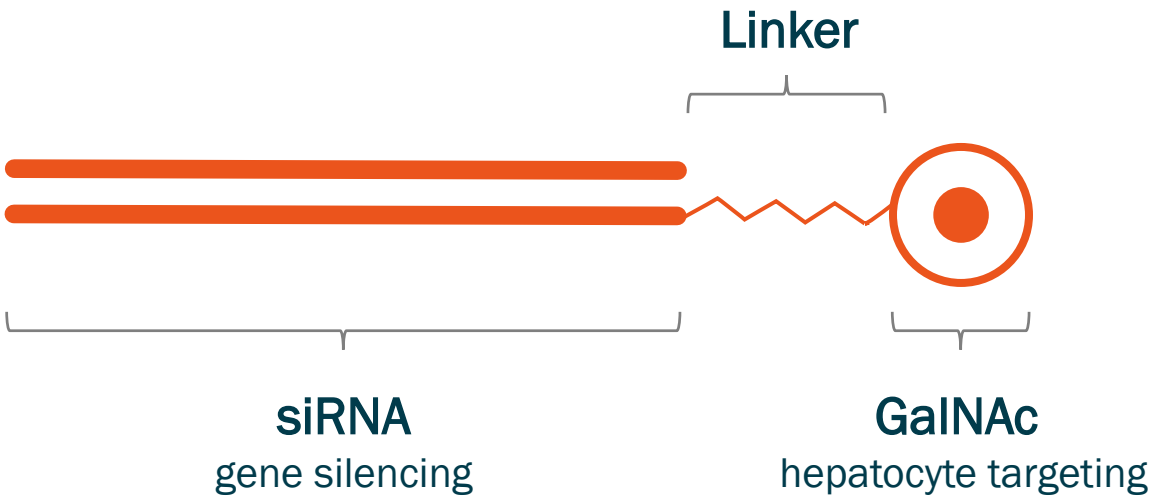
Technology Innovation efforts in 2017



- Provide the best technology platform for our therapeutic pipeline
- Secure our position as a world leader in RNA therapeutics
- Strengthen and expand Silence's intellectual property (IP) portfolio
- Maintain freedom to operate (FTO) for our programmes and create out-licensing opportunities

© Silence Therapeutics 2017

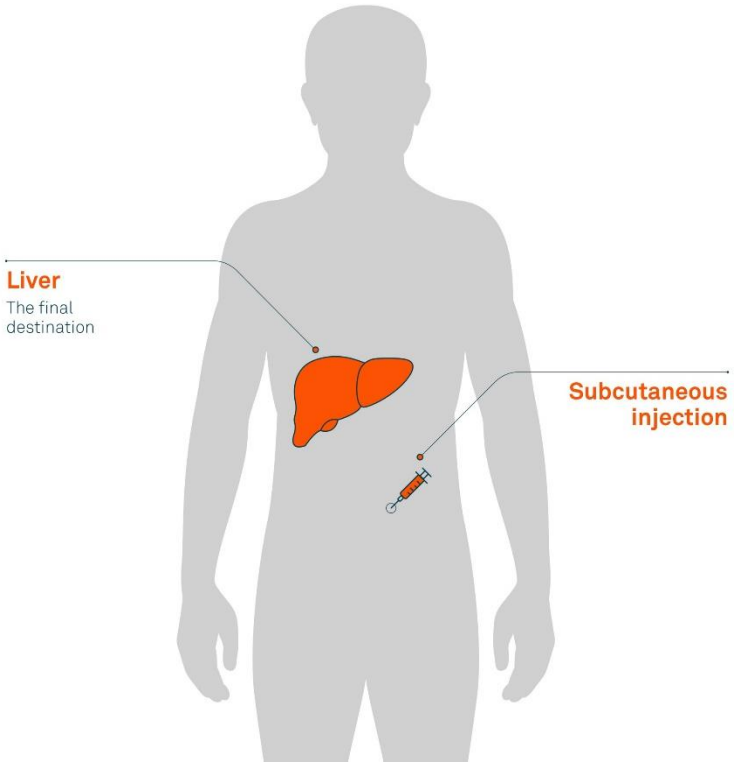
Our therapeutic GalNAc-siRNA molecules

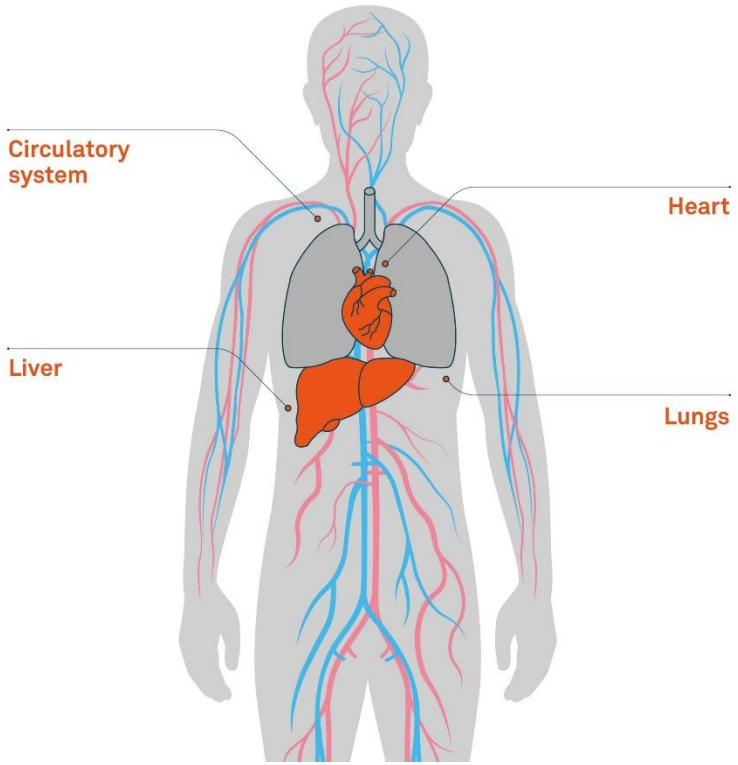


> Harness the power of RNAi to silence disease-causing genes in the liver, specifically in hepatocytes

