SILENCE THERAPEUTICS

Non-confidential presentation

BIO partnering

June 2018

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Silence Therapeutics' summary

Valuable Platform	> Reproducible, proprietary RNAi therapeutics platform, rapidly generating internal pipeline and diversifying out-licensing options
Haematology	> SLN124 (Beta-Thalassemia & MDS) planning to enter the clinic in early 2019 after promising efficacy signals in animal models
Strong Experienced Team	> Over 15 years of tenured oligonucleotide R&D expertise in Berlin, growing clinical team, and experienced management team in London
Target Selection	> A flexible mix of rare and large population targets with the ability to rapidly assess new targets
Strong Financial Position	> $58m of cash[1] extends runway to key clinical milestones. IP licensing provides opportunity for non-dilutive funding

HQ in London



R&D in Berlin

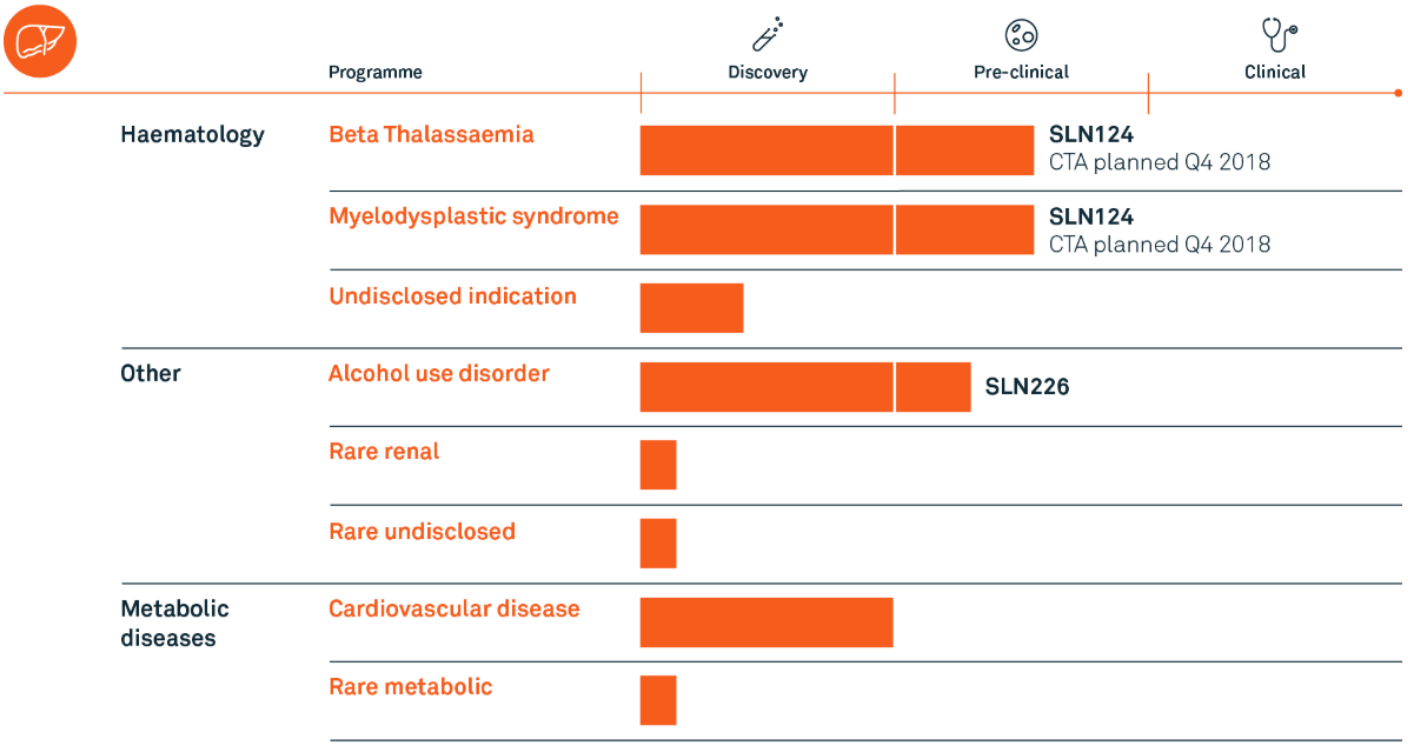


Approx. 45 employees across both sites

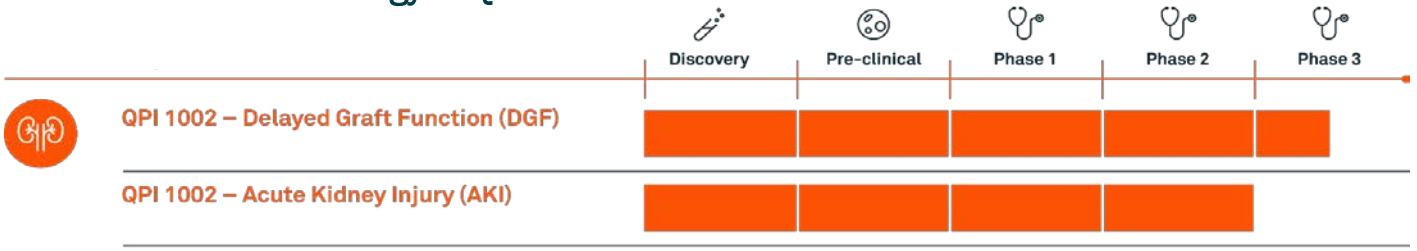
Notes: [1] As of 2nd Jan 2018

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Our pipeline

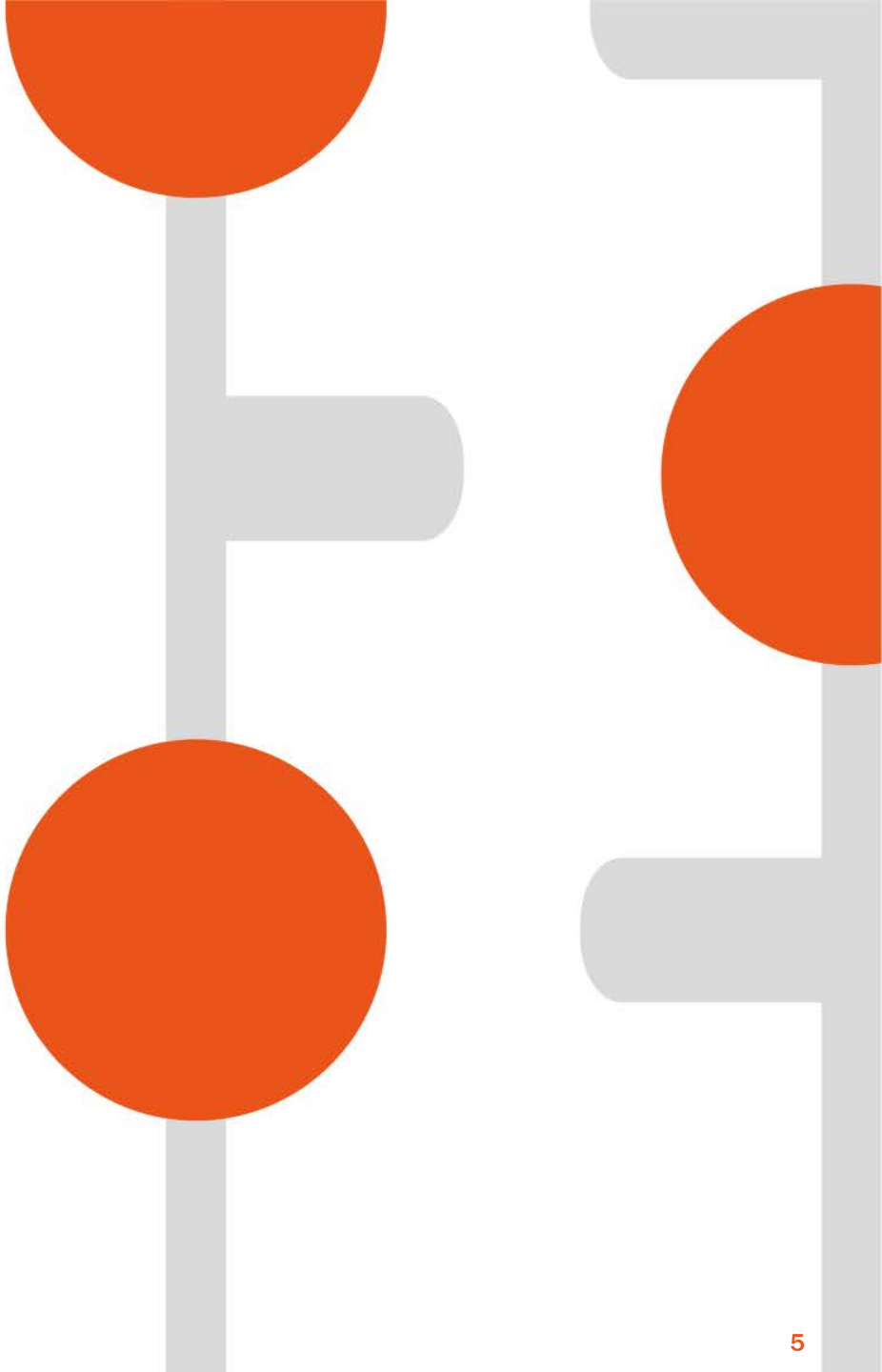


Out-Licensed Technology to Quark Pharmaceuticals



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GalNAc-siRNA Platform Technology



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R&D focused on portfolio and innovation

Technology Innovation

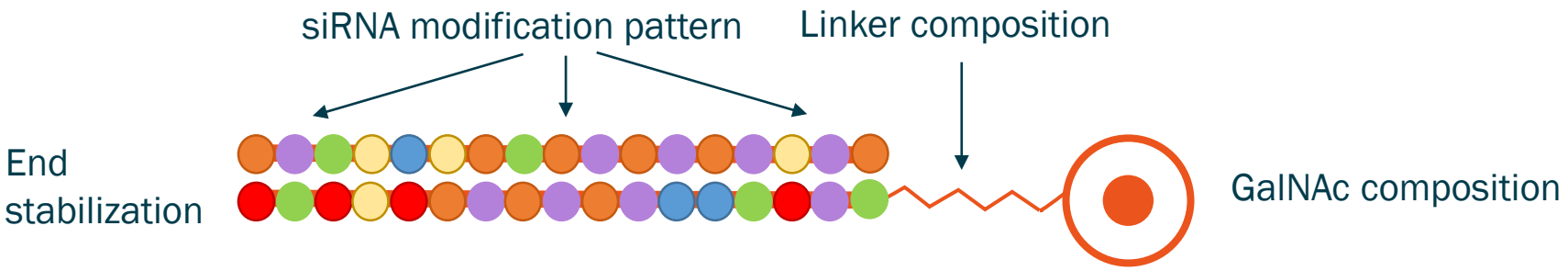
- Improve performance of our GalNAc-siRNA molecules
- Strengthen and broaden IP portfolio
- Expand RNAi horizons beyond hepatocytes
