SILENCE THERAPEUTICS

Silence Therapeutics
Corporate Presentation

January 2020

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Silence Therapeutics - Summary

Valuable Platform	> Reproducible, proprietary gene silencing (RNAi) therapeutics platform, rapidly generating internal pipeline and out-licensing options. Platform validated through collaborations with Mallinckrodt and Takeda
Growing Clinical Pipeline	> SLN124 (β-Thalassemia and MDS[1]) - Phase Ib trial underway > SLN360 (CVD with high LP(a)) - IND/CTA in H2 2020 > SLN500 (C3) - IND/CTA in 2021
Strong Experienced Team	> Pioneers in siRNA for over 18 years, growing clinical team, and experienced biopharma Board and Management team > New CEO recruitment ongoing
Target Selection	> Focused on targeting indications in rare diseases and large population targets, including new medicines for cardiovascular disease and complement-mediated diseases
Strong Financial Position	> $44m of cash[2] extends runway to key clinical milestones such as SLN360 and SLN124 Phase I trial readouts

HQ in London



R&D in Berlin



Approx. 45 employees across both sites

Notes:
[1] MDS = Myelodysplastic syndrome
[2] Unaudited, 31st Dec 2019, £=$1.32

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2019 Accomplishments & 2020 Outlook

2019

SLN124
Phase Ib CTA filed.
Several sites open and recruiting.
Orphan drug designation granted by EMA for β-Thalassemia.

SLN360
Pre-IND meeting held with FDA in Dec.
IND-enabling studies progressing well.

MNK collaboration
SLN500 partnered in July, targeting C3 for complement-mediated diseases.
1st $2m milestone met in Sep.

Strengthened team
Management team strengthened with several new hires, including Giles Campion as Head R&D and CMO.

Cash - $44m at ye
Balance sheet solidified with $27m from MNK.
Cash into 2021 and clinical readouts for SLN124 and SLN360.

RNAi momentum
1st GalNAc siRNA approved by the FDA (Givosiran – Alnylam).
The Medicines Co (Inclisiran) acquired by Novartis for c.$9Bn.

2020

SLN124
First patient dosed expected in Q1 2020.
On track to report interim results in H2 2020.

SLN360
On track for IND/CTA in H2 2020.
Expect First Patient dosed shortly afterwards.

MNK Collaboration
SLN500 lead candidate in H1 2020.
Potential for MNK to license up to two further targets.

People
Recruitment of new CEO ongoing.
Scientific Advisory Board (SAB) to be formed - led by Sir Gordon Duff.

BD opportunities
Technology Evaluation Agreement with Takeda signed in Jan.
Targeting further platform deals to leverage our technology.

Corporate
Given our increased US focus, a US subsidiary to be formed during 2020.

CTA: Clinical Trial Application. IND: Investigational New Drug. EMA: European Medicines Agency. MNK: Mallinckrodt Pharmaceuticals

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Leadership

Interim Executive Chairman
Iain Ross

- Appointed as Chairman in April 2019 and Executive Chairman in Dec 2019 until new CEO is appointed
- Over 40 years' experience in the international life sciences and technology sectors, where he has completed multiple financing transactions, multiple IPOs and has over 25 years in cross-border management as Chairman and CEO



Head R&D, CMO
Giles Campion

- Former Chief Medical Officer and SVP R&D at Prosensa (2009-2016), playing a major role in their Nasdaq IPO and subsequent sale to Biomarin for $680m
- Most recently CMO at Albumedix
- Spent 4 years in senior R&D roles at Novartis
- Medical degree and doctorate from Bristol University



CFO
Rob Quinn

- Chartered accountancy training at Deloitte before joining GSK
- Area Finance Director for Africa and Developing Countries at GSK
- Joined Silence in early 2017 as Head FP&A
- PhD in Biochemistry from the University of Manchester



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Experienced Broader Management Team

Head of Manufacturing
Jorgen Wittendorff

- Over 25 years' experience in the development of pharmaceutical products
- Most recently Senior Director, CMC Manufacturing and Supply at Ablynx, prior to acquisition by Sanofi



Head of HR
Linnea Elrington

- Experienced HR professional. Formerly Global Head of Organization Development at Glory Global Solutions
- Earlier served in senior HR roles at Deloitte
- Chartered member of the Institute of Personnel and Development



Head of BD
John Strafford

- Broad experience in biotech, management consulting and specialty pharma. Including Advanz Pharma, Navigant and Antisoma
- PhD in Biochemical Engineering from University College London



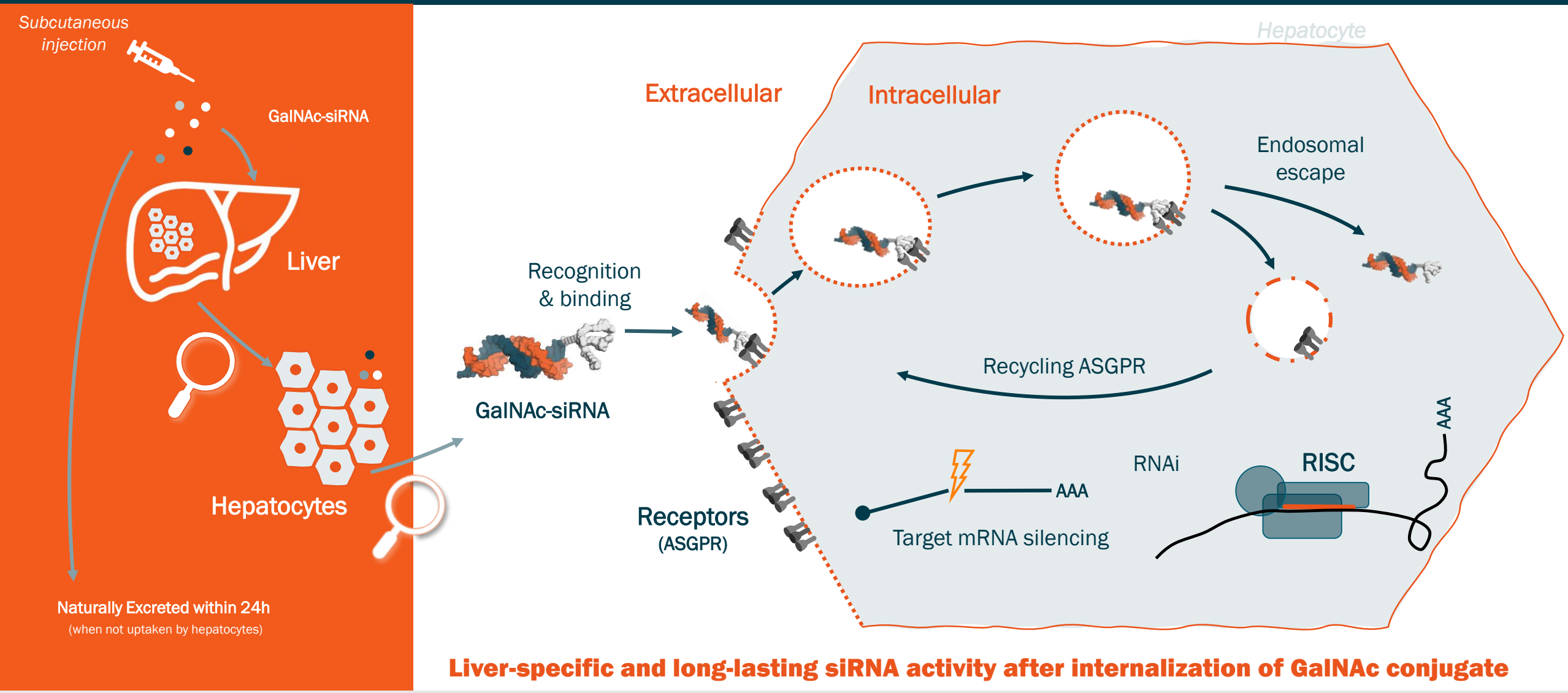
General Counsel
Barbara Ruskin

- GC and Chief Patent Officer
- Over 25 years' experience in IP and corporate law, including as Partner at Ropes & Gray and GC roles at Bionor and MTEM
- PhD in Biochemistry from Harvard University



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GalNAc (Ligand) Conjugation Allows for Delivery of siRNA to Liver Cells



Liver-specific and long-lasting siRNA activity after internalization of GalNAc conjugate

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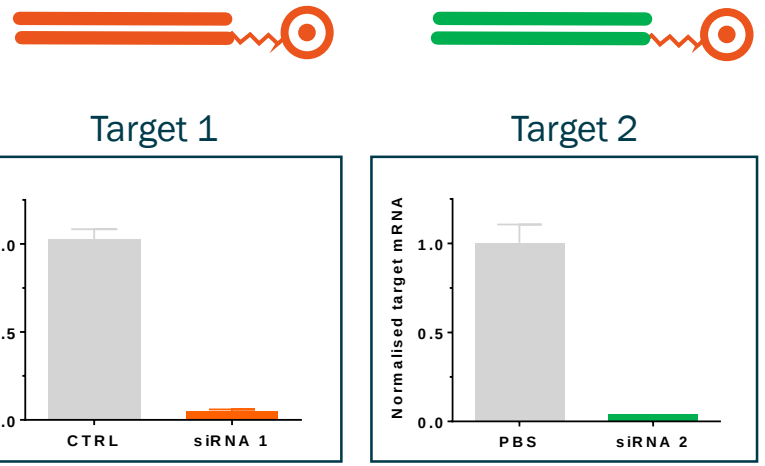
Reproducibly Silencing Disease-Associated Genes Using our Proprietary Platform Technology