© Silence Therapeutics 2017

Delivery of GalNAc-siRNA molecules

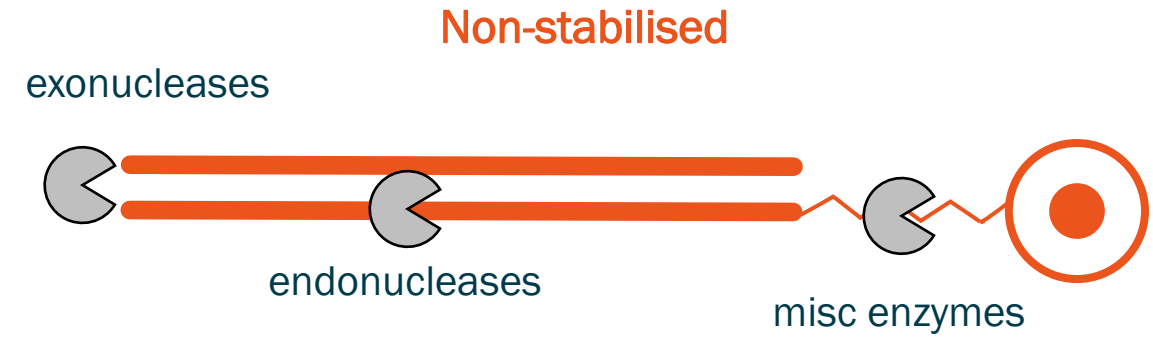


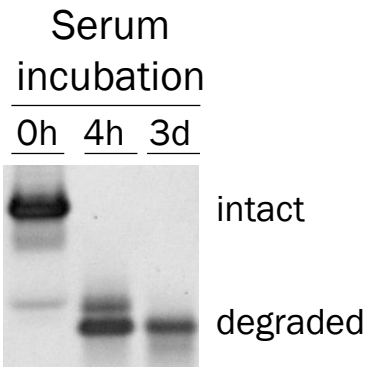


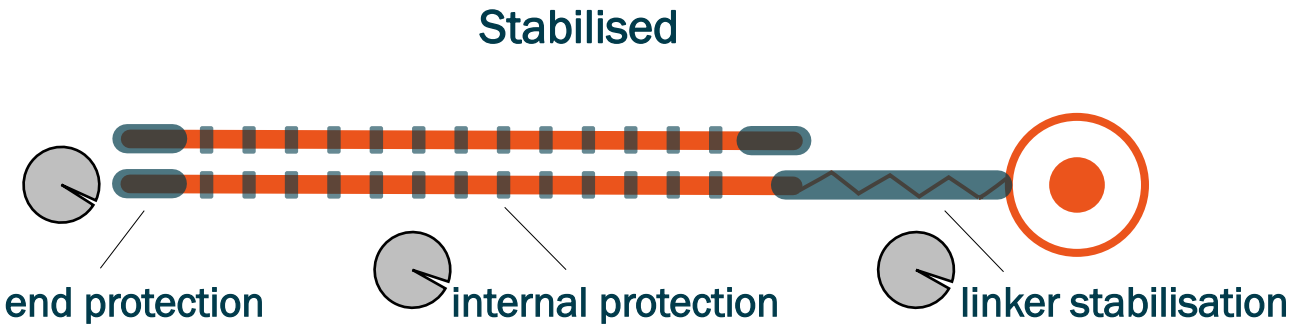
> On its journey to the liver, GalNAc-siRNA molecules are exposed to various body fluids, which contain ubiquitous nucleases