- Apply to therapeutic portfolio upon validation

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

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Fine-tuning molecular design to enhance performance



> Modification pattern: reduced number of non-natural modifications
> End stabilization: increased circulation half-life, activity and duration of action
> Linker: simplified synthesis, increased activity
> GalNAc: lower dosing via optimization of number & placement of monomers

> Gen 1 → Gen 2 → Gen 3 → Gen 4 →

Evolving a better molecule: Increasing activity & duration, lowering COGS and dosing

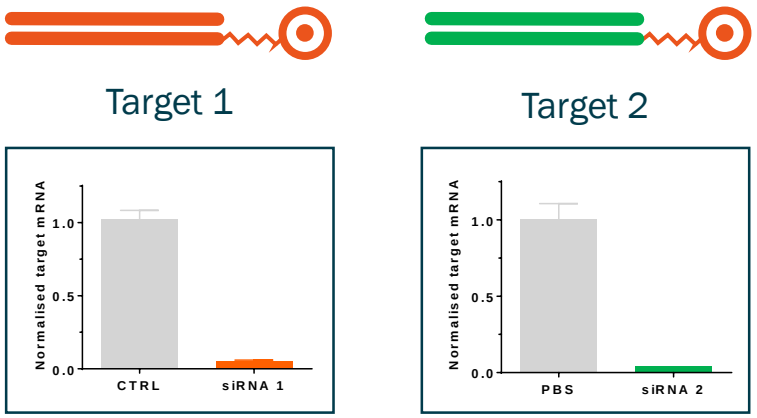
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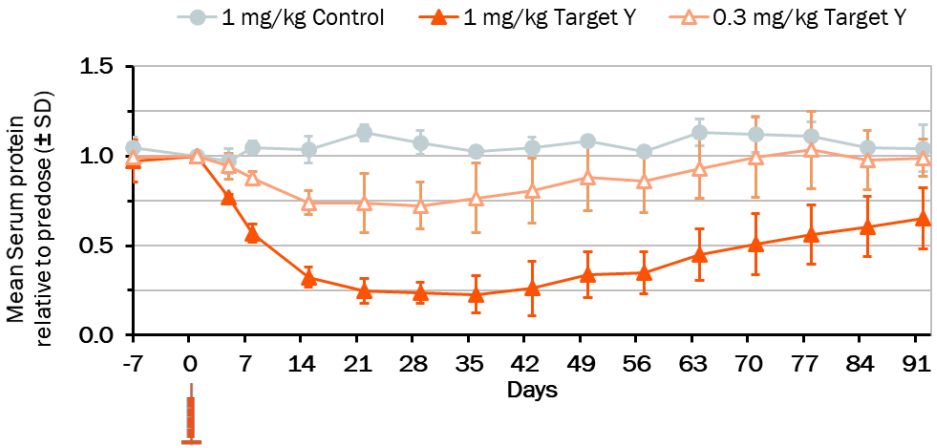
Platform performance

