SILENCE THERAPEUTICS

Silence Therapeutics

R&D Day

September 12 2019

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Welcome and Agenda

- **Welcome and Introduction** 8:00
  - *Dr. David Horn Solomon, Chief Executive Officer*
- **2019 Half Year Results** 8:30
  - *Dr. Rob Quinn, Chief Financial Officer*
- **Iron Loading Anemias** 8:45
  - *Prof. John Porter, University College London*
- **R&D Progress: SLN124** 9:30
  - *Dr. Giles Campion, Head of R&D and Chief Medical Officer*
- **Q&A** 9:45
- **Coffee break** 10:00
- **Elevated Lp(a) and Cardiovascular Disease** 10:15
  - *Prof. Henry Ginsberg, Columbia University*
- **R&D Progress: SLN360 and SLN500** 11:00
  - *Dr. Giles Campion, Head of R&D and Chief Medical Officer*
- **Q&A** 11:15
- **Closing remarks** 11:40
  - *Dr. David Horn Solomon, Chief Executive Officer*

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Leadership Presenting Today

CEO
David Horn Solomon



> Experienced public company CEO, board member and biotech investor
> CEO of Zealand Pharma from 2008 to 2015, during which time the company went public on Nasdaq OMX and its lead product, Adlixin® was approved in the US
> Previously Faculty Columbia University and founder Carrot Capital Healthcare Ventures

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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Silence Therapeutics - Summary

Valuable Platform	> Reproducible, proprietary gene silencing (RNAi) therapeutics platform, rapidly generating internal pipeline and out-licensing options. Platform validated through recently announced collaboration with Mallinckrodt
Growing Clinical Pipeline	> SLN124 (β-Thalassemia and MDS[1]). Phase Ib trial to start in H2 2019. SLN360 (LPa) IND/CTA in 2020. SLN500 (C3) IND/CTA in 2021.
Strong Experienced Team	> Pioneers in siRNA for over 18 years, growing clinical team, and experienced biopharma management team
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. Cash position recently strengthened by Mallinckrodt collaboration ($25m in upfronts[3])

HQ in London



R&D in Berlin



Approx. 45 employees across both sites

Notes:
[1] MDS = Myelodysplastic syndrome
[2] As of 31st Aug 2019 and £=$1.22
[3] $20 upfront and $5m equity investment

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2019 – Year-to-Date Accomplishments

R&D Highlights

> SLN124 Clinical Trial Application filed in March 2019 with first patient dosed expected in H2 2019

> SLN124 granted Orphan Drug Designation in January by the European Medicines Agency for the treatment of β-Thalassemia

> SLN360 entered IND-enabling studies in February 2019 and is on track for IND and/or CTA in H2 2020

Corporate Highlights

> Collaboration with Mallinckrodt Pharmaceuticals for up to 3 targets for complement-mediated diseases. Exclusive license for C3-targeting siRNA (SLN500). $20m upfront payment

> Management team strengthened with the addition of Dr. Rob Quinn as Chief Financial Officer, Dr. Giles Campion as Head of R&D and Chief Medical Officer, and Jorgen Wittendorff as Head of Manufacturing

> Board augmented with the appointment of Iain Ross as Chairman and James Ede-Golightly and Dr. Steven Romano as Non-Executive Directors

> Collaboration with Genomics England to identify novel target genes associated with human disease

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Experienced Management Team

Head of Manufacturing
Jorgen Wittendorff



- Joining in Oct 2019
- 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 Bio-chemistry from Harvard University

Head of Technology
Marie W Lindholm



- Over 10 years in oligo technology development, including at Santaris and Roche
- Formerly Associate Professor in Experimental Cardiovascular Research at Lund University
- PhD in Medicinal Chemistry and post-doc at UC Berkeley

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Strong Board, Augmented by Recent Additions

Chief Executive Officer
Dr. David Horn Solomon



Non-Executive Chairman
Iain Ross



Non-Executive Director
Dr. Steven Romano



Non-Executive Director
Alistair Gray



Non-Executive Director
Dave Lemus



Non-Executive Director
James Ede-Golightly



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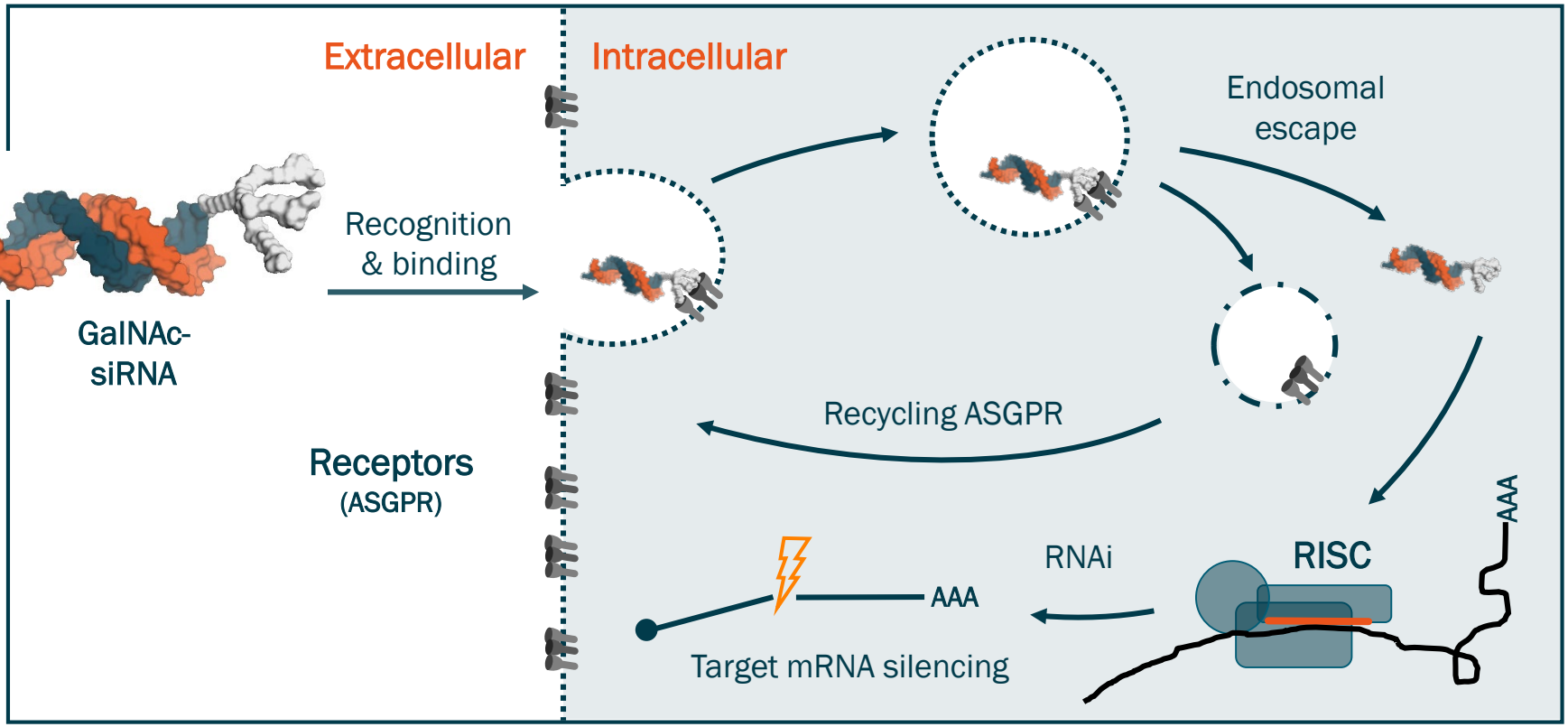
GalNAc-siRNA for Treatment of Disease



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

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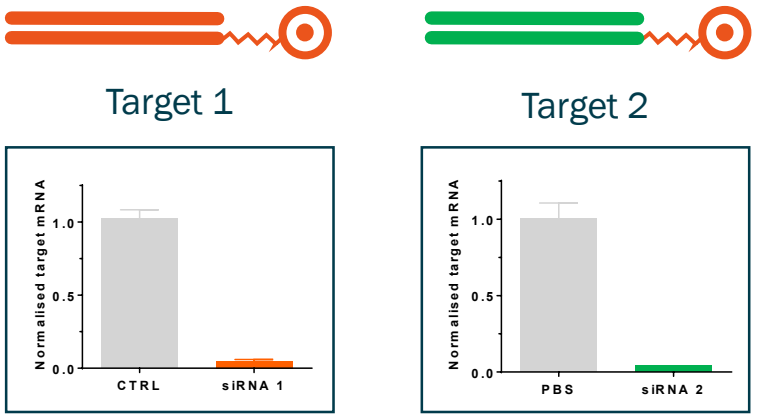
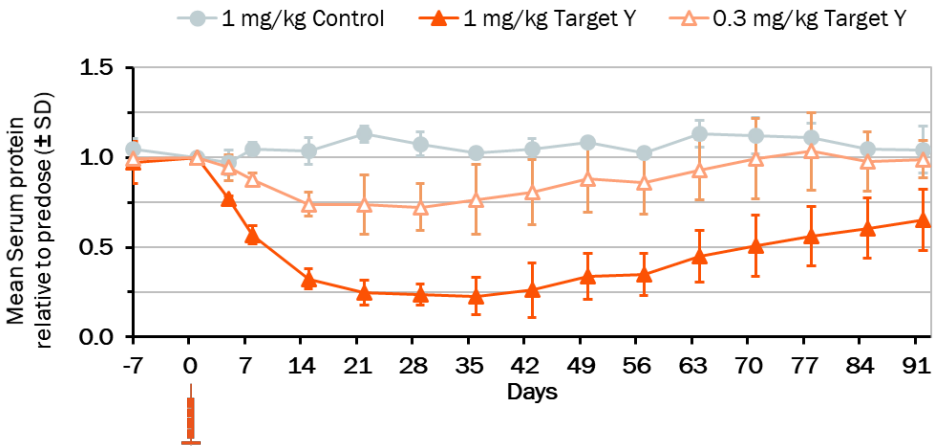
Reproducibly Silencing Disease-Associated Genes Using our Proprietary Platform Technology