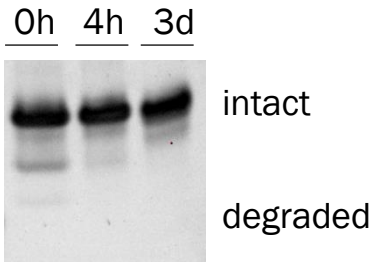
© Silence Therapeutics 2017

In biological fluids, unmodified GalNAc-siRNA molecules are quickly degraded





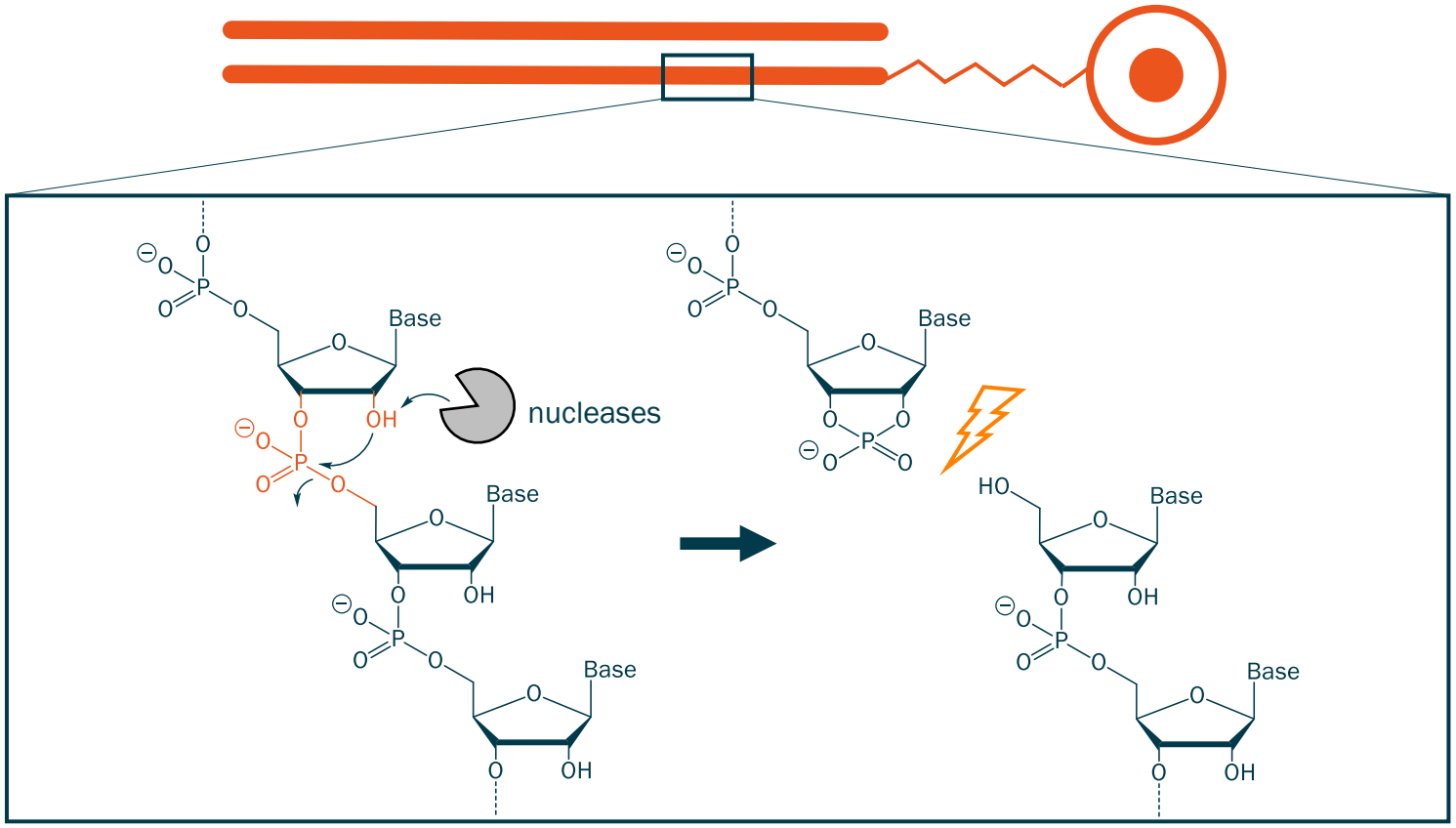




> Incorporation of chemically modified nucleotides can protect GalNAc-siRNA molecules from degradation

© Silence Therapeutics 2017

Mechanism of RNA backbone cleavage

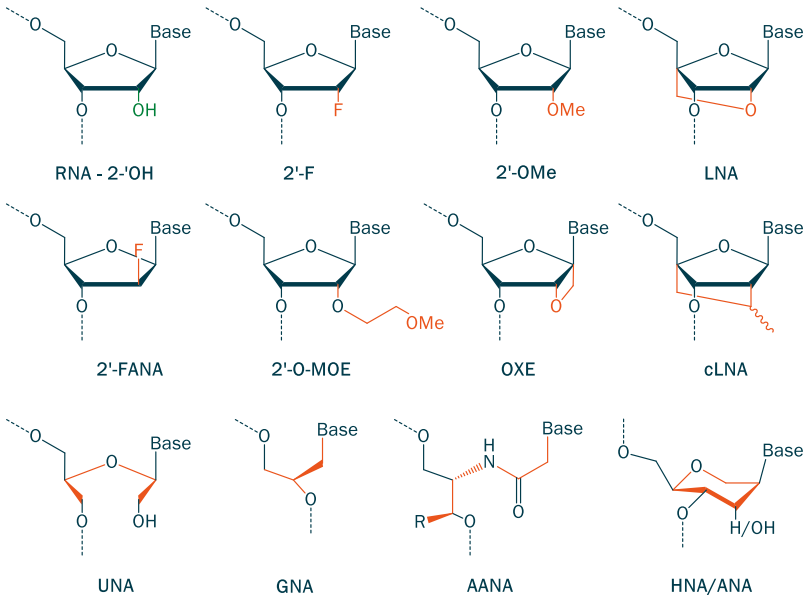


> Most nucleolytic degradation reactions engage the 2'-OH and the neighbouring phosphate linkage of the RNA