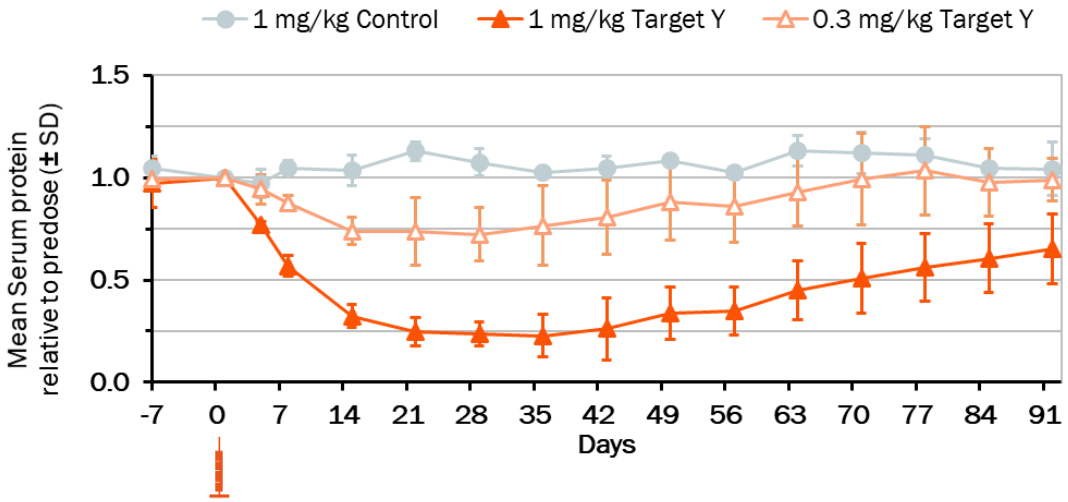
Platform delivery technology: GalNAc-siRNA able to mediate highly specific gene silencing in hepatocytes (liver) – "Specificity upon specificity".

Patient friendly: Subcutaneous delivery and infrequent dosing (monthly or longer). Well tolerated[1].

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

[1] Well tolerated in animal models tested.

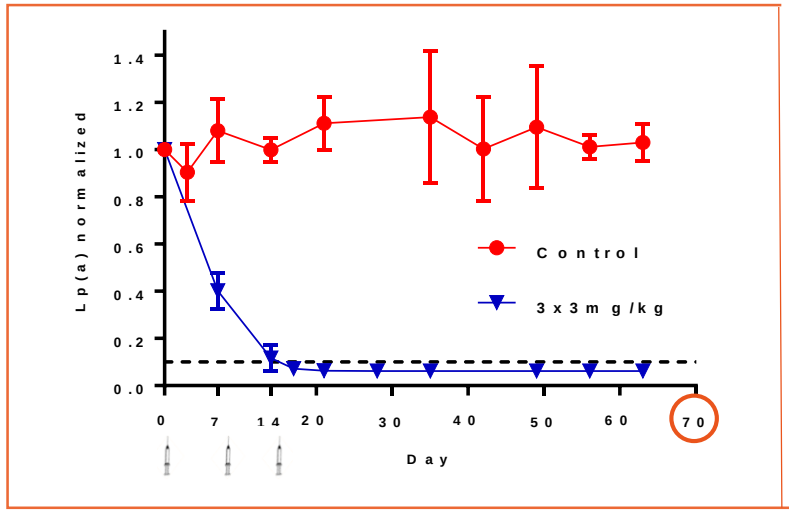




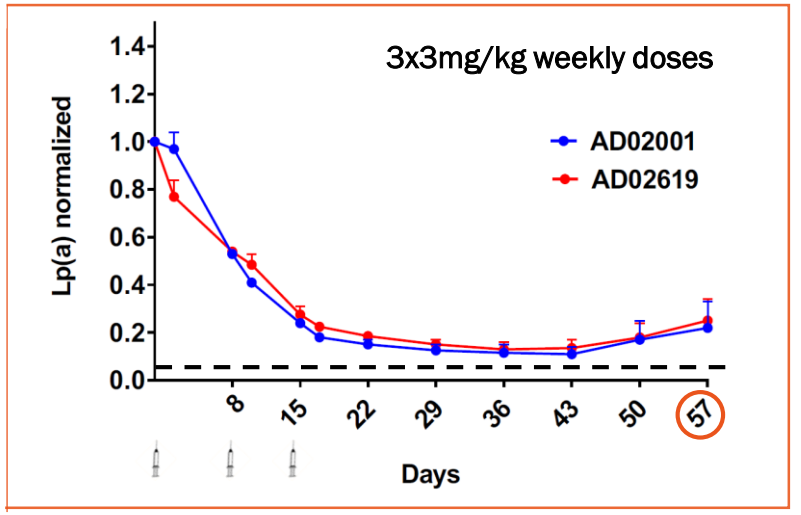
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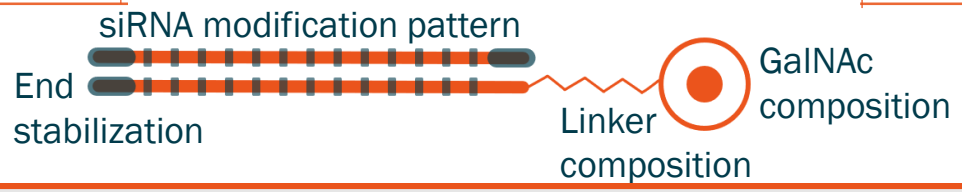
A Competitive Platform, With Continuous Fine-Tuning to Further Improve Performance

SLN360



AMG 890



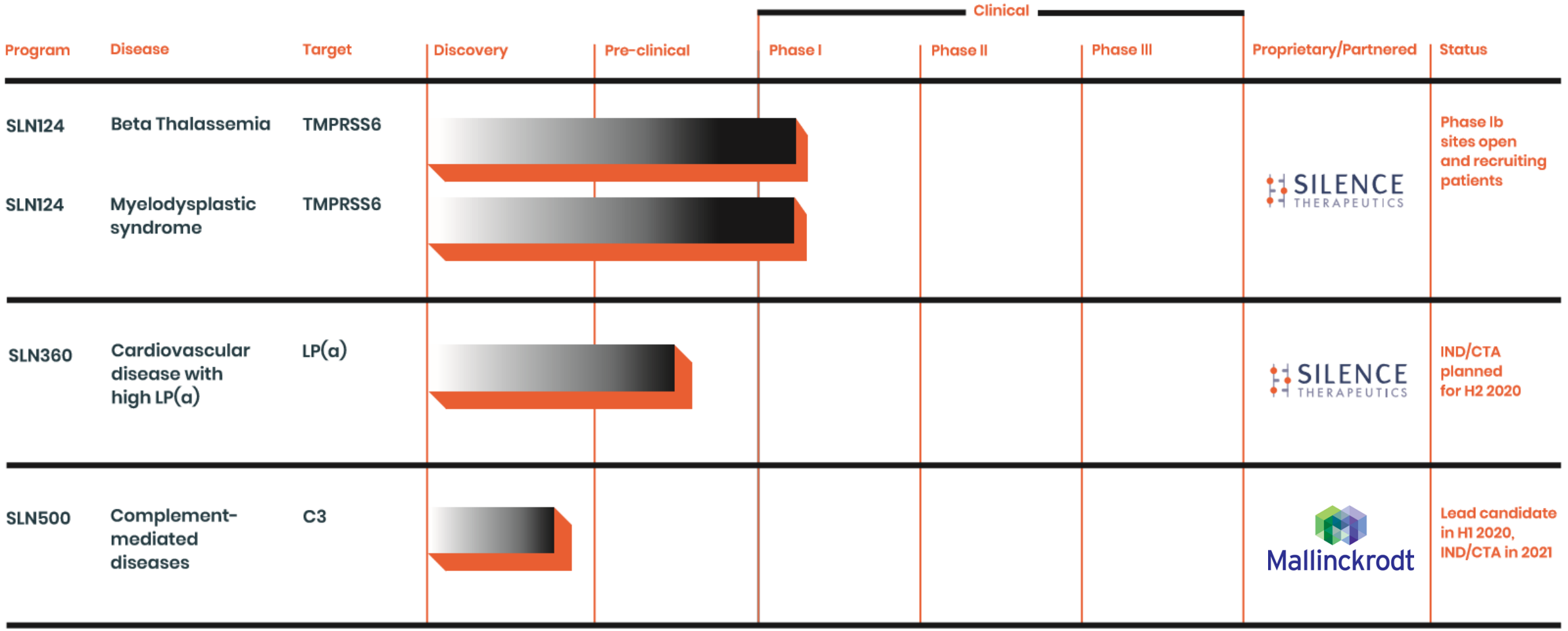


- **Modification pattern**: number of non-natural modifications reduced from c.50% to <15% through the discovery of novel modification patterns
- **End stabilization:** increased circulation half-life, increased activity and duration of action
- **Linker:** simplified and flexible synthesis, increased activity, and option to control circulation and intracellular half-life
- **GalNAc:** 2-3 fold increase in activity achieved through optimization of number and placement of GalNAc units
- **IP:** 10 siRNA chemistry patent applications filed 2017-2019

AMG 890 chart reproduced from Melquist et al "Targeting apolipoprotein(a) with a novel RNAi delivery platform as a prophylactic treatment to reduce risk of cardiovascular events in individuals with elevated lipoprotein(a)" AHA 2016 Scientific Sessions

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Development Pipeline



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Our siRNA Platform is Validated Through Strategic Partnerships with Leading Pharma Companies

January 2020 – Silence Therapeutics entered into a Technology Evaluation Agreement with Takeda to explore the potential of Silence's platform to generate siRNA molecules against a novel, undisclosed target discovered by Takeda.