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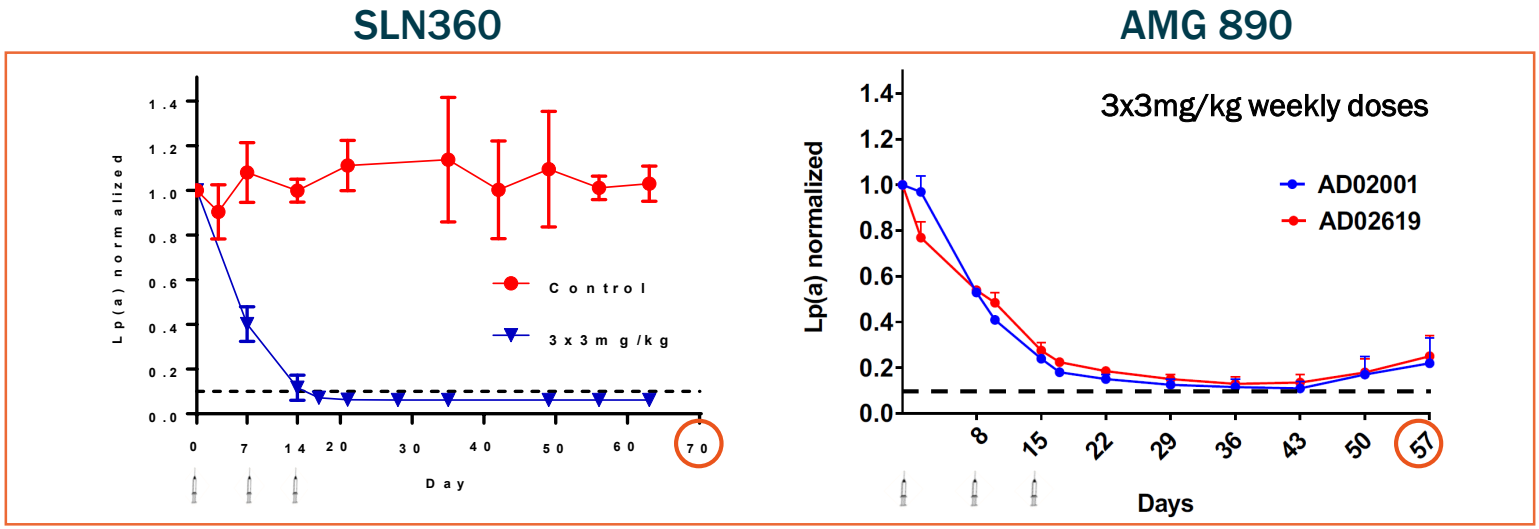
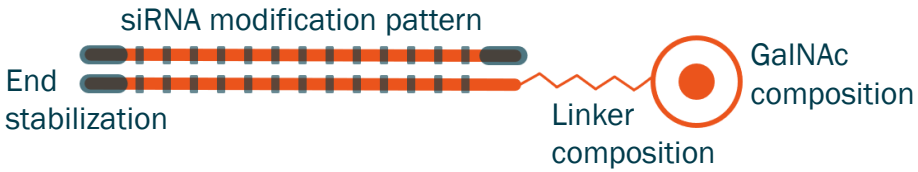
A Competitive Platform, With Continuous Fine-Tuning to Further Improve Performance





- **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:** 12 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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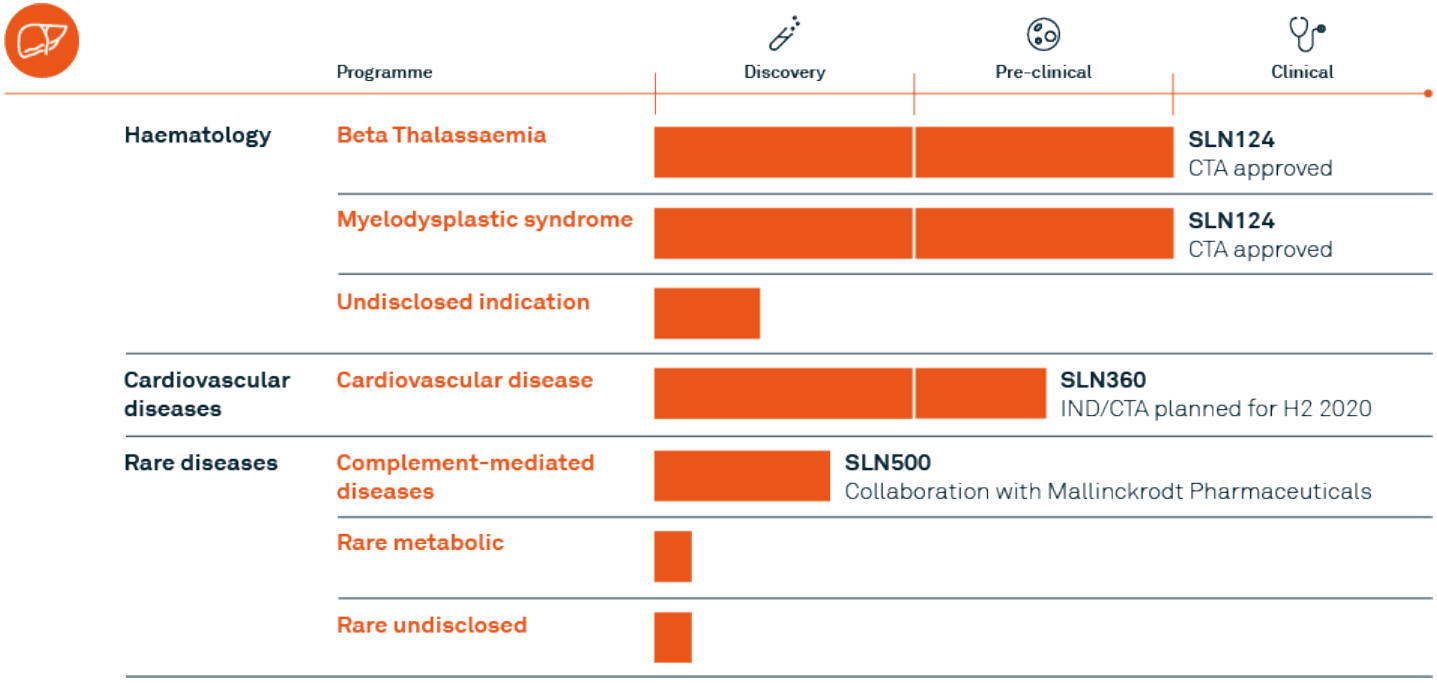
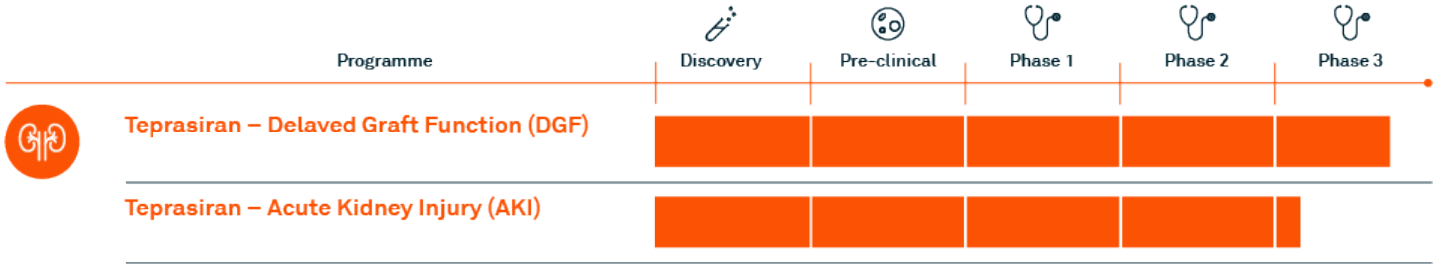
Development Pipeline



Out-Licensed Technology to Quark Pharmaceuticals



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SLN124

for the treatment of

Iron Overload Disorders

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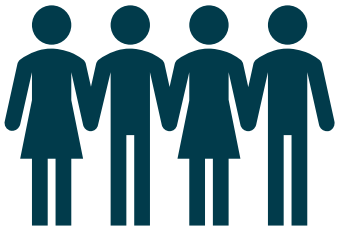
Market Opportunity of SLN124