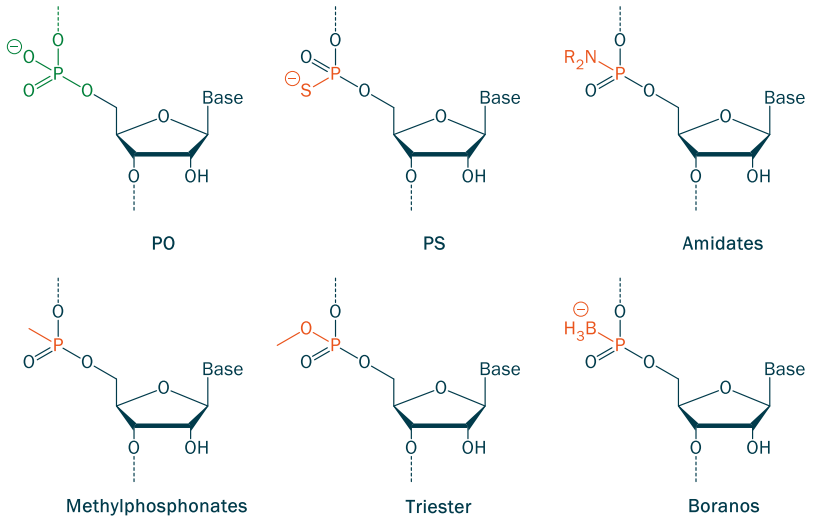
© Silence Therapeutics 2017

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**

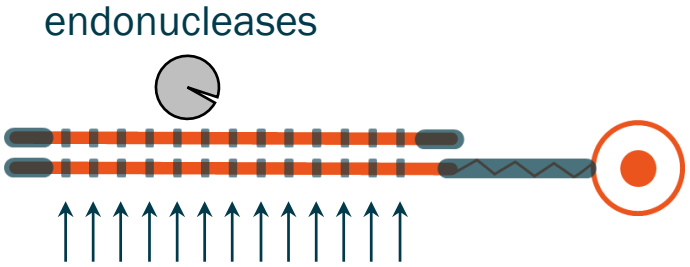
> Our strategy is to minimise the use of non-natural nucleotides while preserving or improving both stability and potency