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

Patient friendly: Subcutaneous delivery and infrequent dosing (monthly or longer). Well tolerated.

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





Able to reproducibly and competitively silence disease-associated genes using our proprietary platform technology

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Populating our pipeline: Target selection strategy

Selection criteria

- High unmet need
- Validated target gene
- Good clinical feasibility
- Established and attractive regulatory path
- Competitive environment understood
- Strong commercial rationale
- Rare-to-common and other expansion opportunities
- Exclusion criteria: oncology, viral hepatitis, pre-natal intervention

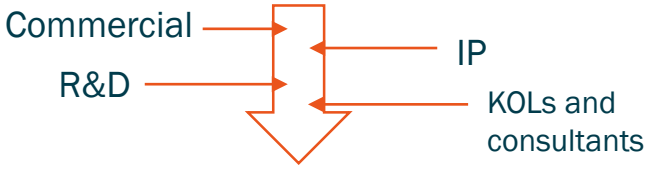
In-house

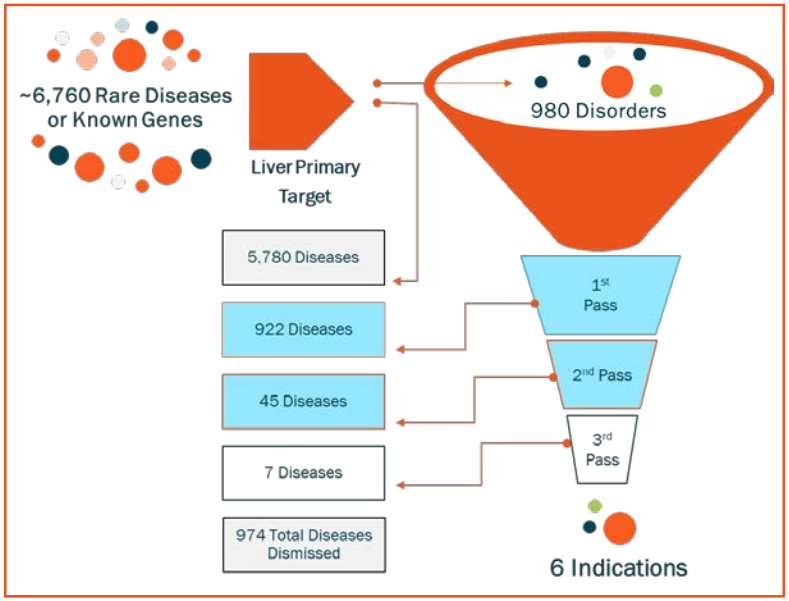
Preference to develop rare programmes internally (smaller trials, lower costs, faster timelines)

Partnering

Large markets requiring large complex clinical trials. Opportunistic strategy

Identification of high conviction target genes and indications





Internal target selection process - Example funnel

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Risk-diversified portfolio

Haematology franchise

- **SLN124:** Lead candidate for two indications (beta-Thalassemia and MDS): additional expansion potential in larger populations (Hemochromatosis)
- Developing **another candidate** in the space enables us to build on existing expertise and KOL network