US and EU patients



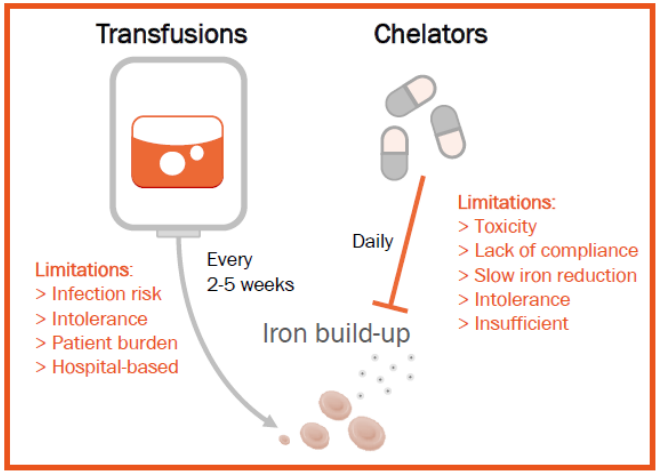
β-Thalassemia

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

MDS[3]

>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

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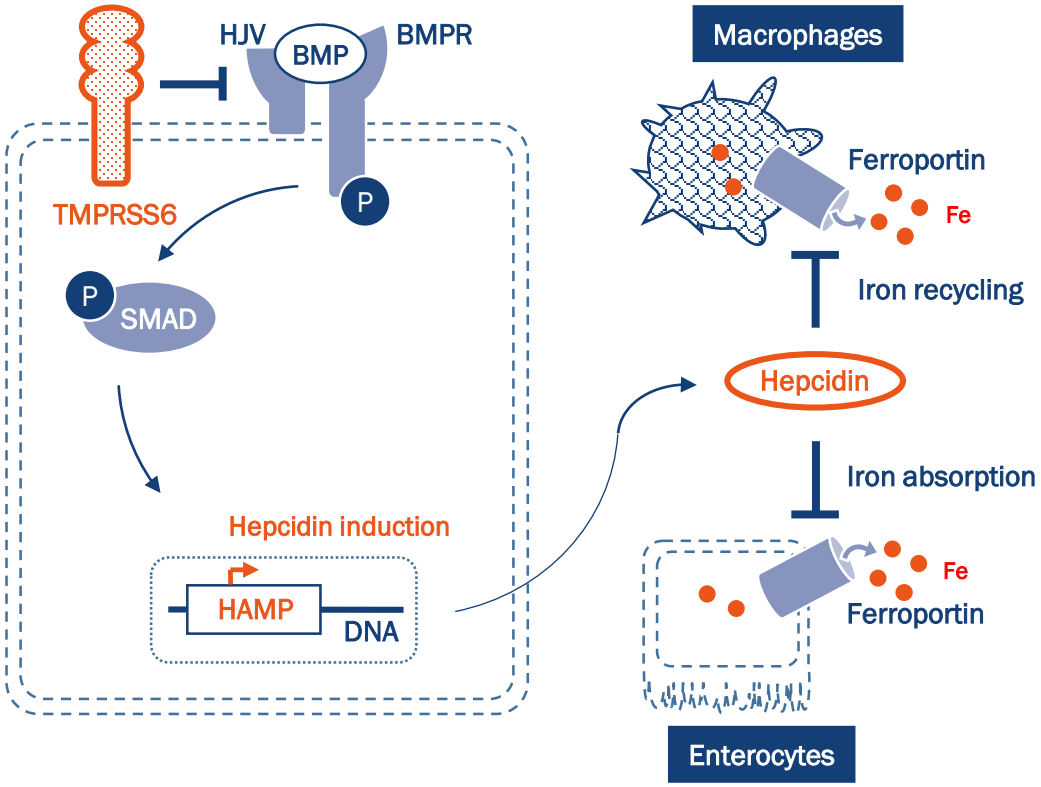
SLN124 Mechanism of Action: Increasing Hepcidin by Silencing its Repressor TMPRSS6



- **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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Therapeutic Activity of SLN124 - Disease Model of Hereditary Hemochromatosis ($HFE^{-/-}$ mice)

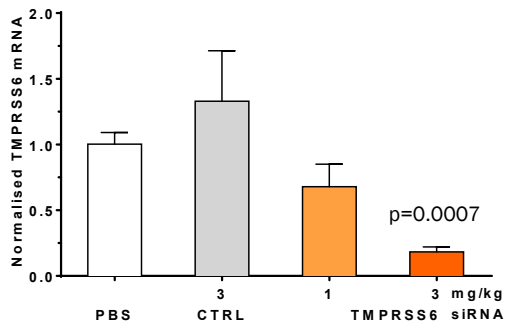
Collaboration with
Prof. Dr. Martina Muckenthaler
Heidelberg University, Germany

Study design

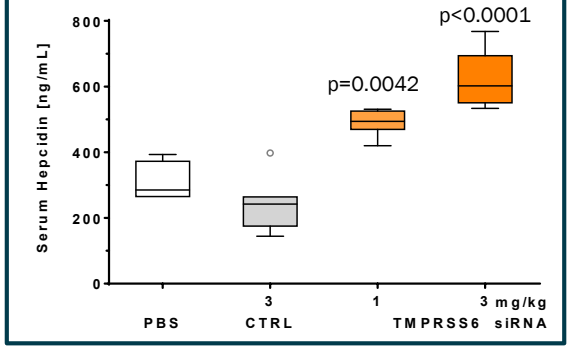
d1 — wk 3

SC, n=6-7 $HFE^{-/-}$ mice, 1 mg/kg or 3 mg/kg

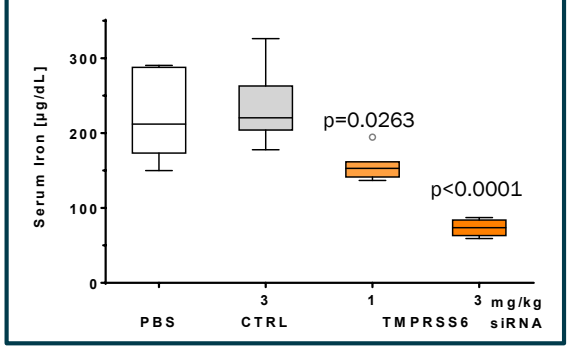
TMPRSS6 mRNA (liver)



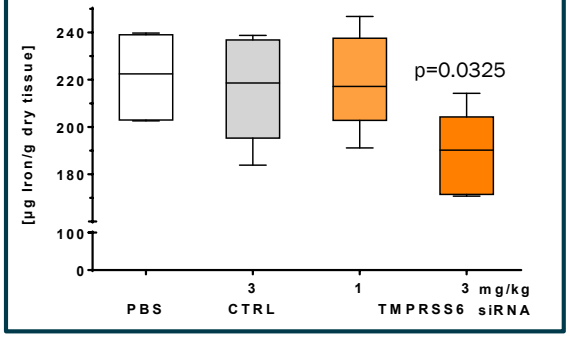
Hepcidin (serum)



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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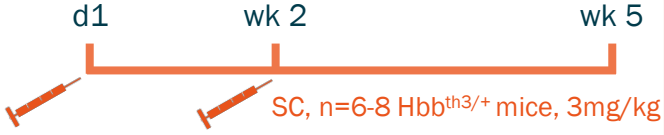
SLN124 Reduces ROS and Improves RBC Parameters in a β-Thalassemia Disease Model

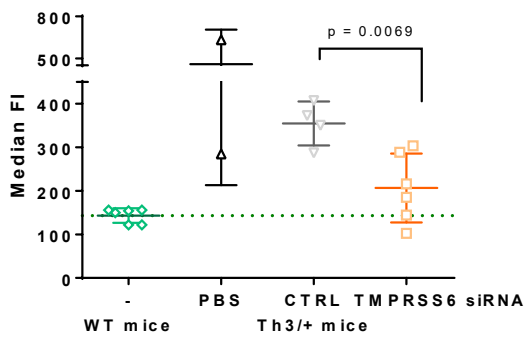
Collaboration with
Prof. J. Vadolas & Dr. Grigoriadis
Monash Medical Centre/Melbourne, Australia

HUDSON INSTITUTE OF MEDICAL RESEARCH

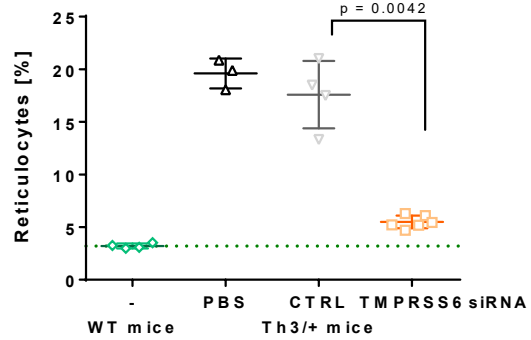
Study design



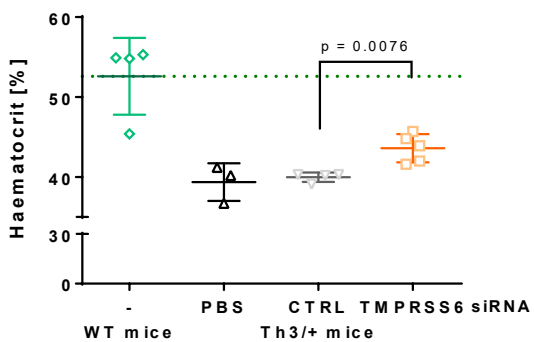
Reactive oxygen species (ROS)