© Silence Therapeutics 2017

Internal siRNA modifications for endonuclease protection

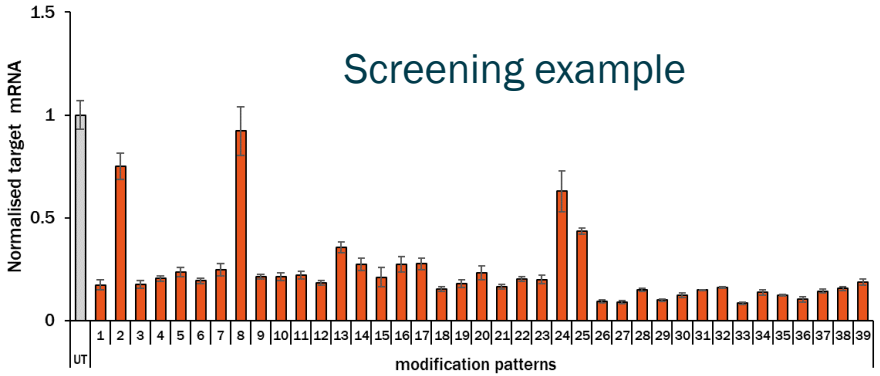
© Silence Therapeutics 2017

Minimising the use of non-natural nucleotides

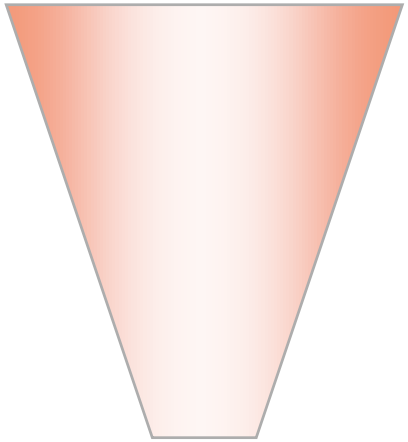


Internal siRNA modifications

Screening example



Hundreds of chemical modification patterns
≥50% non-natural



Unique chemical modification patterns
<15% non-natural

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

Serum stability: with or without GalNAc

Primary hepatocyte activity: with GalNAc

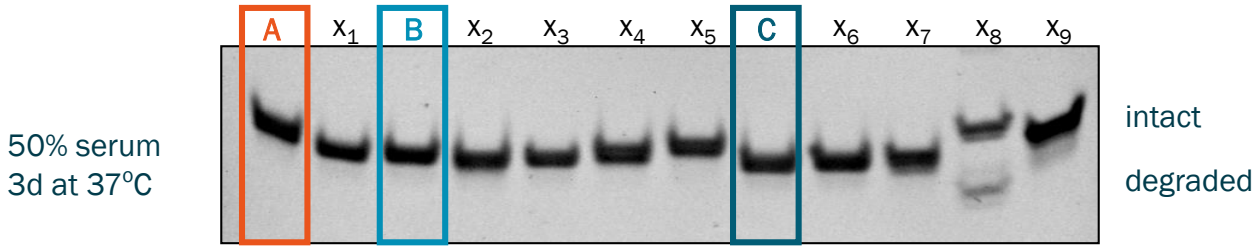
Animal activity: with GalNAc

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

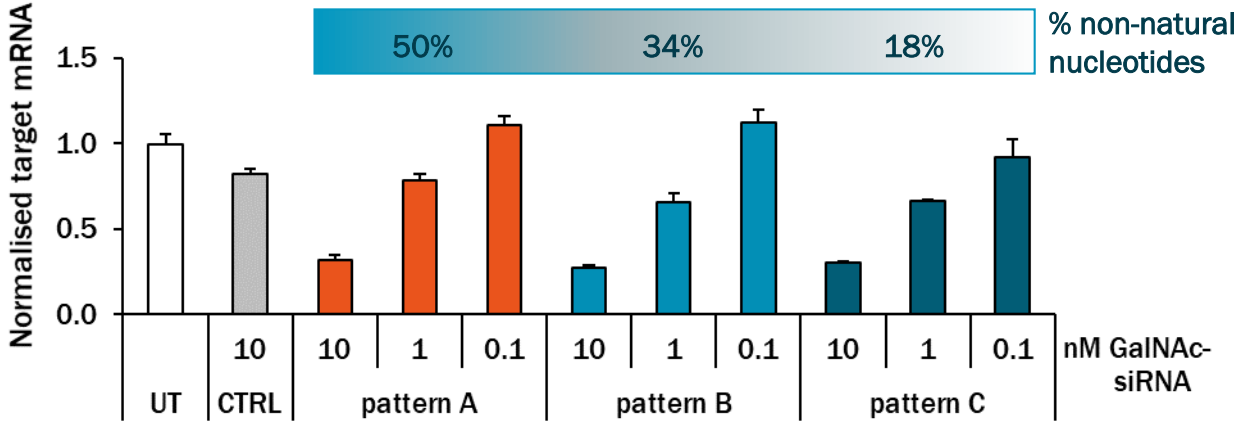
© Silence Therapeutics 2017

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

Serum stability



Silencing activity in primary hepatocytes



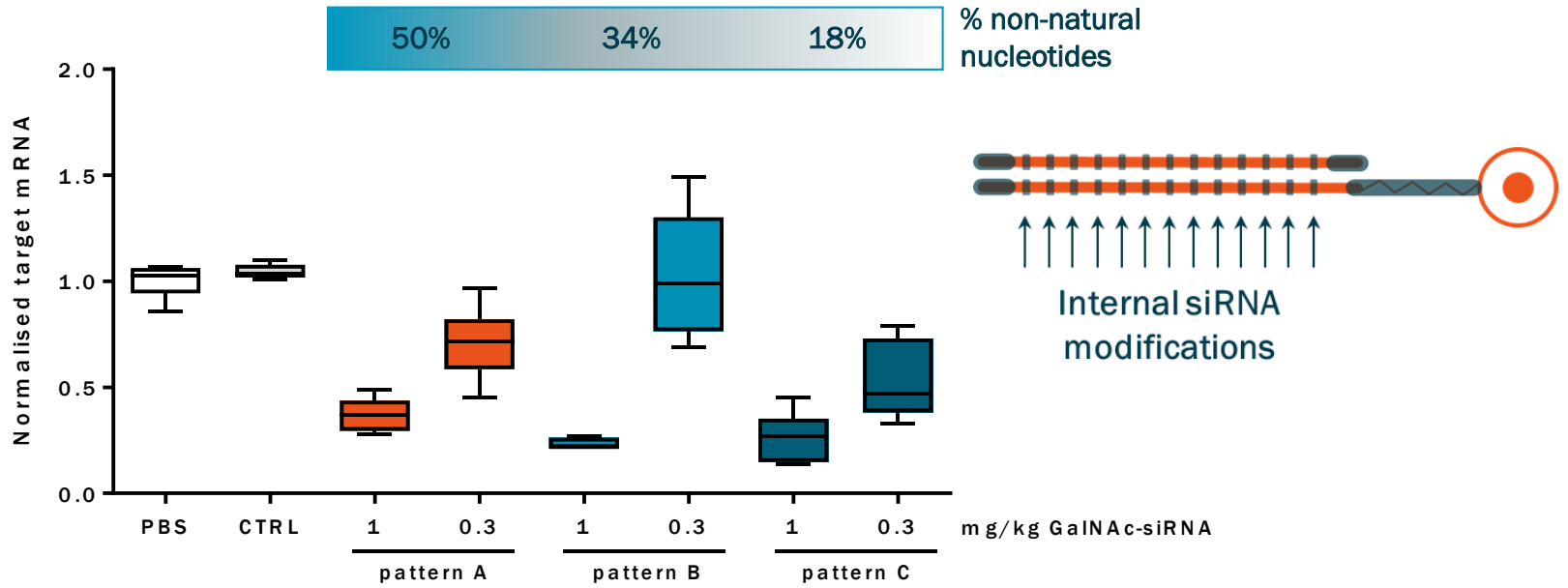
> Molecules with dramatically reduced non-natural nucleotide content retain excellent nuclease resistance and activity in primary hepatocytes

© Silence Therapeutics 2017

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

© Silence Therapeutics 2017

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

© Silence Therapeutics 2017

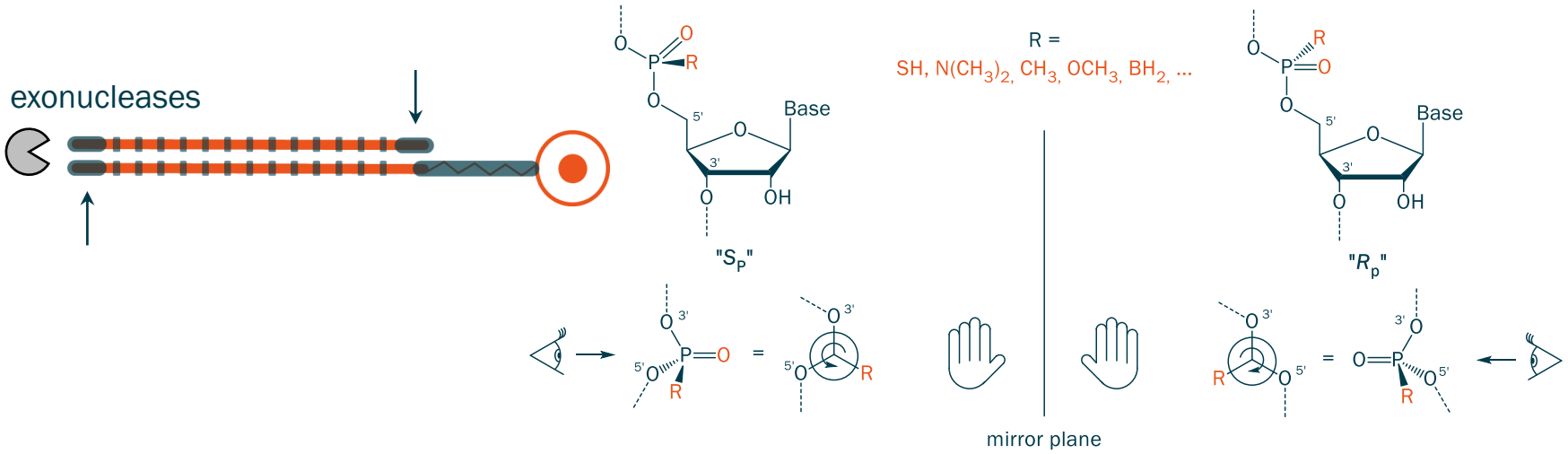
End protection against exonucleases



© Silence Therapeutics 2017

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 may add stereogenic ('chiral') centres that may increase complexity of compound manufacturing and characterisation