> Takeda will provide Silence with single-digit millions USD of research funding

> Silence and Takeda have further agreed to negotiate the terms of a License Agreement should the initial evaluation study prove successful

July 2019 - Silence Therapeutics entered into a Research and Collaboration Agreement with Mallinckrodt for the development of RNAi therapeutics targeting the complement system. The agreement included SLN500, Silence's preclinical asset targeting C3, and options on two further complement targets.

> $20 million cash upfront and $5 million equity investment

> Total deal value $2.1 billion – up to $673 million in milestones for SLN500 and up to $713 million in milestones for each additional target

> Silence will be responsible for development activities until the end of Phase 1, after which Mallinckrodt will assume clinical development and responsibility for global commercialization

> Mallinckrodt will cover the costs of the Phase 1 study and GMP manufacture

> Low double-digit to high-teen royalties on net sales for SLN500 and each optioned asset

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SLN124
for the treatment of

Iron Overload Disorders



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Market Opportunity of SLN124

US and EU patients

β-Thalassemia

~40,000 TDT[1]
~20,000 NTDT[2]

Onset: from birth, but notable incidence of NTDT beyond 35

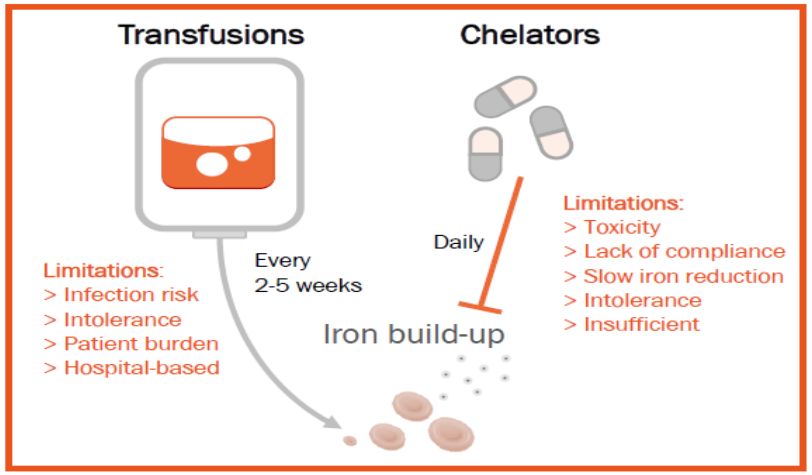
MDS[3]

>100,000

Onset: Typically >70y

Orphan indications

Standard of Care



Benefits of SLN124

SLN124 aims to:

1. Reduce organ iron levels &
2. Enhance erythropoiesis

↓

Reduced transfusion frequency &
Secondary iron overload burden

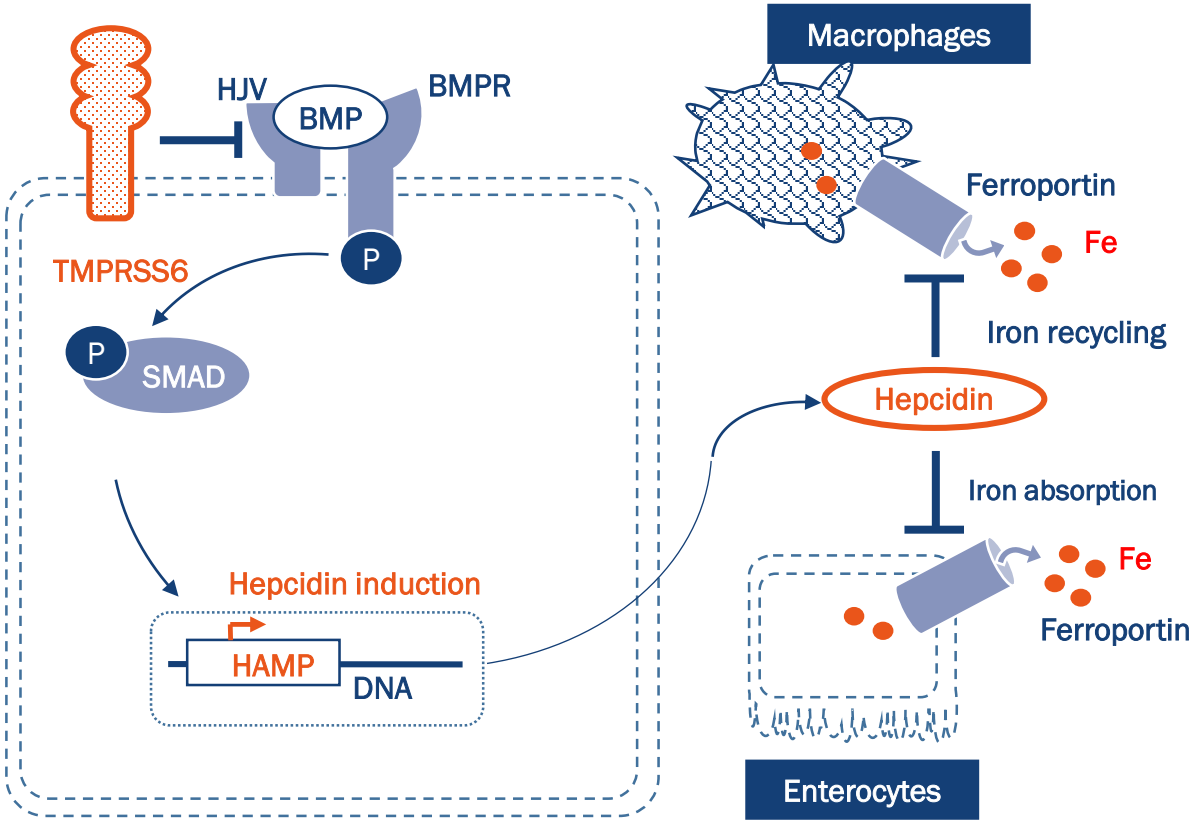
Advantages v Competition

Advantages	Competition
Quality of Life	**SoC:** Transfusions + Chelators
Safety	Antisense RNA
Organ iron levels	Luspatercept
Compliance	Gene therapy
Less frequent dosing	Hepcidin mimetics

Notes: 1 TDT = Transfusion Dependent Thalassemia 2 NTDT = Non Transfusion Dependent Thalassemia 3 MDS = Myelodysplastic Syndrome

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SLN124 Mechanism of Action: Increasing Hepcidin by Silencing its Repressor TMPRSS6



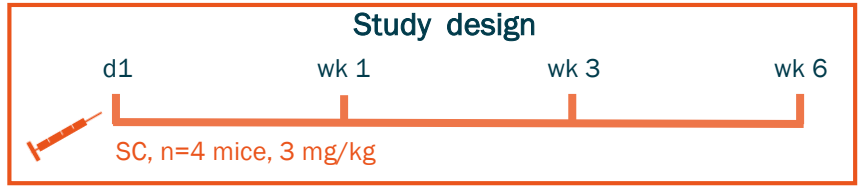
- **TMPRSS6** (Transmembrane Protease Serine 6) is a negative regulator of the BMP/SMAD signaling pathway
- Inhibition of TMPRSS6 in hepatocytes induces hepcidin expression
- Hepcidin reduces absorption of dietary iron and the release of iron from cellular storage, thereby reducing circulatory iron levels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