Reticulocyte proportion



Hematocrit



- Reduction of ROS to levels in healthy mice
- Normalization of reticulocyte proportion and improvement of hematocrit
- SLN124 significantly improves erythropoiesis in animal model for β-Thalassemia intermedia

ROS = reactive oxygen species; RBC = red blood cells

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SLN360

for the treatment of

Cardiovascular Disease with High Lp(a)

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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 >80mg/dL (2x increased MI risk)

Multiple mechanisms by which Lp(a) causes CVD

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

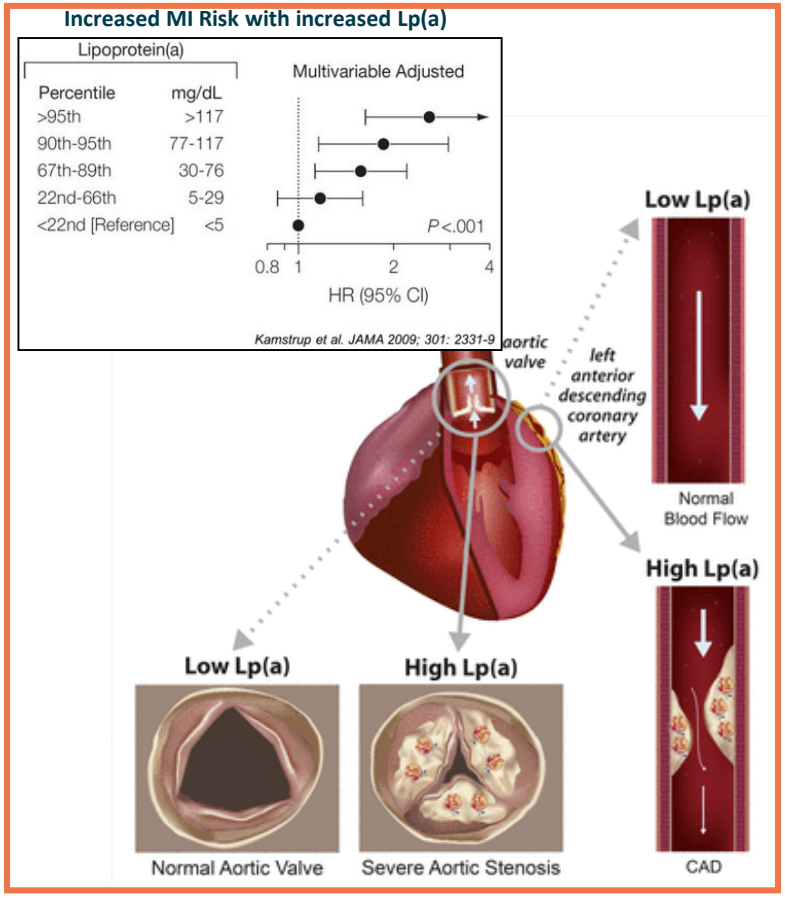

Image obtained from the Journal of Lipid Research March 2016

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

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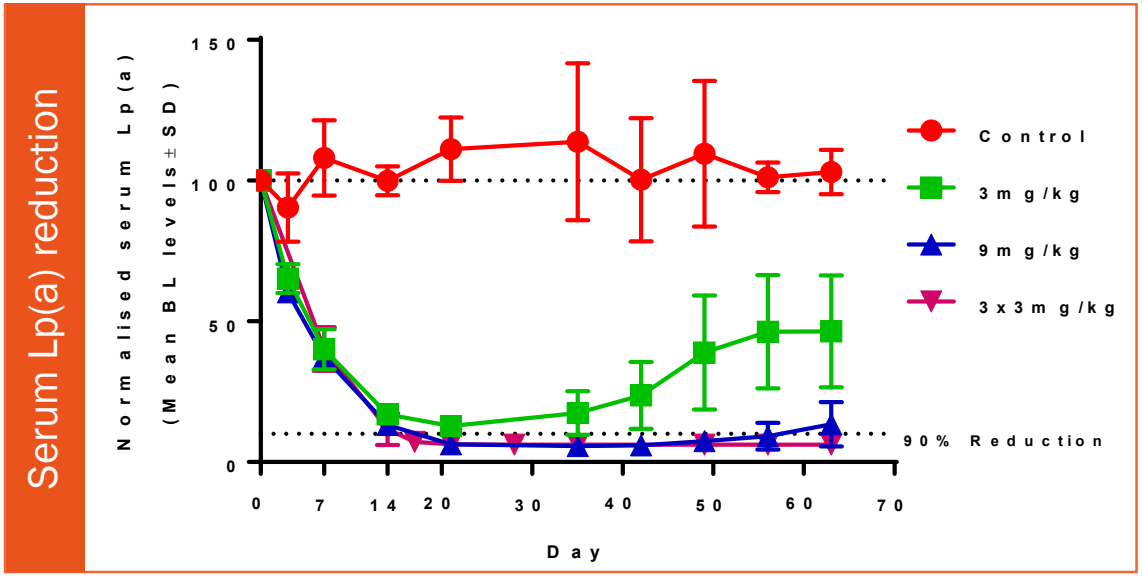
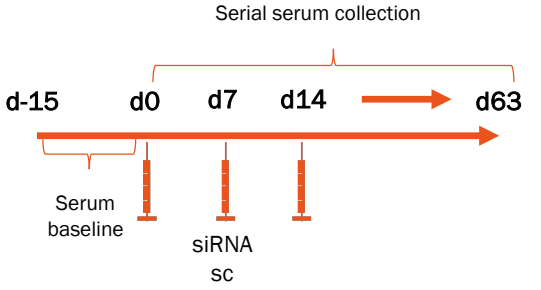
Proof of Mechanism Achieved





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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SLN500

for the treatment of

Complement -Mediated Diseases

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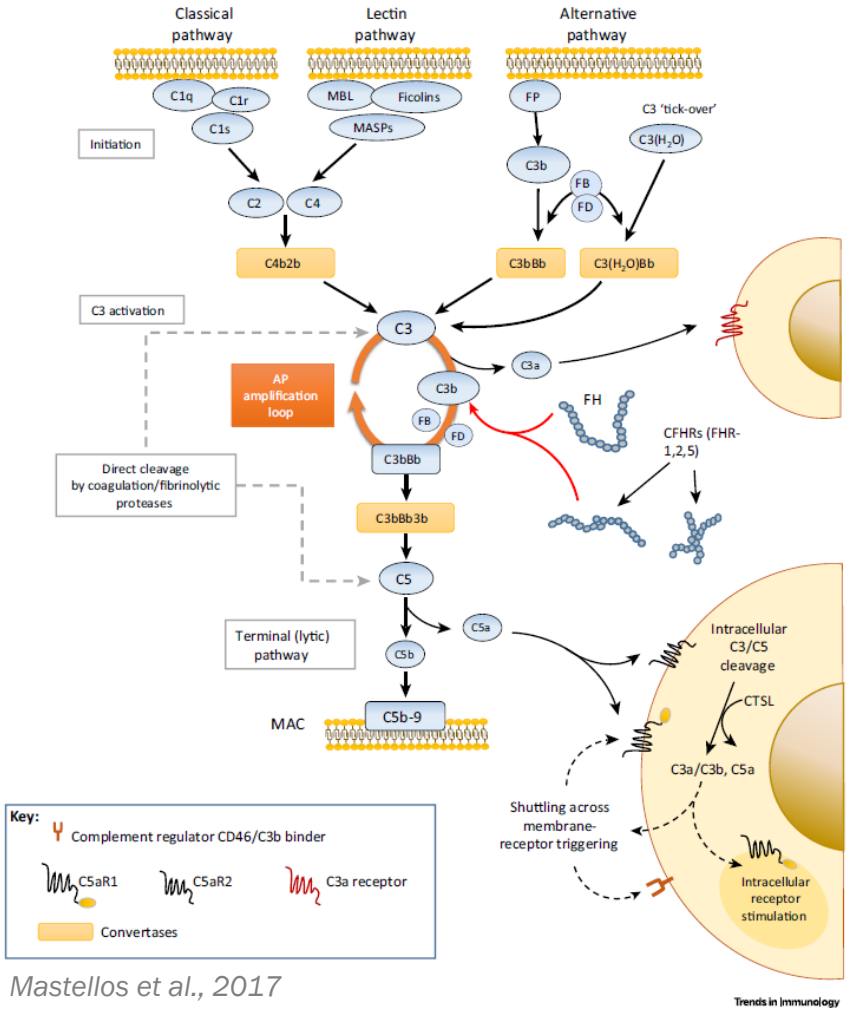
GalNAc siRNAs for the Treatment of Complement-Mediated Diseases