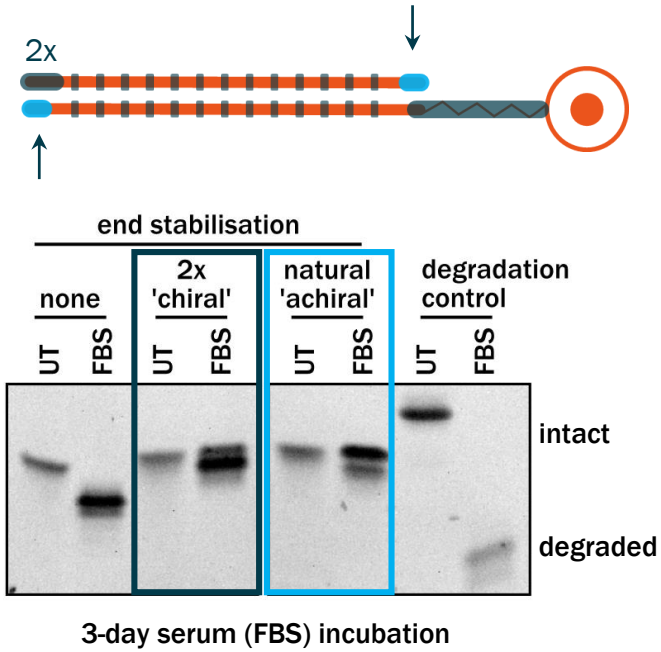


- The goal is to identify and apply **naturally occurring** moieties for the end protection, which do not add stereogenic complexity ('**achiral**')

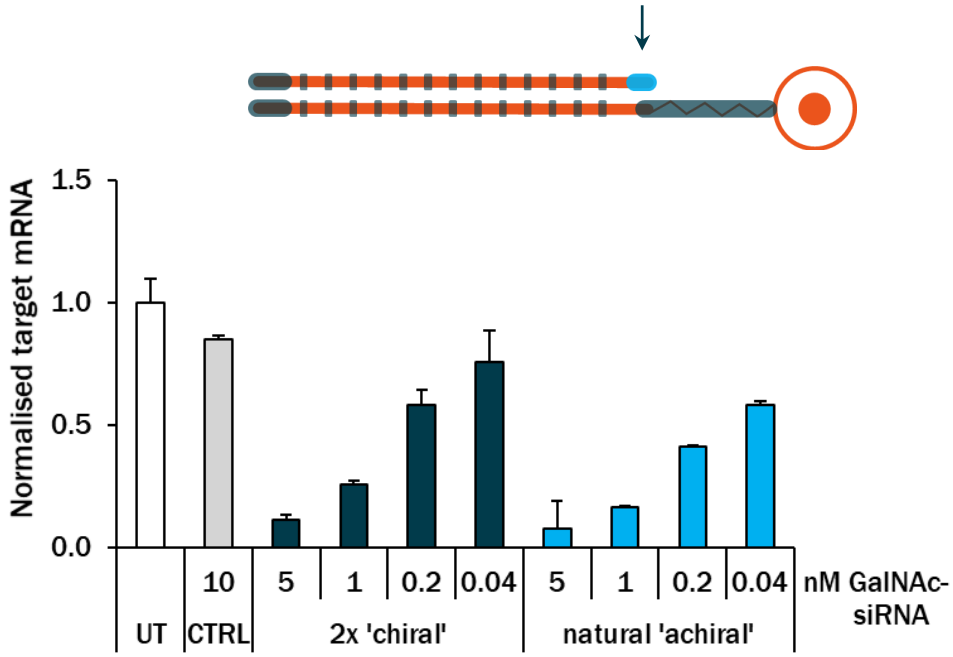
© Silence Therapeutics 2017

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

Serum stability



Silencing activity in primary hepatocytes



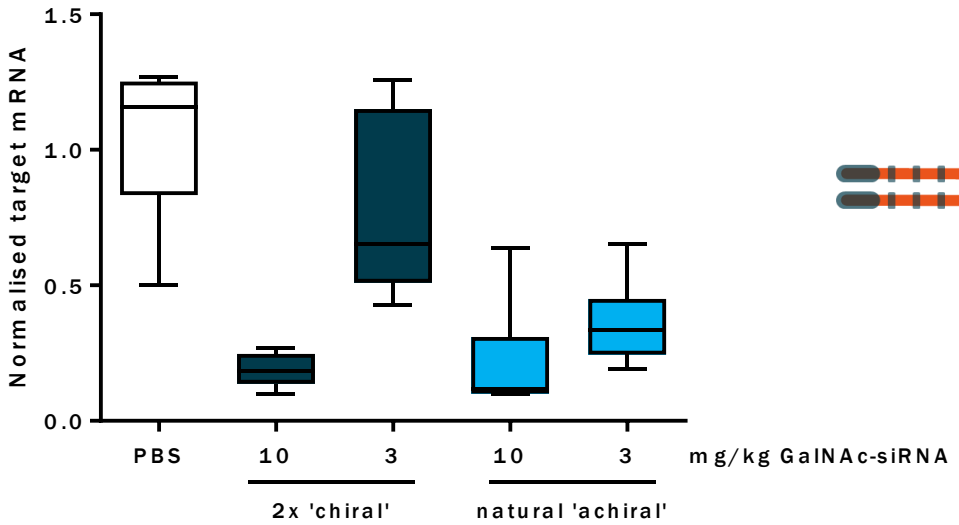
> Single naturally occurring ‘achiral’ end-protecting moieties yield increased stability and robust gene silencing activity