Silencing TMPRSS6

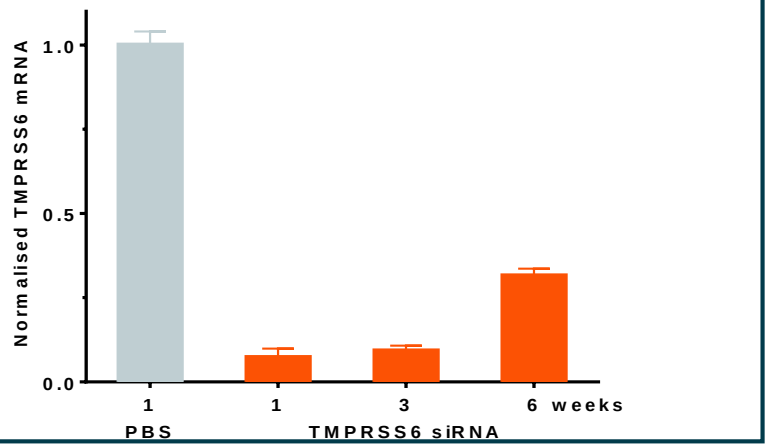
1. Increases hepcidin levels
2. Reduces iron levels
3. Improves erythropoiesis
4. Reduces anemia & iron overload

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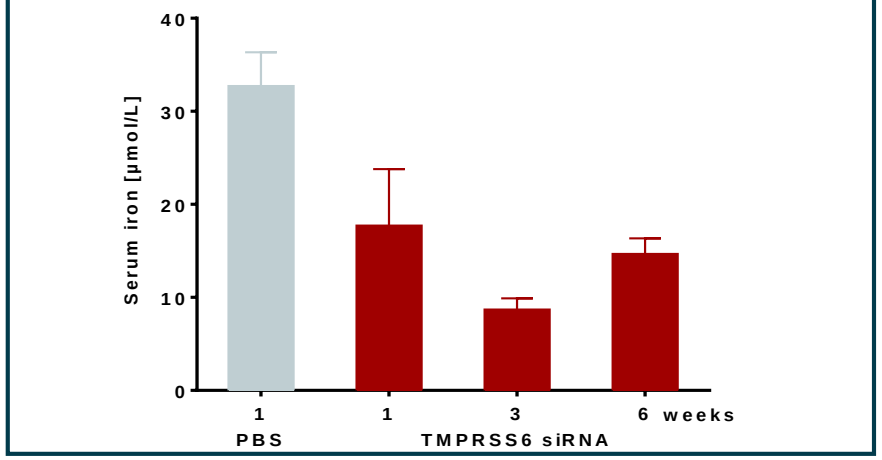
SLN124 Lowers Iron levels for at Least 6 Weeks After Single Administration in Mice



TMPRSS6 mRNA (liver)



Iron (serum)



- 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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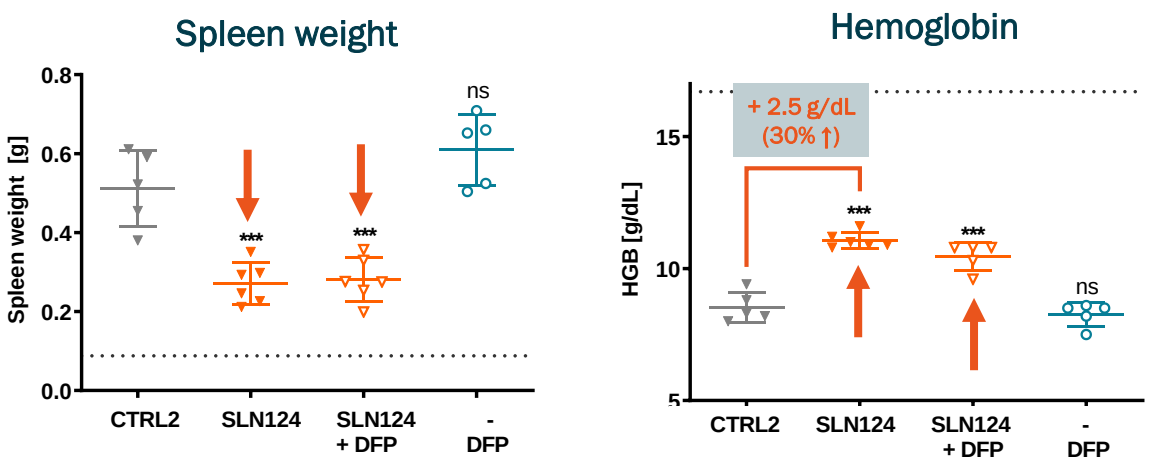
SLN124 Ameliorates Splenomegaly and Improves Anemia in β-Thalassemic Mice

Study design

$Hbb^{th3/+}$ mice, 2-4 m, n=5-8
2x 3mg/kg SLN124 s.c.
1.25 mg/ml deferiprone in drinking water



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



DFP = Deferiprone; CTRL2 = control siRNA

Levels of PBS-treated wild-type mice

- **Hb ↑ by ≥1.5 g/dL defined as "clinically relevant effect"**[1]
- No Δ Hb with 5-weeks DFP exposure
- ↓ need for blood transfusions by ↑ Hb (reflects 2-3 units of RBC)[2]

> SLN124 ameliorates splenomegaly; no impact by iron chelator DFP
> SLN124 improves anemia and ↓ the need for RBC transfusions
> No effect by DFP alone, SLN124 effect maintained in the presence of DFP

[1]Platzbecker et al., Blood 2019; [2]Bosch et al., Vox Sang 2017

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SLN124 Reduces Liver Iron Levels and Restores Normal Spleen Architecture in β-Thalassemic Mice

Study design

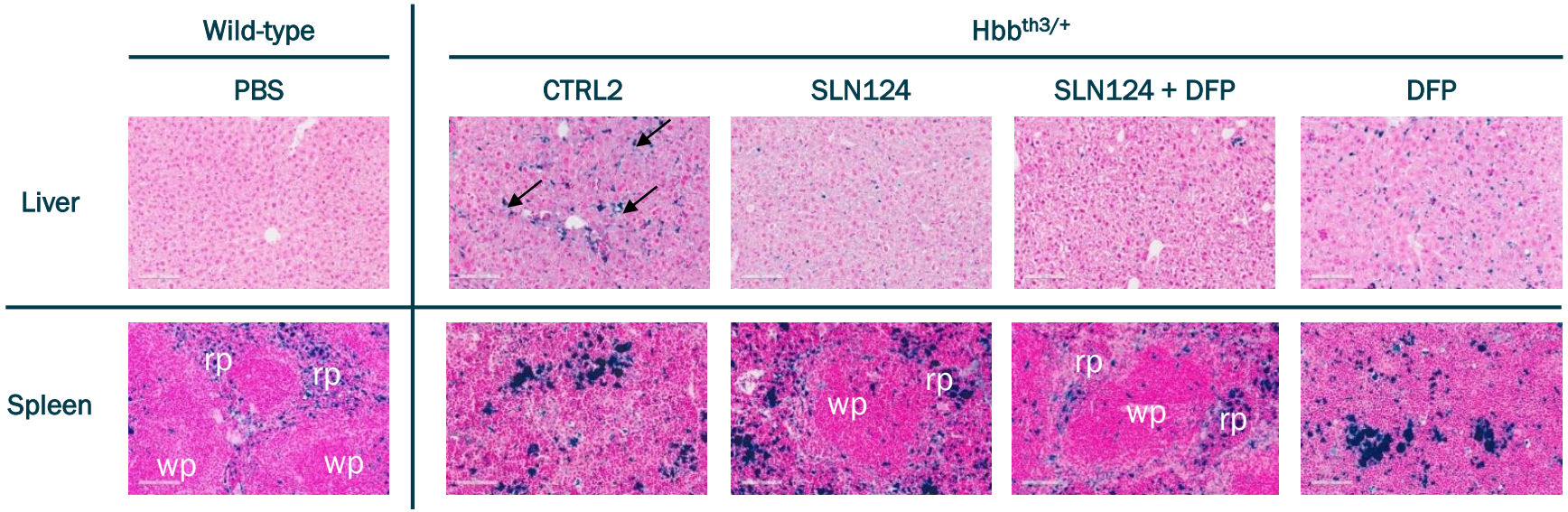
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Collaboration with
Dr. J. Vadolas & Dr. G. Grigoriadis
Monash Medical Centre/Melbourne, Australia

HUDSON INSTITUTE OF MEDICAL RESEARCH

Iron detection in tissue sections (visualized by Pearl's Prussian Blue)



20x magnification; blue deposits indicate iron, see arrow; DFP = Deferiprone; CTRL2 = control siRNA; rp = red pulp, wp = white pulp

> SLN124 prevents iron overload in the liver

> SLN124 restores splenic architecture, but DFP has no effect

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Multicentre, Randomized, Placebo Controlled Phase Ib in 2020

This is a two part first-in-human, multicenter, randomized placebo controlled single ascending and multiple dose study to assess the preliminary safety, tolerability, PK and efficacy of SLN124 administered subcutaneously for the treatment of non-transfusion dependent thalassemia and low risk myelodysplastic syndrome.