Rare diseases

- **Expanding** our existing rare portfolio
- Aiming to progress through **clinical development internally**
- **Pipeline within a target:** prioritising indications with expansion opportunities

Larger indications

- Operating in indications where we can bring a **differentiated approach** and better meet patients' needs
- Objective to **partner** at the appropriate stage of development

'In silico' portfolio

- Target ideas in additional **large metabolic indications** to be explored with potential **partners**
- Further research a subset of indications that were discarded for their **risk profile** against our filters but could be of interest to partners
- Continue monitoring **literature** & working with KOL's for new ideas

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Unlocking value through our BD strategy

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

Our pipeline programmes

Collaborations, JV's and other structures

Technology platform deals

Remaining flexible – able to partner/collaborate at any stage

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SLN124

for the treatment of

Iron Overload Disorders

A case study of our platform

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Treatment of Iron Overload Disorders (IOD)

GOAL

> Provide an effective and safe novel treatment option for patients with iron overload conditions with infrequent s.c. dosing

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 (TMPRSS6) expressed in hepatocytes

CURRENT STAGE

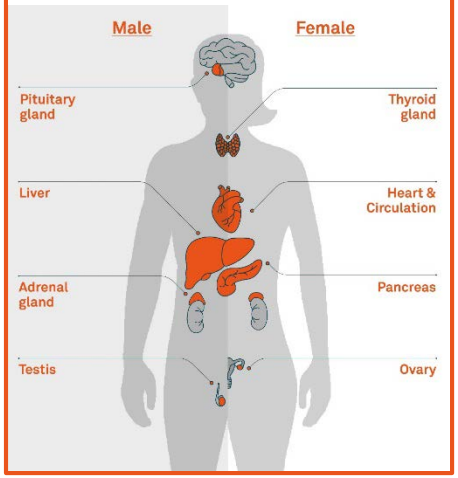
> Preclinical development with plans to enter clinical development in early 2019 after Q4 2018 CTA filing

Iron overload disorders:

> **Myelodysplastic Syndrome (MDS)**
> **β-Thalassemia**
> Hereditary Haemochromatosis
> Aplastic Anaemia
> Sideroblastic Anaemia

If untreated, iron accumulation in organs leads to severe organ damage,

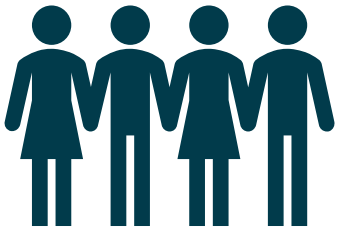
Affected organs



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Market opportunity of SLN124

US and EU patients



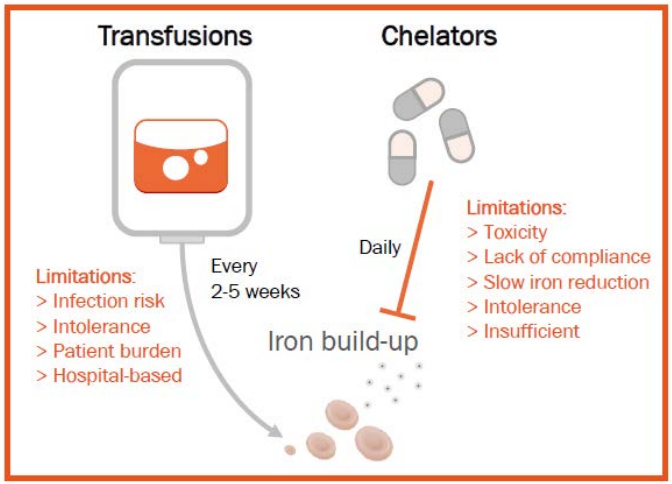
β-Thalassemia

~40,000 TDT
~20,000 NTDT

MDS

>100,000

Standard of Care



Benefits of SLN124

SLN124 aims to:

1. Reduce organ iron levels &
2. Enhance erythropoiesis

↓

Reduced transfusion frequency &
Secondary iron overload burden

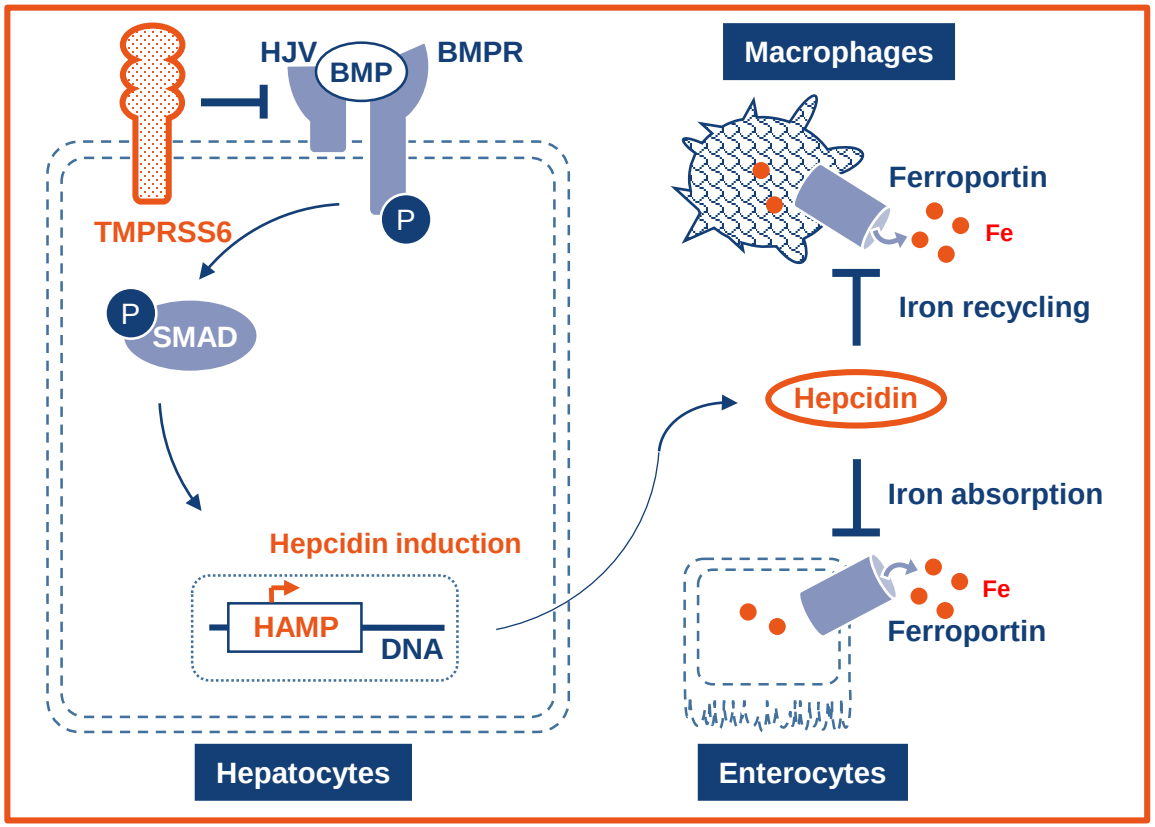
Advantages v Competition

- Quality of Life
- Safety
- Organ iron levels
- Compliance
- Less frequent dosing

- SoC: Transfusions + Chelators
- Antisense RNA
- Luspatercept
- Gene therapy
- Hepcidin mimetics

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SLN124 mechanism of action



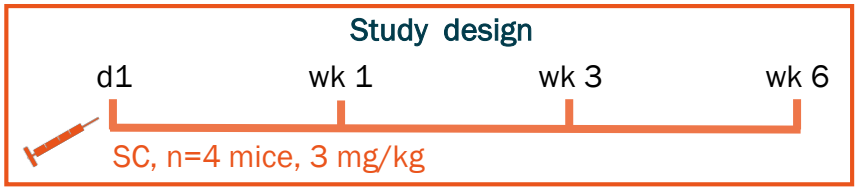
- **TMPRSS6** (Transmembrane Protease, Serine 6) is a negative regulator of the BMP/SMAD signaling pathway
- Inhibition of TMPRSS6 in hepatocytes induces Hepcidin expression
- Hepcidin reduces absorption of dietary iron and the release of iron from cellular storage, thereby reducing circulatory iron levels
- The liver is the predominant source of Hepcidin