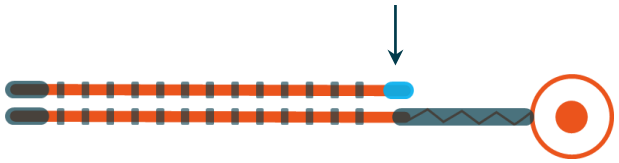
© Silence Therapeutics 2017

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



Silencing activity in mice (target mRNA in liver)





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

© Silence Therapeutics 2017

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

© Silence Therapeutics 2017

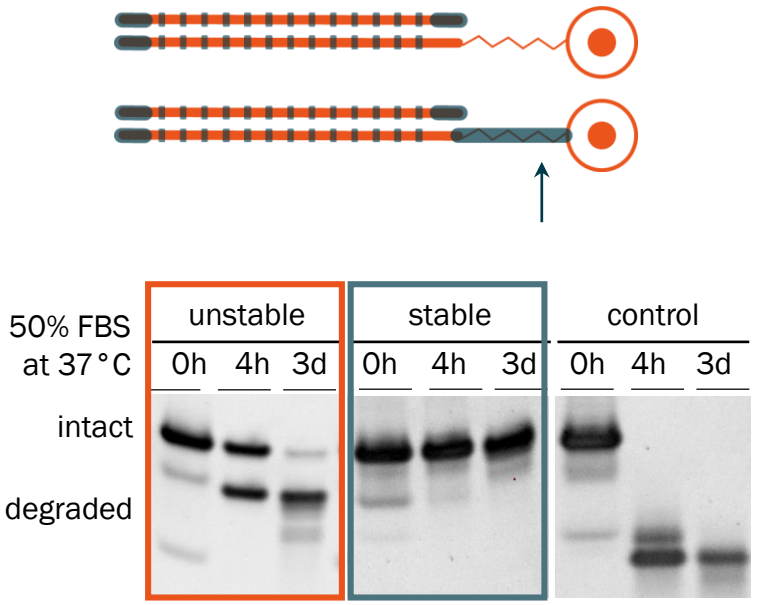
Stabilisation of the linker



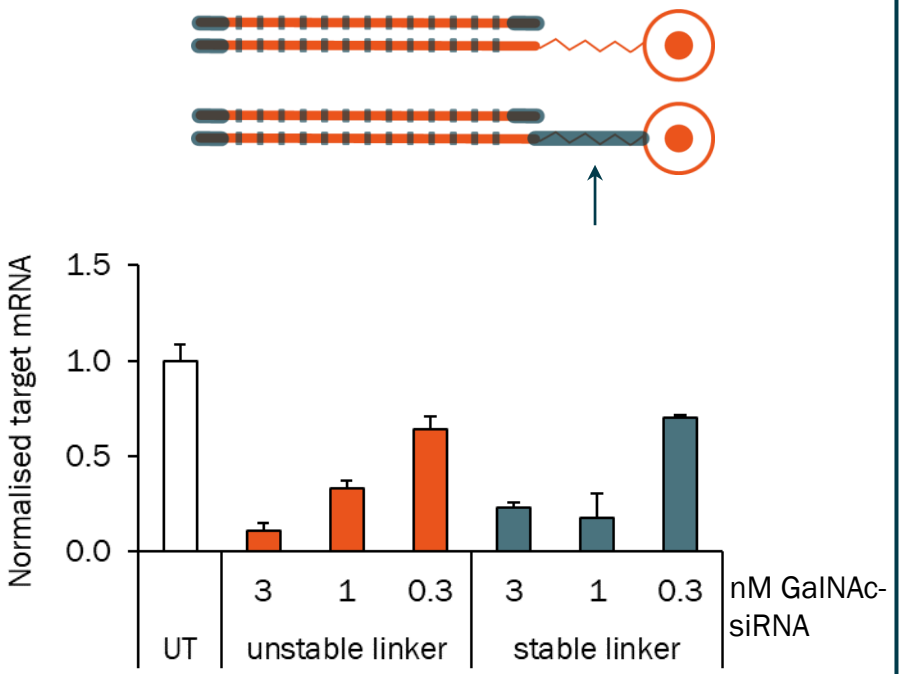
© Silence Therapeutics 2017

Performance of GalNAc-siRNA molecules with stabilised linker

Serum stability



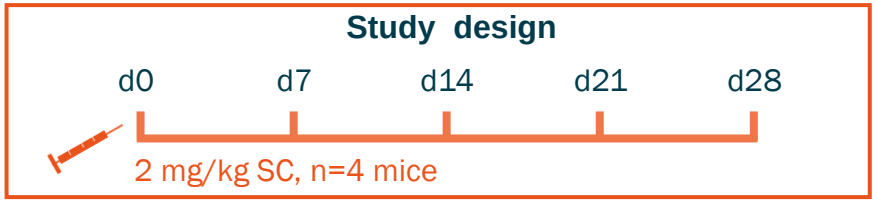
Silencing activity in primary hepatocytes