Study design

> Part A:

- Single dose escalation study to evaluate the dose response to SLN124 with a view to identify the most appropriate dose to bring forward into the multiple dose portion of the study
- Primary aim to determine the safety and tolerability of SLN124 for the treatment of non-transfusion dependent β-thalassemia

> Part B:

- Bring forward the most efficacious and best tolerated dose to evaluate multiple administrations of SLN124 on hematinic parameters in patients with β-thalassemia and MDS
- Primary aim to determine the safety and tolerability of multiple doses of SLN124 for the treatment of non-transfusion dependent β-thalassemia and low risk myelodysplastic syndrome

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SLN124 Summary

- **Preclinical package:** Robust data generated in several disease models.
- **Status:** Clinical Trial Application approved in UK (MHRA), Bulgaria (BDA), Germany (BfArM) and Turkey. First patients expected to enter a Phase Ib study in Q1 2020. Orphan Designation granted for β-Thalassemia.
- **Clinical plans:** Phase Ib in patients (β-Thalassemia and MDS). Network of KOLs established.
- **Dosing regimen:** Patient-friendly, with monthly or less frequent dosing expected and subcutaneous administration route.
- **Regulatory**: Positive feedback received at Scientific Advice meetings with both the UK (MHRA) and German (BfArM) national regulators.
- SLN124 is well positioned for **commercial success** against current standard of care and other medicines in development.

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SLN360
for the treatment of

Cardiovascular Disease with high Lp(a)



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Lp(a): What is it?

Discovered in 1963 by Kare Berg

Expressed predominantly in the liver

> Highly variable in size

> Expression restricted to human and non-human primates

Lp(a) levels are genetically defined

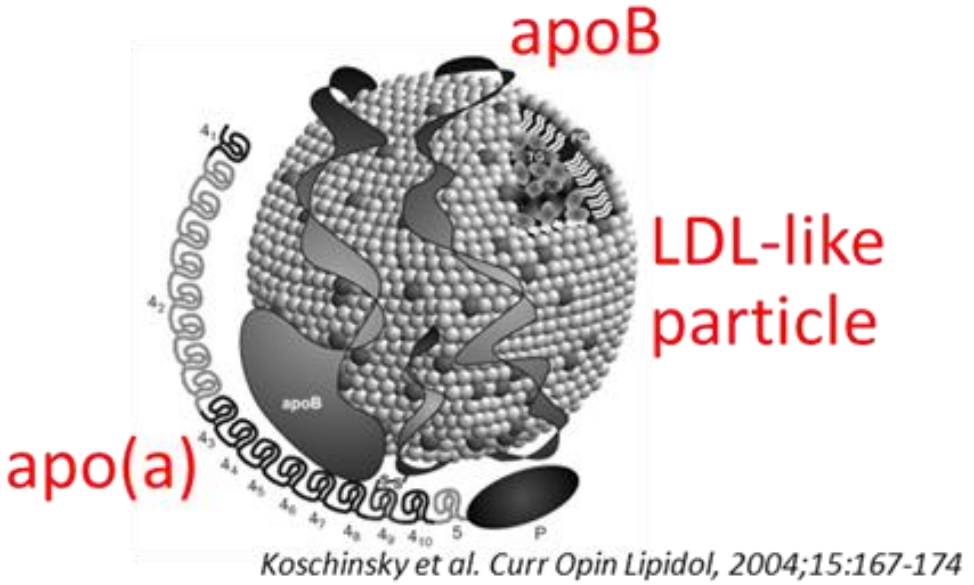
> Not modified through lifestyle interventions

Contributes to total LDL-C

Considered to be pro-atherogenic, pro-thrombotic and pro-inflammatory

Major untreated risk factor in CVD

> Currently approved therapies do not address Lp(a)

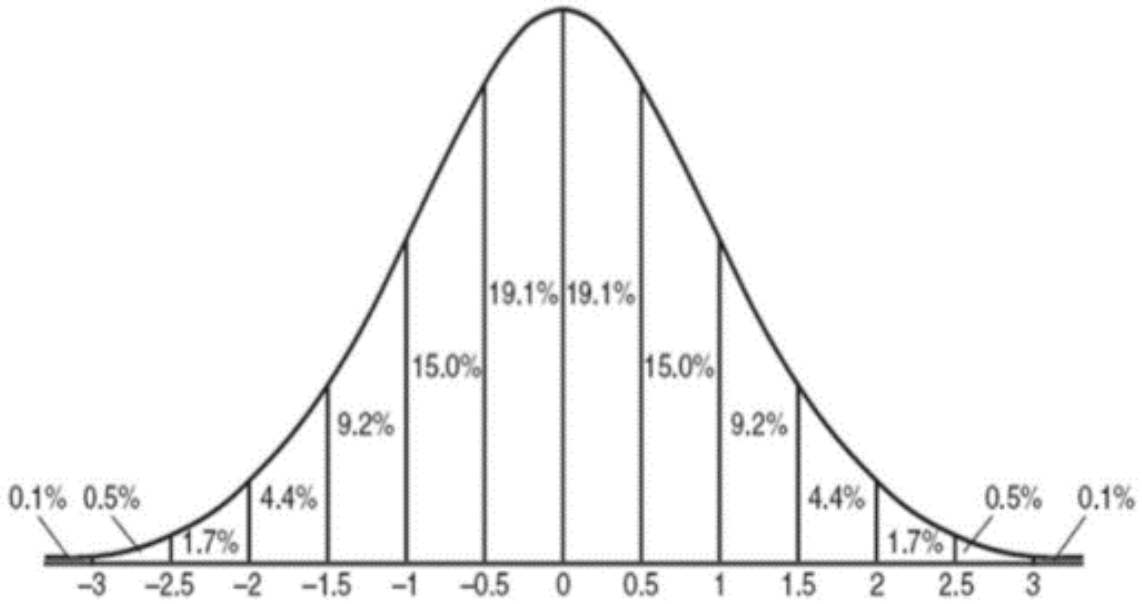


Koschinsky et al. Curr Opin Lipidol, 2004;15:167-174

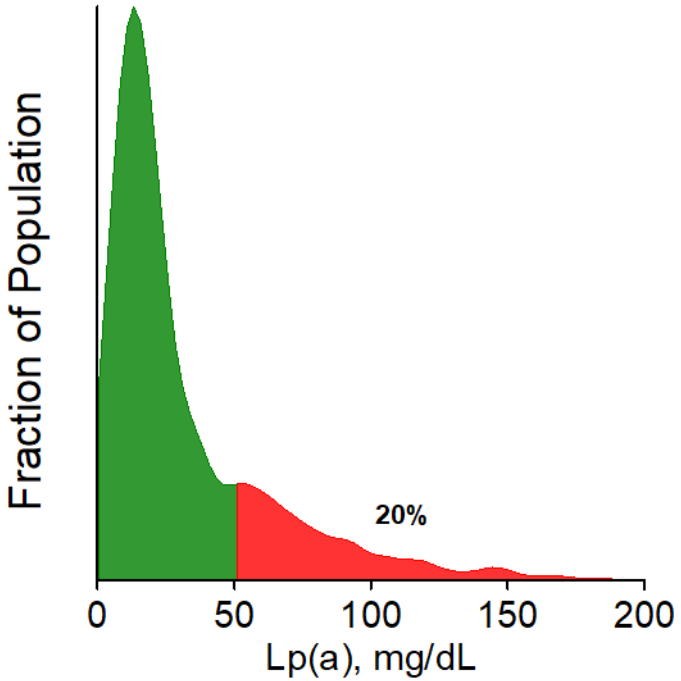
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Lp(a) Distribution in the Population

Most biological entities show a normal distribution in a population



Lp(a) distribution is skewed with 20% of the population with higher than 50 mg/dL