Silencing TMPRSS6

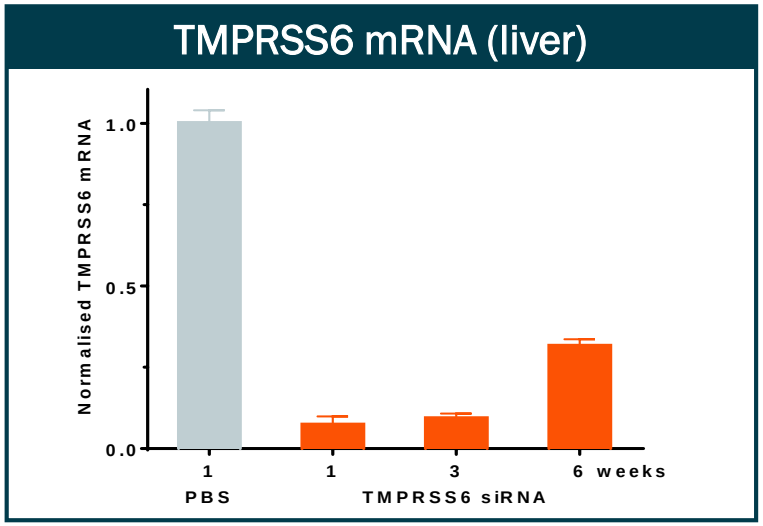
1. Increases Hepcidin levels
2. Reduces iron levels
3. Improves erythropoiesis
4. Reduces anaemia & iron overload

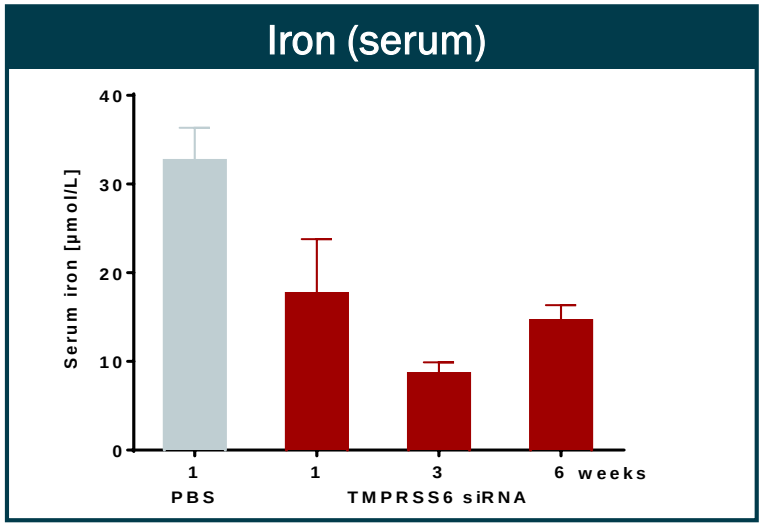
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SLN124 lowers iron levels for at least 6 weeks after single administration in mice









> Long-lasting functional mRNA KD in liver

> Reduction of serum iron levels for at least 6 weeks

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

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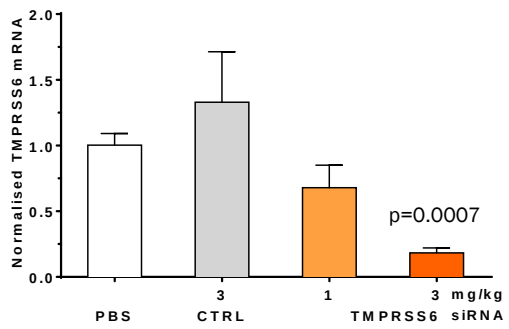
Therapeutic activity of SLN124 in a disease model of hereditary haemochromatosis (HFE$^{-/-}$ mice)

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

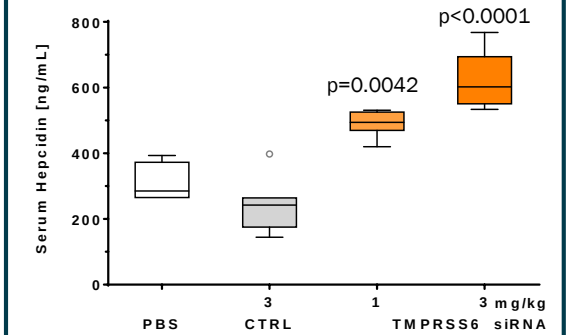
Study design



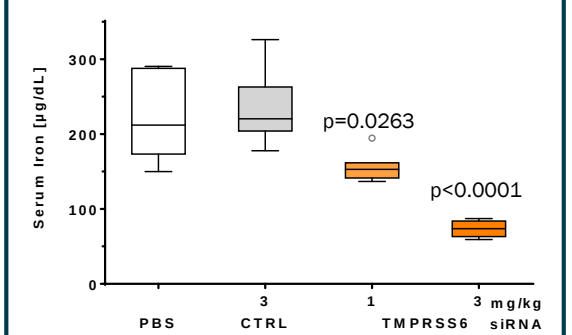
TMPRSS6 mRNA (liver)