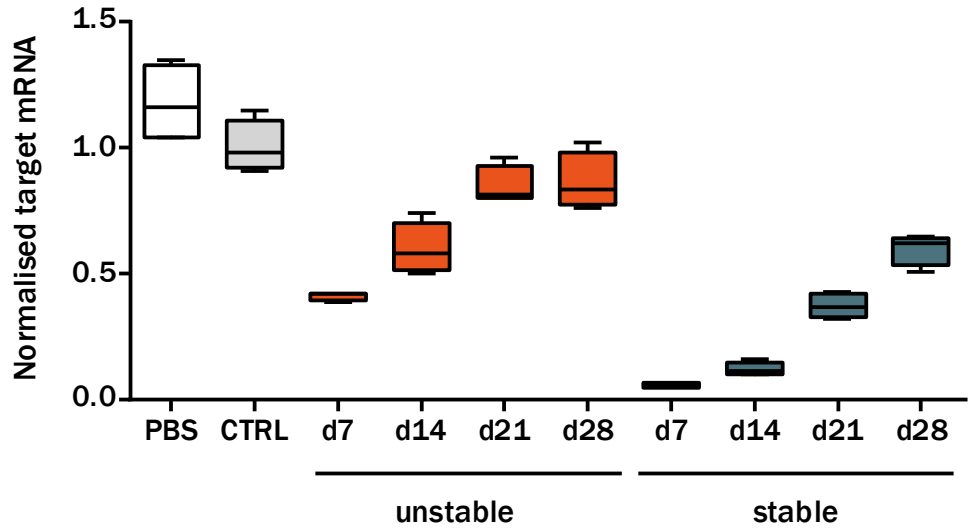
> GalNAc-siRNA with stabilised linker produces robust silencing activity in primary hepatocytes

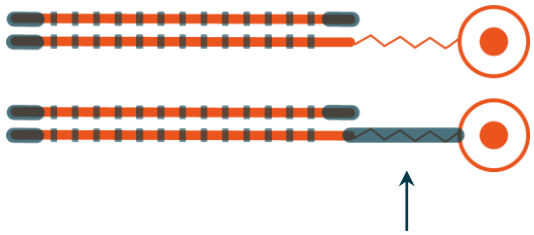
© Silence Therapeutics 2017

In vivo activity of GalNAc-siRNA molecules with stabilised linker



Silencing activity in mice (target mRNA in liver)





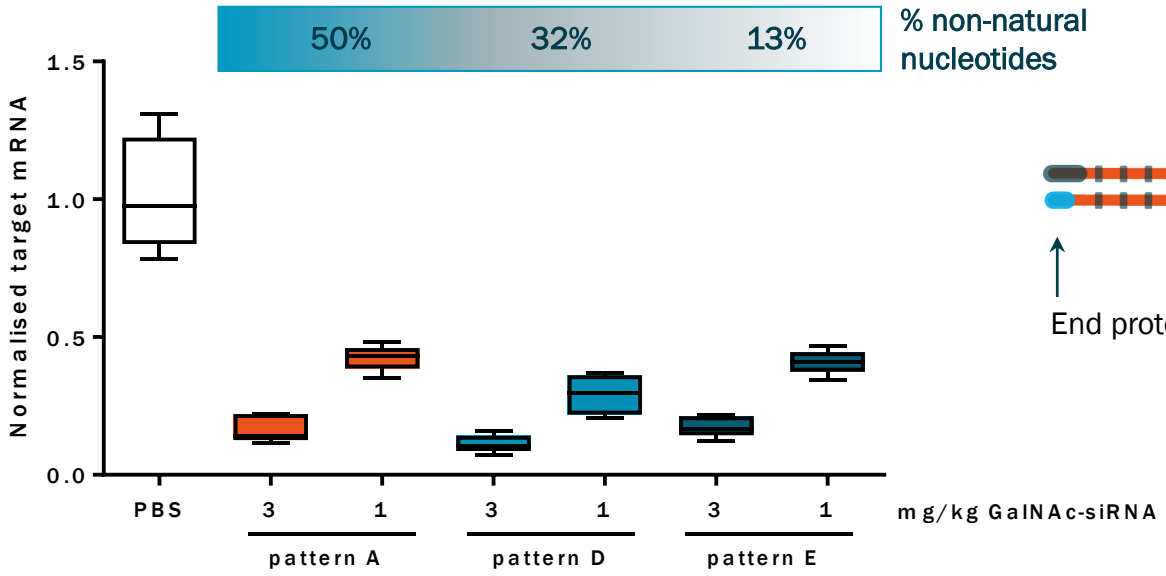
> GalNAc-siRNA with stabilised linker yields stronger and prolonged target silencing in vivo

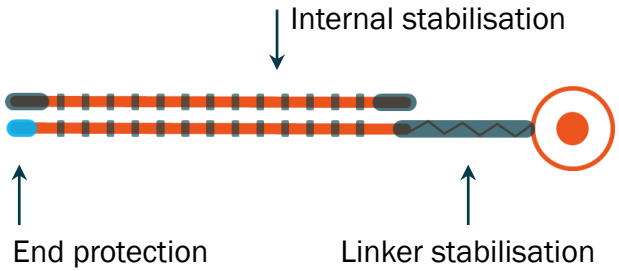
© Silence Therapeutics 2017

Combining internal GalNAc-siRNA modification, end protection and linker stabilisation



Silencing activity in mice (target mRNA in liver)





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

© Silence Therapeutics 2017

Summary – GalNAc-siRNA innovation in 2017



- Designed highly stable and potent GalNAc-siRNA molecules
- Reduced internal non-natural nucleotide content and ‘chiral’ end-protecting moieties 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
- Reduced costs of siRNA building blocks by >25%

- Supported by fundamental IP with additional patents granted in US and Europe in 2017
- 10+ additional patent applications filed

© Silence Therapeutics 2017

THANK YOU!

© Silence Therapeutics 2017