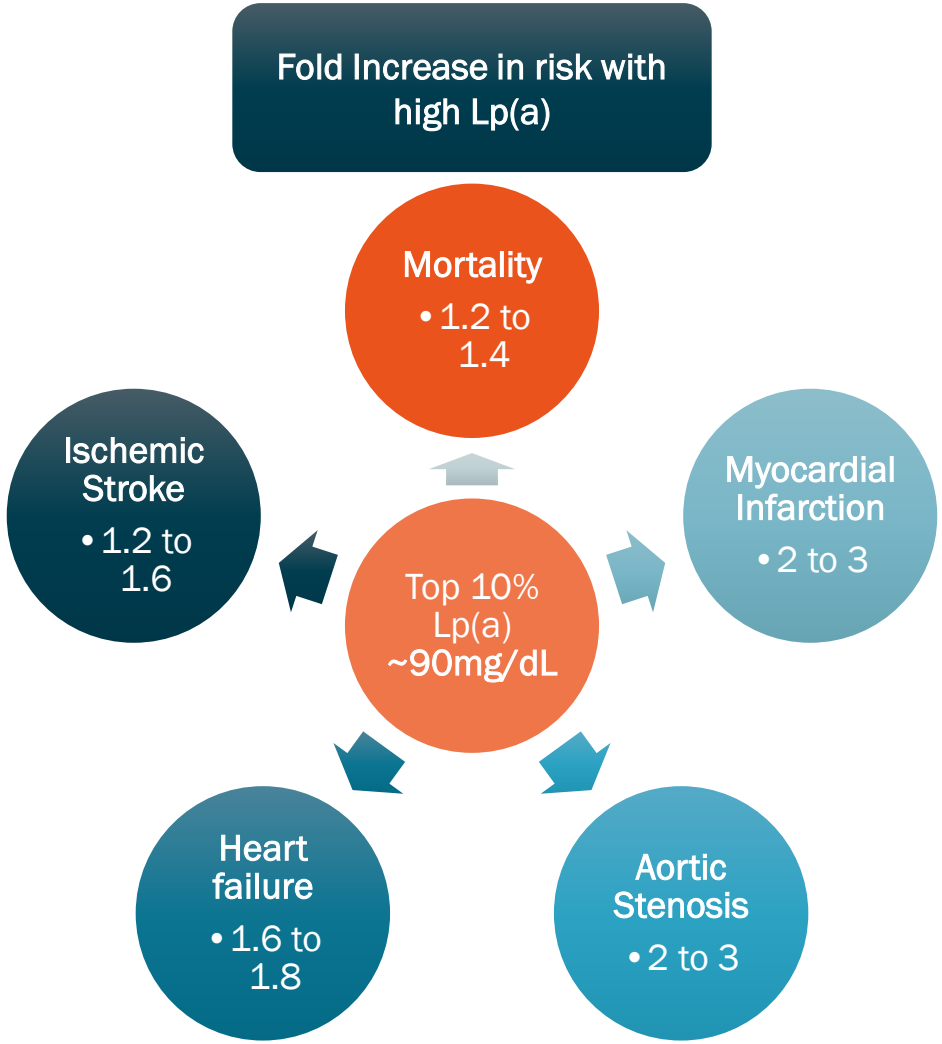
Nordestgaard B Eur Heart J: 2010 31:2844

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Cardiovascular event risk increases with high Lp(a)

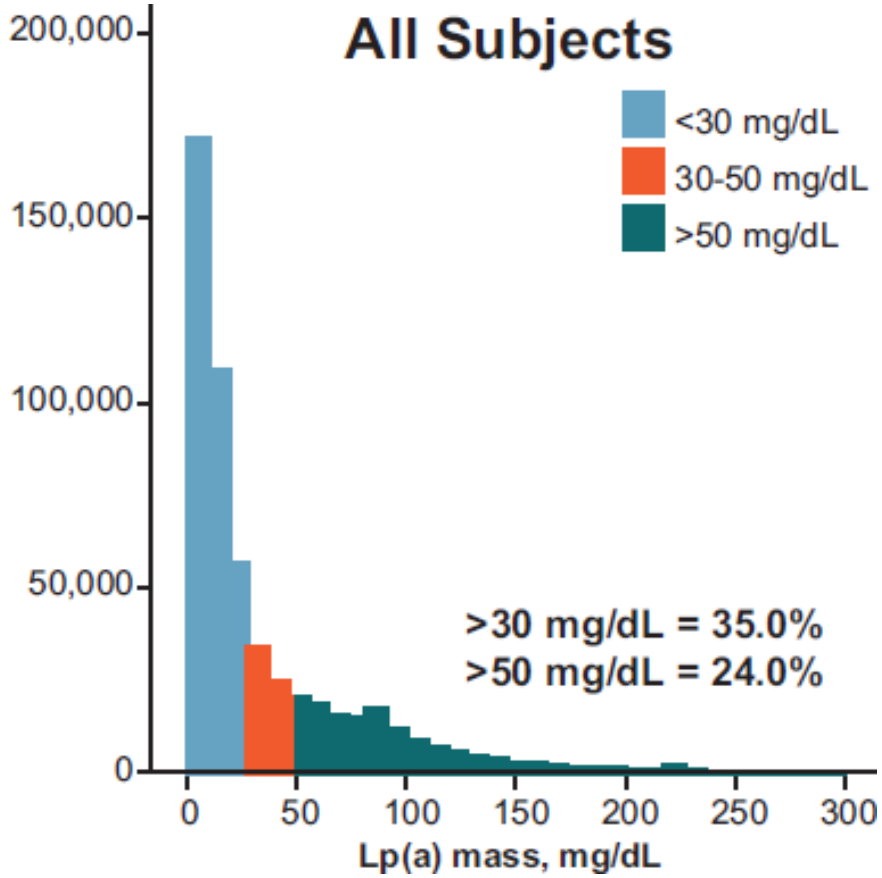
Risk Ratio:

- The probability of one outcome versus another.
- A risk ratio of 2 is double the risk.
- A risk of 0.5 is half the risk



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Up to 700 million globally in top 10% Lp(a) levels



Source: US laboratory Database in 531,144 patients

Global Prevalence of Elevated Lp(a) [millions]

Prevalence	20%	10%	5%	1%
Lp(a) [mg/dL]	*60*	*90*	*116*	*180*
USA	64	30	16	3.2
EU	150	75	37.5	7.5
Globally	1400	700	350	70

Varvel et al Arterioscler Thromb Vasc Biol. 2016;36:2239

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SLN360 Targets Lp(a) - an Independent Risk Factor for Cardiovascular Disease

Lp(a) levels are genetically determined

Recognized as a major untreated risk factor in cardiovascular disease

Lp(a) levels are not significantly modifiable through diet or approved pharmacological therapies

Large population worldwide with up to 10% with >90mg/dL (2x increased MI risk)