Schematic overview - complement system



Mastellos et al., 2017

Targeting the complement system offers a broad indication spectrum (such as Paroxysmal Nocturnal Hemoglobinuria, Myasthenia gravis, C3 Glomerulopathy, atypical Hemolytic Uremic Syndrome or Cold Agglutinin Disease)

> **The complement system** is part of the innate immune system and consists of 3 pathways

> >30 serum proteins (many made in hepatocytes)

> It represents an activation cascade with various effector functions, such as MAC (membrane attack complex) formation for pathogen destruction and activation of immune cells

> First drug on the market targeting the complement pathway is Eculizumab (Soliris, C5 Ab)

> **There is unmet need** because Eculizumab is not consistently effective for all patients (mutations, non responders) and indications

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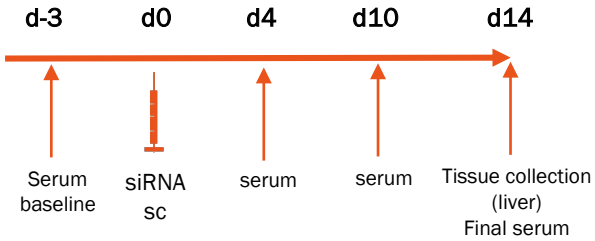
SLN500 - Proof of Mechanism in Vivo

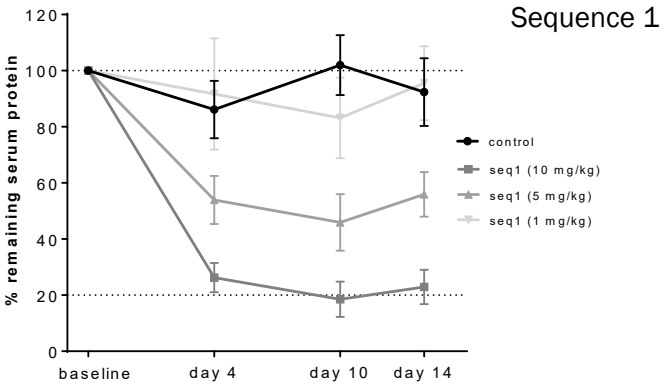
Study design:

> n=4 healthy mice per group, serum sampling at day -3, 4, 10 and 14, liver tissue at day 14

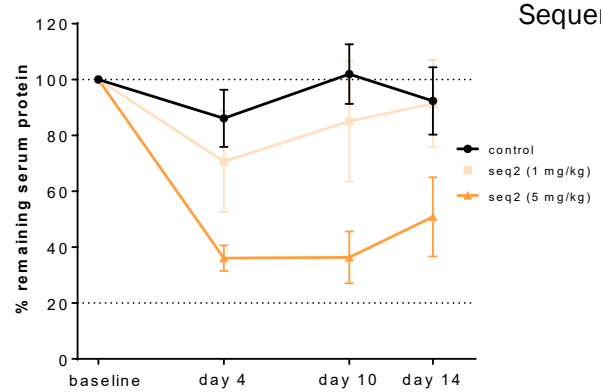
> siRNAs: **non-optimized** GalNac conjugated chemistry



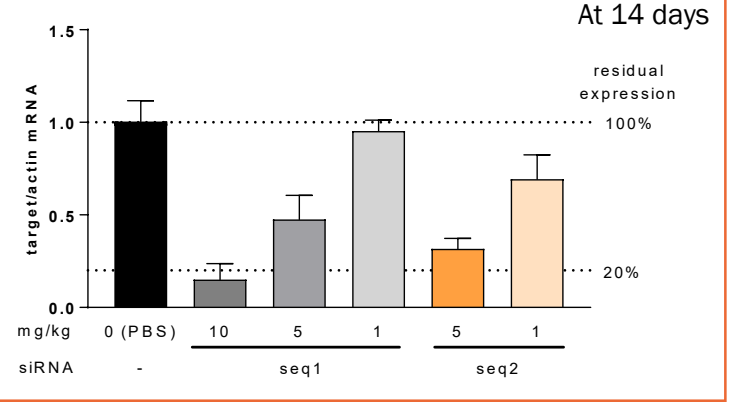
C3 SERUM PROTEIN



C3 SERUM PROTEIN



C3 RNA



C3 knock down:

>80% mRNA and protein knock down achieved using non-optimized siRNAs

→ Identification of 2 potent siRNA sequences for lead optimization and NHP studies (using advanced chemistry)

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Expected Newsflow & Company Milestones

	H1 2019	H2 2019	2020
SLN124			
File CTA	✓		
First In Human Dosing		✓	
First Interim Results			✓
SLN360			
Clinical candidate nomination	✓		
IND/CTA filing			✓
SLN500			
Clinical candidate nomination		✓	
IND-enabling studies			✓
Quark Out-License in QPI-1002			
Potential release of DGF Phase 3 results		✓	

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SILENCE THERAPEUTICS

R&D Day, September 12 2019

Financial Update

Dr. Rob Quinn
Chief Financial Officer

Agenda



1. Corporate overview
2. H1 2019 Results
3. Partnered programs
4. Outlook

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Corporate Overview

- Silence Therapeutics (SLN.L) is listed on the AIM sub-market of the London Stock Exchange
- The company was formed in 2005 through the reverse merger of Atugen AG with AIM-listed SR Pharma. Through the Atugen legacy we have over 18 years' experience in siRNA and some of the foundational patents
- Corporate and clinical development operations in London. Research in Berlin through a German subsidiary. US presence expanding
- 78.1m shares outstanding with a market cap of c.$175m[1]. 2.6m options outstanding with weighted average strike price of 76p[1]
- All ordinary shares. No debt, no preferred shares, warrants, convertibles etc
- Cash of $44m[1] as of end August 2019 expected to support the company operations through clinical readouts for both SLN124 and SLN360, based on current operating plan



[1] As of 31st Aug 2019 and £=$1.22. Unaudited

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H1 2019 Results

Financial Results ($USm)	H1 2019	H1 2018	FY 2018
Revenue	–	–	–
R&D costs	(6.1)	(6.4)	(11.9)
G&A costs	(5.7)	(5.7)	(13.2)
Operating loss	(11.8)	(12.1)	(25.1)
Other income	0.1	0.1	0.1
Tax	1.7	1.4	2.5
Loss after tax	(10.0)	(10.6)	(22.5)
Cash & cash equivalents[1]	20.1	41.9	32.3

Converted to $US for all periods and presented at £=$1.22. [1] Includes £5m on short term deposit

- R&D spend at $6.1m (£5.1m) is similar to H1 2018, but with an underlying change in balance as we invest in CRO spend for the SLN124 Phase Ib, offset by lower consultant and patent costs due to investments in in-house capabilities
- G&A remained steady at $5.7m (£4.7m)
- Tax credit is a cash inflow under the UK R&D Tax Credit scheme
- Cash balance of $20m does not reflect $25m of upfront payment and equity investment from Mallinckrodt

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Collaboration with Mallinckrodt Pharmaceuticals for Complement-Mediated Diseases

- Agreement provides Mallinckrodt with exclusive worldwide license for Silence's C3 complement asset (SLN500), with options to license up to two additional complement-targeted assets
- Silence will be responsible for development of each asset until the end of Phase I, after which Mallinckrodt will take over clinical development and responsibility for commercialization
- This deal provides further validation for Silence's proprietary siRNA platform, strengthening our position as a leader in RNA interference therapeutics

SILENCE THERAPEUTICS

Mallinckrodt Pharmaceuticals

Summary of Terms

$20M Upfront

Up to $10M in research milestones for SLN500 and each optioned asset, in addition to funding for Phase I clinical development, including GMP manufacturing

Potential clinical and regulatory milestones of up to $100M for SLN500, as well as commercial milestones of up to $563M. Up to $703M in clinical, regulatory and commercial milestones per additional asset, should Mallinckrodt exercise its option

Tiered low double-digit to high-teen royalties on net sales

Equity investment of $5M, non-executive Director role for Steven Romano, M.D., Mallinckrodt Chief Scientific Officer

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Out-Licenses: Alnylam and Quark

Alnylam Pharmaceuticals

> Settlement and license agreement in Dec 2018

> Tiered royalty of 0.33%-1% on EU sales of ONPATTRO® through 2023. All legal proceedings resolved

> First royalties expected to be received in Q4 2019

Quark Pharmaceuticals

> Out-licensed oligo chemical modification technology being used in two Phase 3 clinical trials for QPI-1002; Acute Kidney Injury following cardiac surgery and Delayed Graft Function following kidney transplant

> Silence to receive 1.5%-4% royalties from Quark OR 15% of clinical, regulatory and commercial milestone payments and royalties received by Quark from its partner Novartis

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Outlook

SLN124

> SLN124 Phase Ib commences soon with interim results for the Part A (Single Ascending Dose) expected in 2020

> Phase Ib trial is expected to fully readout in H2 2021

SLN360

> IND and/or CTA expected to be filed in H2 2020

> Phase I trial to start shortly thereafter and funding this program is a key priority for us

SLN500

> Fully funded (directly or through milestones) by Mallinckrodt. IND and/or CTA targeted in H1 2021

Earlier stage, as yet undisclosed, proprietary programs

> At least two Discovery programs ready to enter IND-enabling studies during 2020