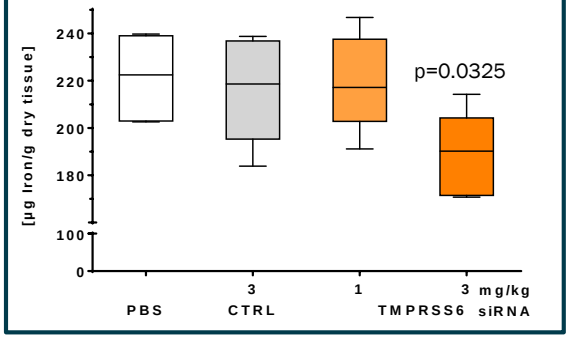
Hepcidin (serum)



Iron (serum)



Iron (kidney)



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



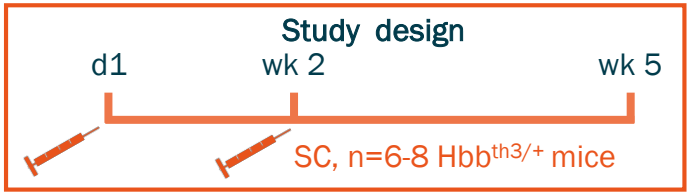
Kruskal-Wallis test with uncorrected Dunn's test against non-targeting control CTRL

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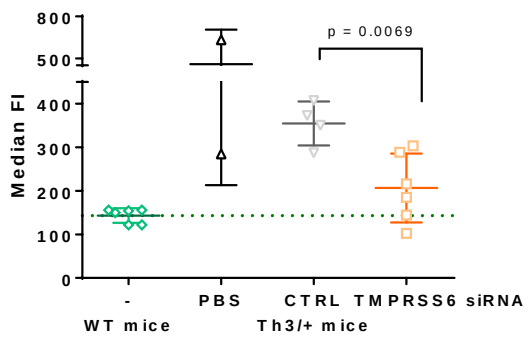
SLN124 reduces ROS and improves RBC parameters in a b-Thalassemia disease model

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

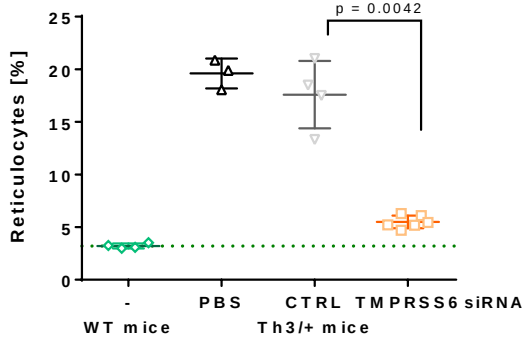
HUDSON INSTITUTE OF MEDICAL RESEARCH



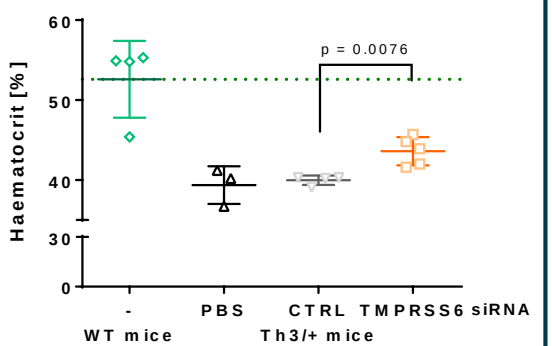
Reactive oxygen species (ROS)



Reticulocyte proportion



Haematocrit



> Reduction 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

Proof of Concept

ROS = reactive oxygen species; RBC = red blood cells

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Upcoming corporate milestones (2018)



- SLN124: file CTA in Q4 2018
- Add new targets to pipeline utilising next generation technology
- Add further clinical development expertise to the senior team as pipeline progresses
- Secure further validating collaborations utilising our GalNAc platform technology
- UK litigation action against Alnylam: court date in December 2018

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