Multiple mechanisms by which Lp(a) causes CVD

> Pro-atherogenic
> Pro-thrombotic
> Pro-inflammatory

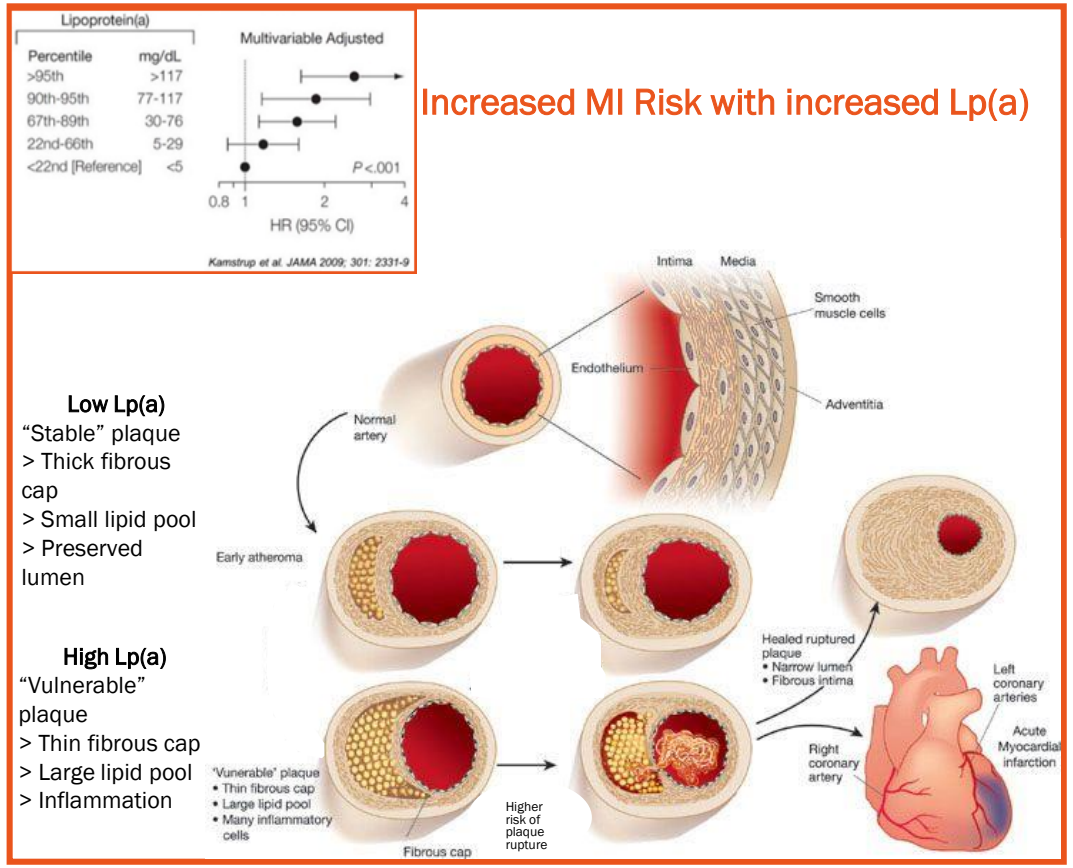


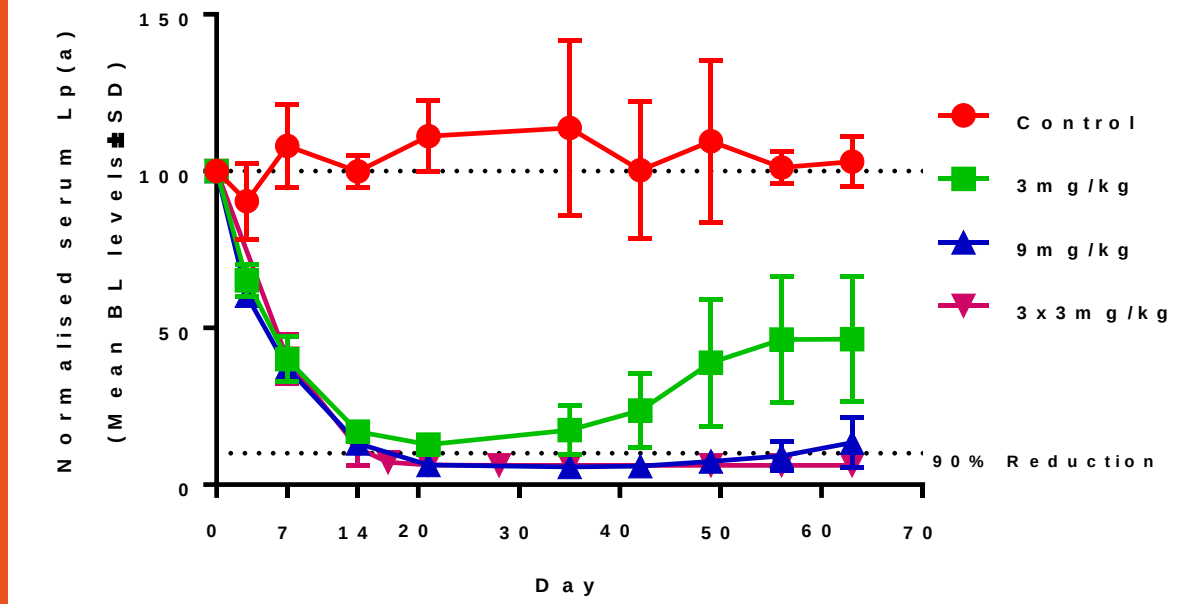
Image modified from Libby 2002, Nature 420, 868

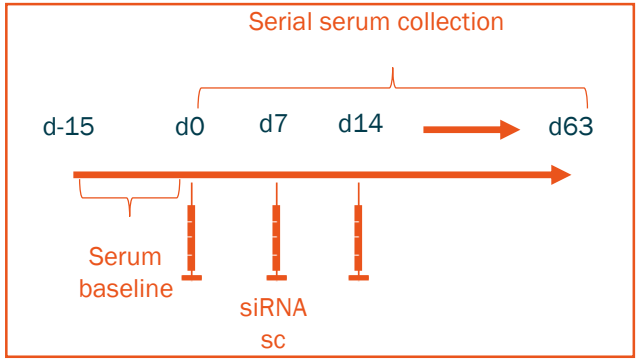
Targeting Lp(a) with SLN360 has the potential to address major unmet needs in cardiovascular disease

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Sustained and Deep LP(a) Knockdown Demonstrated in Animal Model

Serum Lp(a) reduction





Group	mg/kg	Days
1	0	0
2	3	1
3	9	1
4	3	1, 7, 14

Prolonged serum knockdown of Lp(a) in NHP

- Multiple dosing at 3mg/kg resulted in sustained reduction of Lp(a) serum levels (>90%) for at least over two months after first dose (max ~>95% KD)
- Similar outcome after single subcutaneous injection of SLN360 at 9mg/kg
- Over 85% KD at NADIR for single 3mg/kg injection with 50% KD still observed after 2 months post treatment

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Compliance in Cardiovascular Disease

Compliance and Statins

- Patients with ASCVD who stop taking statins are *50% more likely to die* over a 2-3 year period than those that are compliant[1]

Compliance and Intensity of Treatment

- Outcome variable compositive endpoints of CV death or hospitalization for MI, unstable angina, ischaemic stroke, heart failure or revascularization[2]
- With optimal intensity and compliance estimated reduction of endpoint of 23.7 per 1000 person years[3]

1:Retrospective cohort analysis of 347104 Veteran's Affairs patients (Rodriguez et al, Jama Cardiology 2019)
2:Retrospective cohort study of 29 797 newly treated patients receiving statin and/or ezetimibe from UK Clinical Practice Research Data Link followed for 3 years
3:Khunti et al, Jama Cardiology, 2018

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SLN360 Summary

Rationale

- Lp(a) is a low-density lipoprotein produced predominantly by the liver and composed of Apo(a) and Apo B, both hepatocyte expressed genes.
- Genetically defined high Lp(a) serum levels are unaffected by diet and exercise and are an independent risk factor for CVD. There is no specific Lp(a) targeting therapy available at the moment.
- An *LPA* silencing siRNA would provide a specific, safe and durable approach for reducing Lp(a) levels in high risk patients.

Our Program

- A potent lead sequence has been selected and tested *in vivo* in non-human primates (NHP).
- Proof of mechanism has been achieved in NHP: dose dependent reduction in both LPA (liver mRNA) and Lp(a) (serum protein) observed, with max 95% KD observed after multiple dosing.
- Our drug compares positively against published data by competitors, suggesting a superior performance.
- **IND/CTA is planned for H2 2020**

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SLN500
for the treatment of

Complement-Mediated Diseases

Complement as a Target Cascade

C3 - Hub of the complement cascade

>Complement belongs to the innate immune system

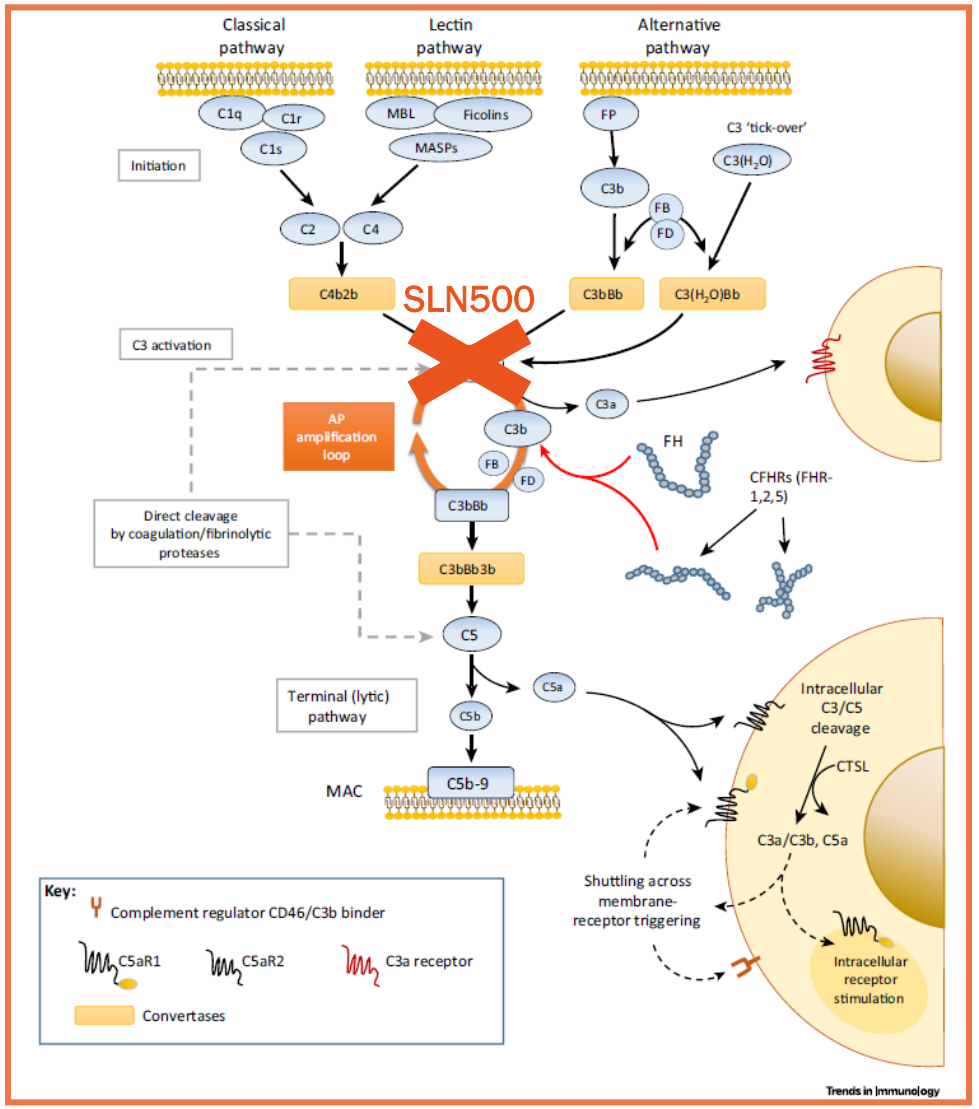
>Over 30 serum proteins

>Three pathways converge to form C3 convertases

>Function: MAC formation and immune cell activation

>Eculizumab (anti-C5 Ab): First FDA-approved drug for complement mediated diseases