Extra-hepatic delivery

> Numerous collaborations being explored. This is a key priority

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SILENCE THERAPEUTICS



R&D Day, September 12 2019

Iron Loading Anemias - β-Thalassemia and Myelodysplastic Syndromes

Prof John Porter
University College London Hospital
Red Cell Disorders Unit

Silence Therapeutics 2019

Thalassemia Etiology

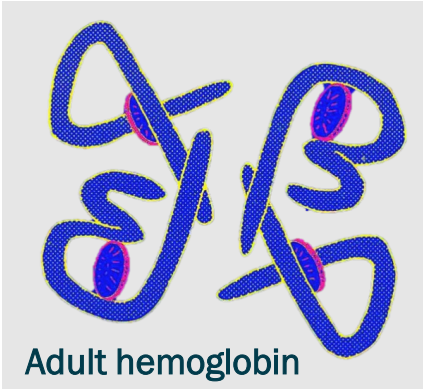
A group of anemias resulting from imbalanced globin chain synthesis

Secondary to reduced synthesis of α or β globin

Excess of the unaffected globin leads to <u>precipitation in</u>:

red cells (hemolysis)

bone marrow (ineffective erythropoiesis)



Adult hemoglobin

<u>Genetic basis</u>

β-Thalassemias

- over 200 β mutations are known - (usually point mutations)
- severe mutations β0 and milder mutations β+

Heterozygotes - small red cells

Homozygotes – severe anemia typically transfusion-dependent

α-Thalassemias

- typically deletional of between 1 and 4 of the normal complement of 4 α genes

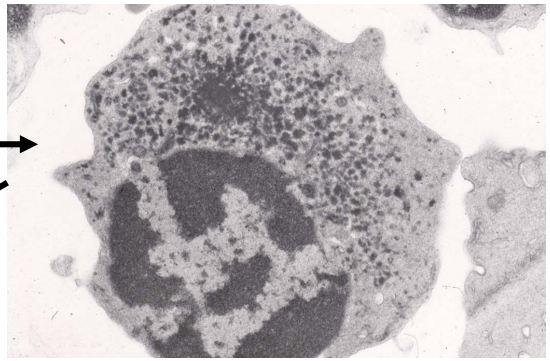
1 or 2 deletions – small red cells

3 deletions – anemia, mild-moderate

4 deletions – death *in utero*- hydrops fetalis

β-Thalassemia

β-Thalassemia Pathophysiology



Decreased β globin synthesis
Unpaired α globin

Splenomegaly

Hemolysis

Ineffective erythropoiesis

Anemia

Transfusion

Erythropoietin

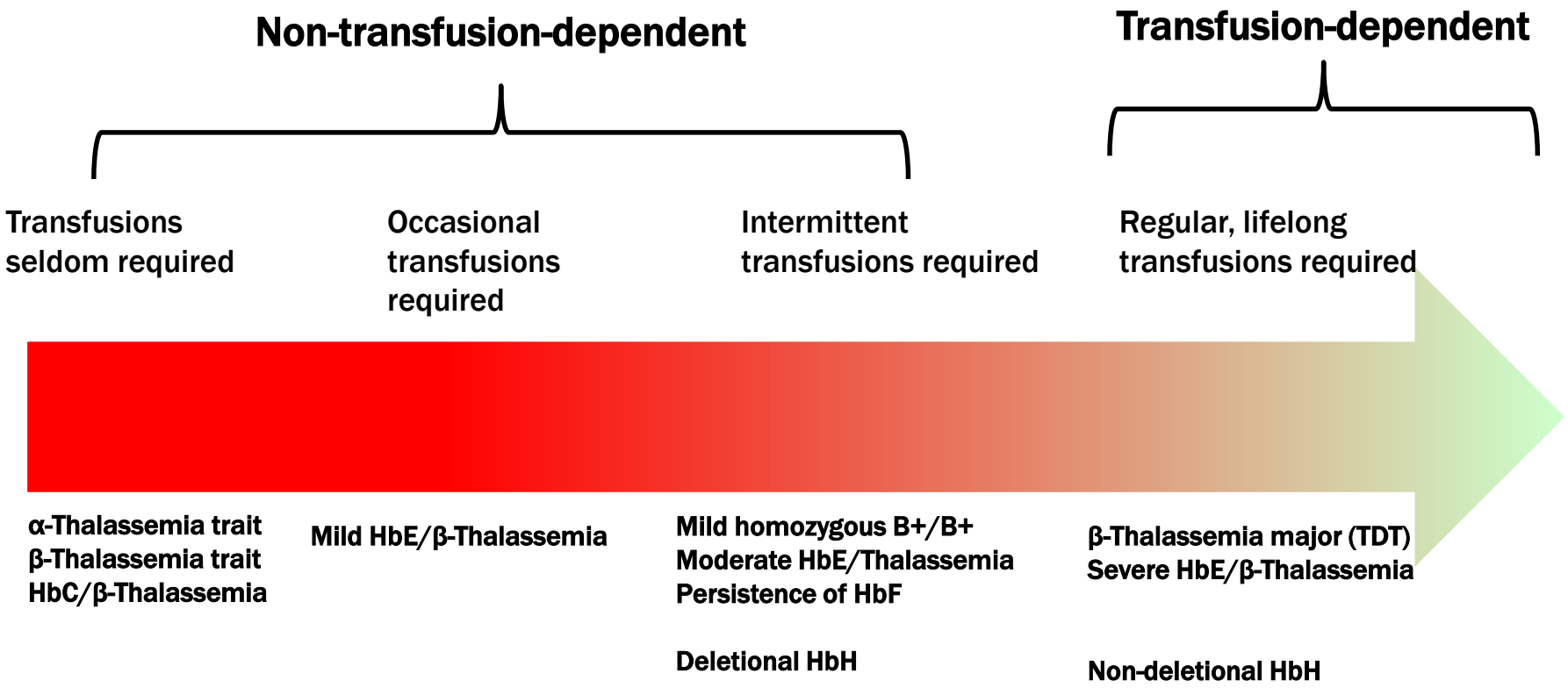
Erythroid marrow expansion

Skeletal deformities, osteopenia

Iron absorption
Decreased hepcidin

Iron overload

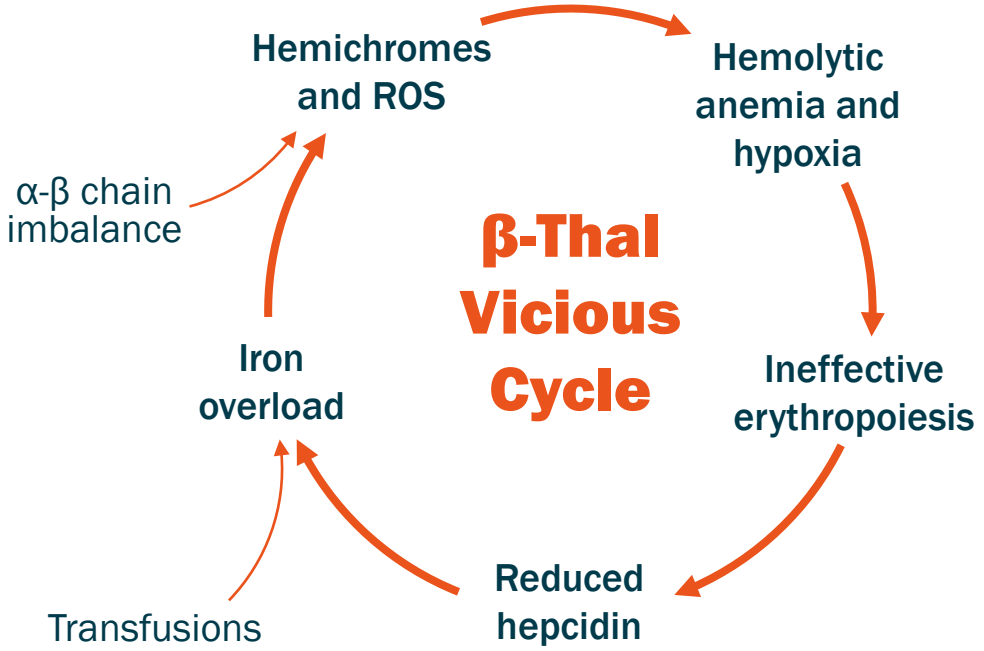
Spectrum of Thalassemias



Cohen AR, et al. Hematology Am Soc Hematol Educ Program. 2004;14-34. Galanello R, Origa R. Orphanet J Rare Dis. 2010;5:11. Harteveld C, Higgs D. Orphanet J Rare Dis. 2010;5:13. Muncie HL, Campbell JS. Am Fam Physician. 2009;80:339-44.

Ineffective Erythropoiesis is Integral to a Vicious Cycle Driving Morbidities of Untransfused β-Thalassemias (NTDT)

Pathophysiology of β-Thalassemia

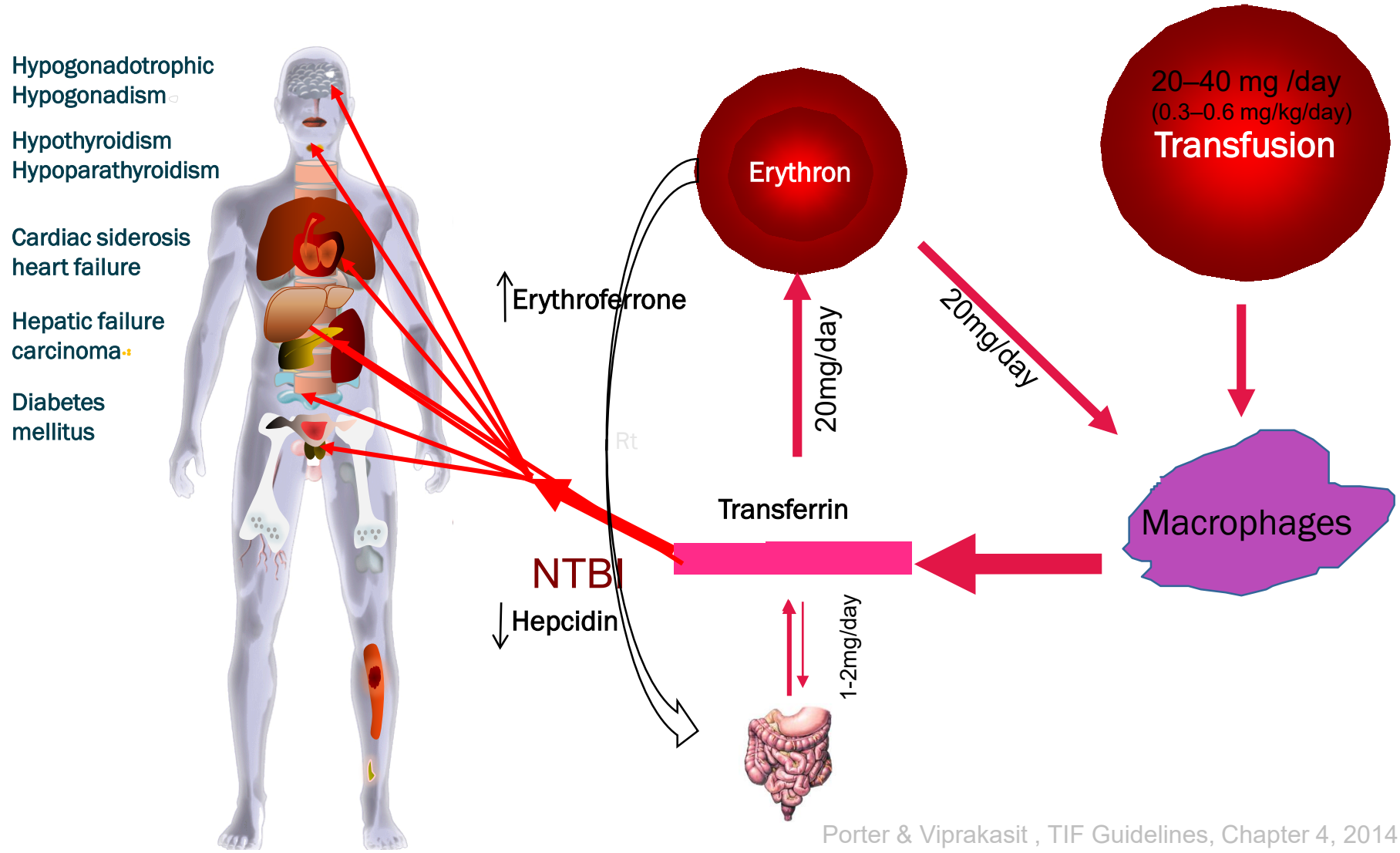


Morbidities

Chronic hemolytic anemia	Detrimental effects on growth, organ and vascular function, gall stones
Erythroid precursor proliferation	Medullary expansion, bone deformities, low bone mass
Extramedullary hematopoiesis	Splenomegaly, hepatomegaly, extramedullary pseudo tumors
Senescence antigens	Hypercoagulability and vascular disease (splenectomy heightens risk)
Primary iron overload	Organ damage – heart, liver, endocrine (exacerbated by transfusions)

Taher et al Lancet 2018 391:155-167

Iron Overload in NTDT and TDT



Porter & Viprakasit , TIF Guidelines, Chapter 4, 2014

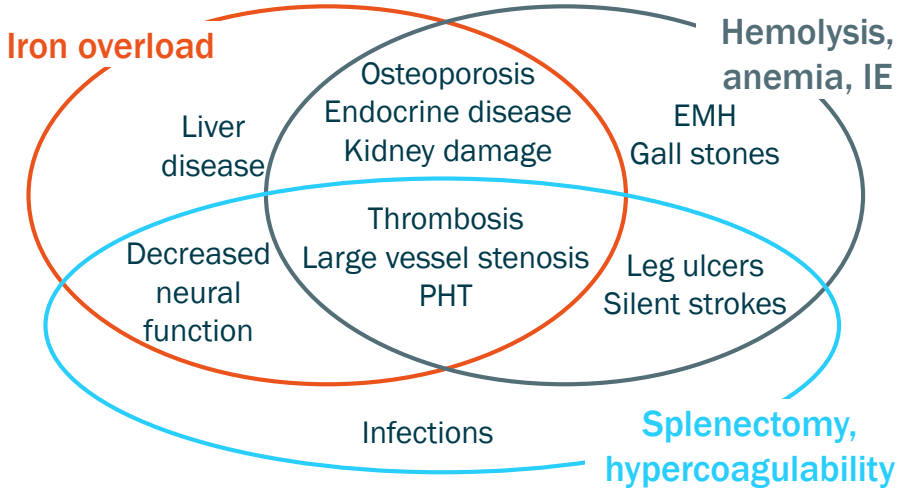
Transfusion Intensity Reflects the Underlying Severity and Contributes to Secondary Morbidities

NTDT
Non-Transfusion Dependent β-Thalassemia

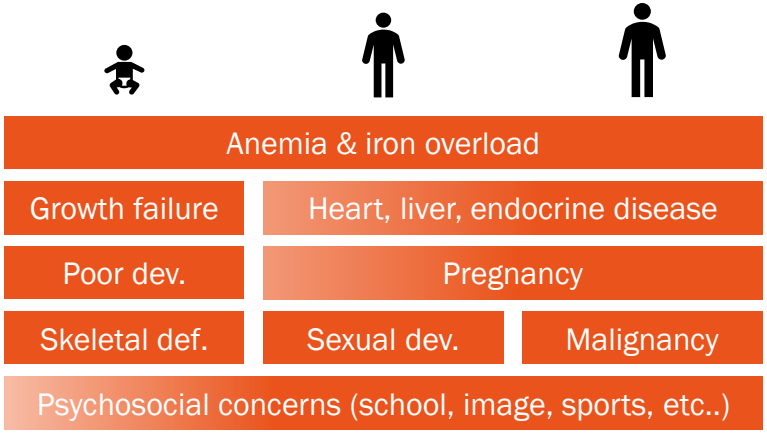
TDT
Transfusion Dependent β-Thalassemia

Spectrum of Severity and transfusion dependence

- Transfused sporadically (e.g. growth failure, management of morbidities, etc.)
- Main driver of morbidity is ineffective erythropoiesis and peripheral hemolysis
- Anemia is progressive and morbidities increase as patients age – notable incidence beyond 35 years



- Regular lifelong transfusions required for survival
- Main driver of morbidity is secondary iron overload due to regular transfusion (fatal in adolescence without chelation)
- Onset of complications can begin in childhood but risk increases with age and depends on management



Taher and Capellini Blood 2018 132(17):1781-1791; Taher et al Lancet 2018 391:155-167

Therapeutic Options in Transfusion-Dependent β–Thalassemia

Non curative

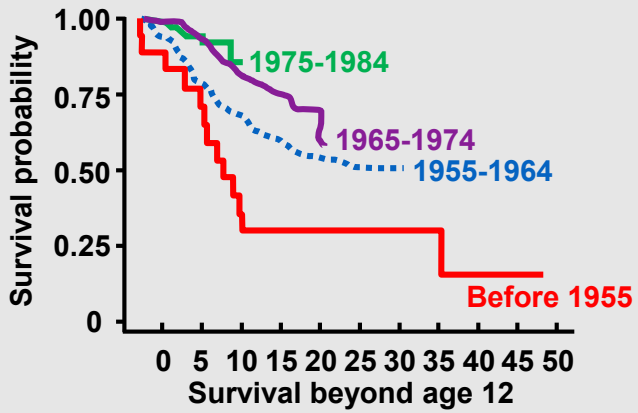
- Transfusion and chelation
- Pharmacological enhancers of effective erythropoiesis

Curative

- Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)
- Gene therapies

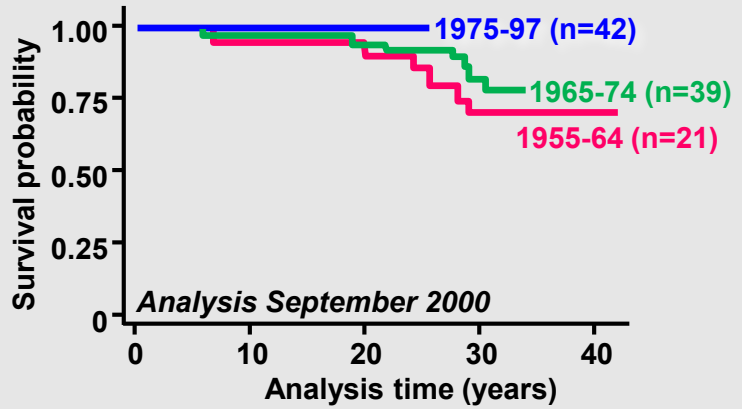
Improving Survival in Birth Cohorts of TM Patients