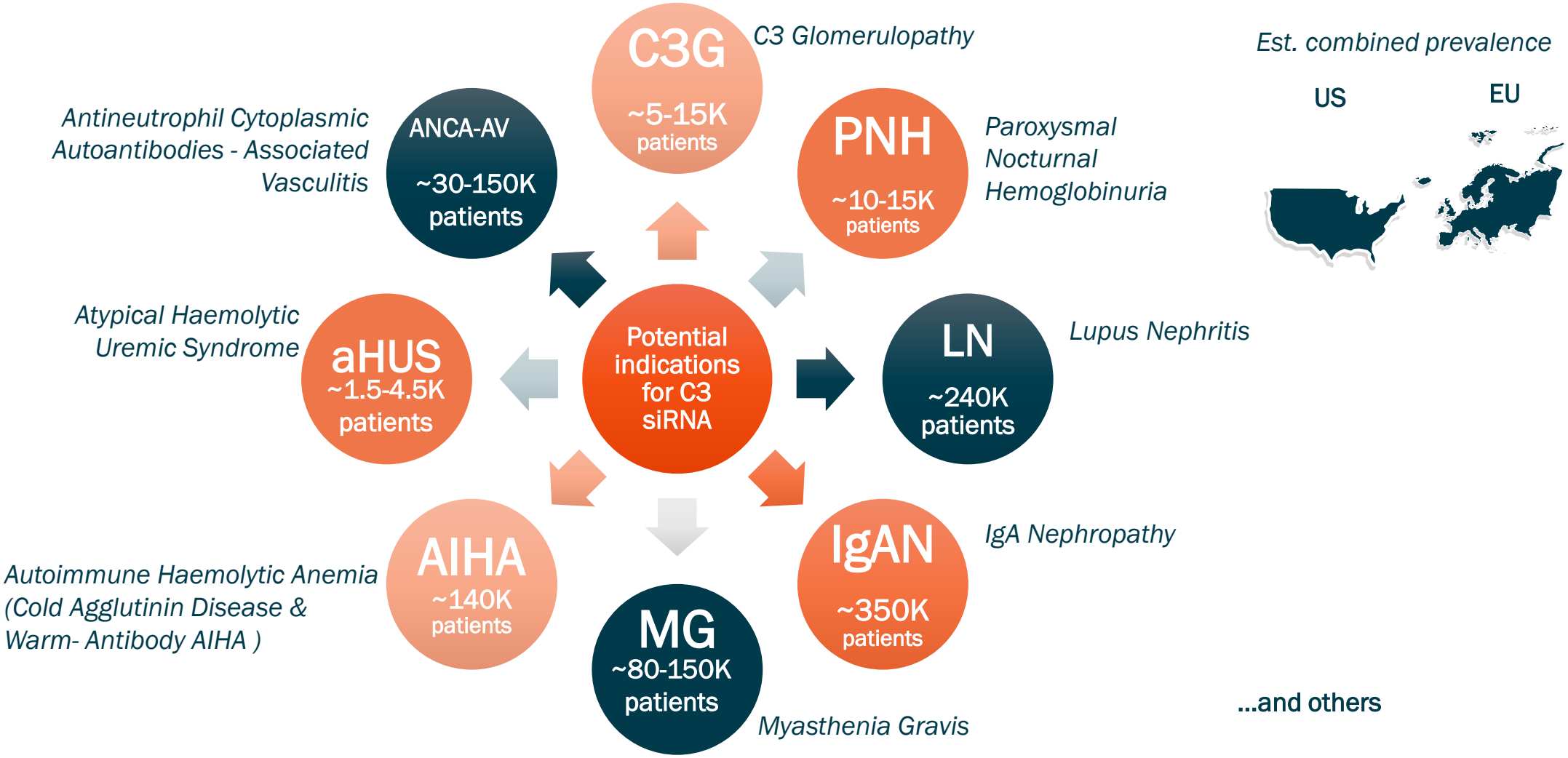
SLN500 is a promising therapeutic approach allowing for blockade of complement activation downstream of C3



MAC: Membrane attack complex

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Attractive Market Size
Combined Opportunity in Multiple Orphan Indications

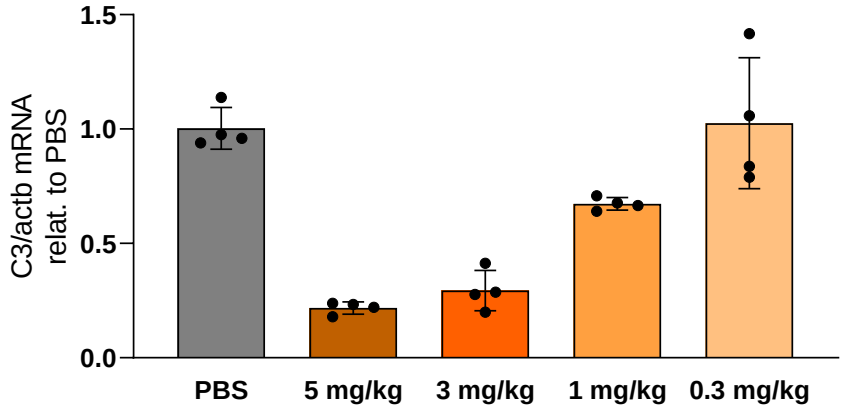


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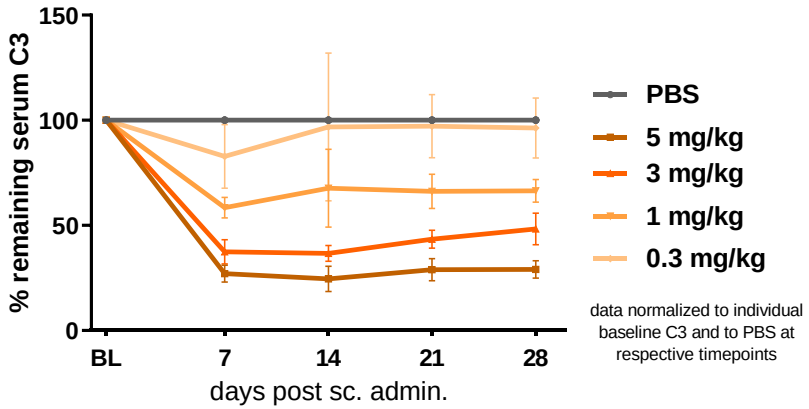
SLN500 Proof of Mechanism Data

Dose response study with SLN500 in healthy mice

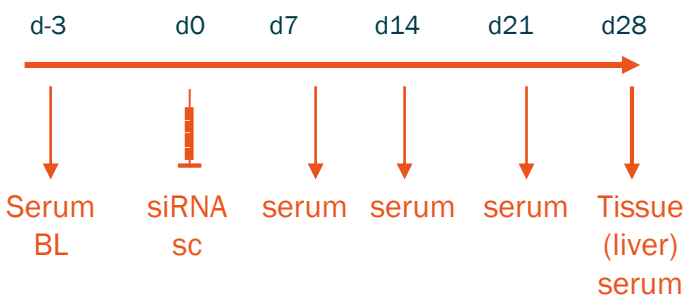
RNA DAY 28



PROTEIN TIME COURSE



> Study design:



Single ascending doses of SLN500 (0.3 - 5 mg/kg) in healthy mice produce a reduction in both C3 mRNA and protein levels in a dose response manner

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SLN500 Summary

Rationale

- Activation of the complement system is a pathologic feature of several diseases (such as C3 glomerulopathy, paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome and myasthenia gravis)
- Mutations and/or deficiencies in complement regulating factors or stabilizing autoantibodies of convertases are evident in patients with complement-mediated diseases
- C3 represents a hub in the complement cascade where all three pathways converge
- Blocking the complement cascade and its detrimental downstream effects is a promising therapeutic strategy

SLN500

- siRNA has significant advantages over other modalities, enabling potent and durable knock-down with a high therapeutic index, allowing for an improved dosing regimen for patients suffering from debilitating diseases
- Proof of mechanism has been achieved in mice: Dose-dependent reduction in both C3 mRNA and C3 serum protein was observed
- Collaborative deal signed with Mallinckrodt for C3 and up to 2 other complement targets
- **IND/CTA filing is planned for 2021**

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Silence Therapeutics - Summary

Valuable Platform	> Reproducible, proprietary gene silencing (RNAi) therapeutics platform, rapidly generating internal pipeline and out-licensing options. Platform validated through collaborations with Mallinckrodt and Takeda
Growing Clinical Pipeline	> SLN124 (β-Thalassemia and MDS[1]) - Phase Ib trial underway > SLN360 (CVD with high LP(a)) - IND/CTA in H2 2020 > SLN500 (C3) - IND/CTA in 2021
Strong Experienced Team	> Pioneers in siRNA for over 18 years, growing clinical team, and experienced biopharma Board and Management team > New CEO recruitment ongoing
Target Selection	> Focused on targeting indications in rare diseases and large population targets, including new medicines for cardiovascular disease and complement-mediated diseases
Strong Financial Position	> $44m of cash[2] extends runway to key clinical milestones such as SLN360 and SLN124 Phase I trial readouts

HQ in London



R&D in Berlin



Approx. 45 employees across both sites

Notes:
[1] MDS = Myelodysplastic syndrome
[2] Unaudited, 31st Dec 2019, £=$1.32

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