UK registry (N=736)



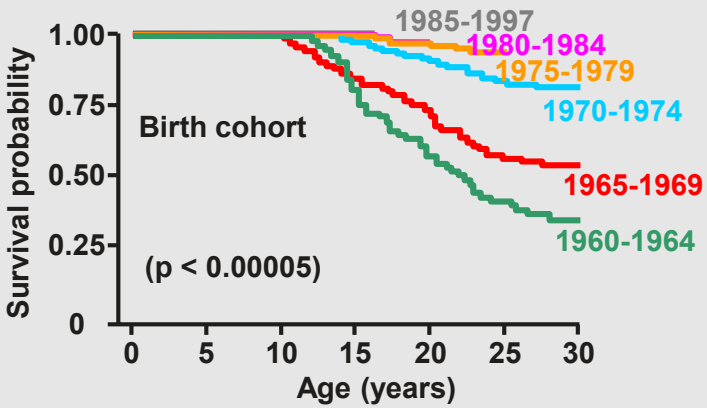
Modell et al. Lancet. 2000;355:2051.

UCLH, UK (N=103)



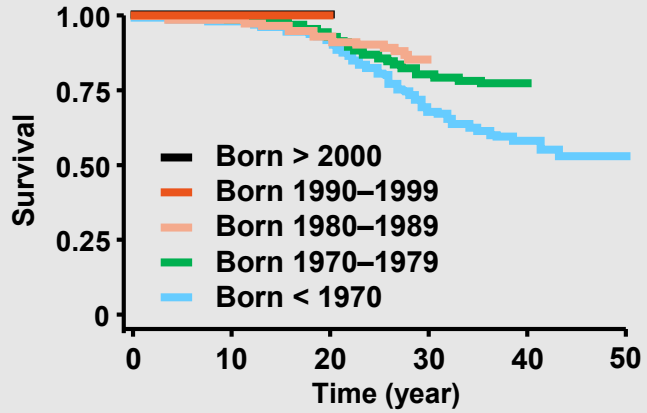
Porter & Davis Best Pract Res Clin Haematol, 15, 328-68 2002

Italian patients



Borgna-Pignatti C, et al. Haematologica. 2004;89:1187-93.

Greek patients



Ladis V, et al. Eur J Haematol. 2011;86:332-8.

Decline in Co-Morbidities in TDT with Introduction of Iron Chelation

Patients with β-thalassemia major born after 1960 (N = 977)

	Birth 1970–1974*	Birth 1980–1984†
Death at 20 years	6.3%	1%
Hypogonadism	64.5%	14.3%
Diabetes	15.5%	0.8%
Hypothyroidism	16.7%	4.9%

*DFO i.m., 1975; †DFO s.c., 1980.

In 1995, 121 patients switched to deferiprone (censored at this time)

Borgna-Pignatti C, et al. Haematologica. 2004;89:1187-93.

i.m. = intramuscular; s.c. = subcutaneous

Co-Morbidities in Transfusion-Dependent Thalassemia (TDT) (%) at UCLH

	2015	*1999*
Cardiac iron high (T2*<10ms)	4	10
Cardiac iron moderate (T2* 15-20ms)	15	47
LIC badly controlled > 15mg/g dry wt (%)	12.8	25

	age < 40 yo	*age > 40yo*
Diabetes (%) insulin dependent	10	24
Hypoparathyroidism (%)	3	13
Hypothyroidism (%)	15.5	13
Hypogonadotrophic (%) hypogonadism	35	74
Osteoporosis (%)	28	42
Thrombosis (%)	3	10.5

Porter et al, Cooley's anemia symposium 2015

Unmet Need
– Issues With Standard Thalassemia Management

High global prevalence of thalassemias

> global birth rate 50-60,000 pa

> global prevalence of 288,000 for severe β-thalassemia

Issues of delivery and adherence to transfusion + chelation

> Only 12% of children with TDT globally receive adequate *transfusion* therapy

> Less than 40% of those transfused receive adequate iron *chelation* globally

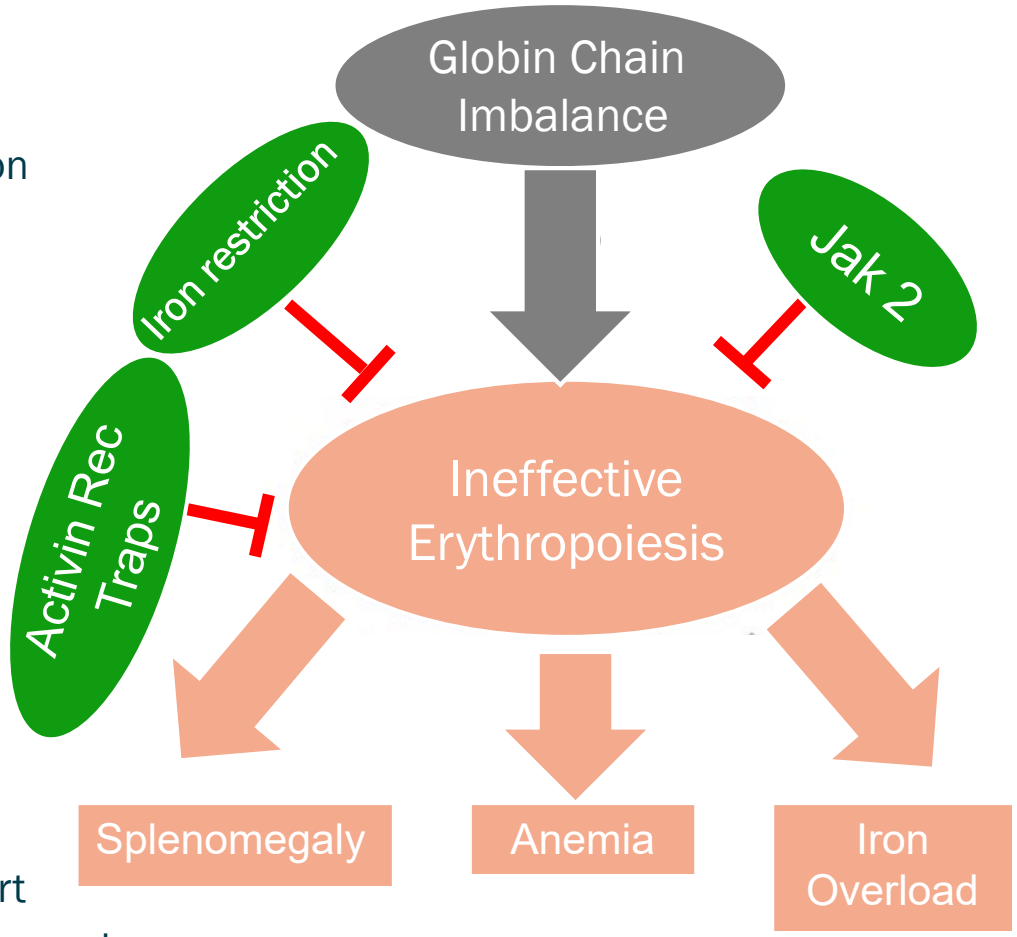
Targeting Ineffective Erythropoiesis (IE) in Thalassemias

Possible benefits of reduced IE[1]

> Improved anemia
> Reduced spleen & extramedullary expansion
> Indirect increase in serum hepcidin
> Improved QOL

Approaches

> Stimulation of proliferation (Epo)
> Decreased globin chain imbalance
  • Hb F promotion
> Jak2 inhibitors[1]
  • Decreased dyserythropoiesis
  • Decreasing spleen size
> Activin receptor traps (ACE-11, ACE-356)[3,4]
> Iron restriction[1,2]
  • Decreased iron overload in liver and heart
  • Decreased dyserythropoiesis and splenomegaly



[1]Adapted from Melchiori L *et al. Adv Hematol* 2010;2010:938640; [2]Gardenghi S, *et al. J Clin Invest* 2010;120:4466–4477
[3]Suragani R et al. *Blood* (ASH annual meeting abstracts) 2012: abst 248; [4]Iancu-Rubin C *et al.* Exp Hematol. 2013;41:155–166

Myelodysplastic Syndromes

What are Myelodysplastic Syndromes (MDS)?

A spectrum of myeloid clonal disorders

> Worldwide incidence ~5 per 100,000

> Median age at onset is in the range 65–70 years[2]

Occurrence:

> De novo (primary MDS)

> Secondary or treatment-related MDS

Significant morbidity and mortality due to:

> Cytopenias – anemia, thrombocytopenia, neutropenia

> Impaired quality of life

> Frequent transfusions, iron overload, etc.

> Risk of transformation to acute myeloid leukemia (AML)

IPSS-R (Revised)
Prognostic Risk Category Clinical Outcomes*

Categorizes patients into 1 of 5 groups, based on risk of mortality and AML transformation

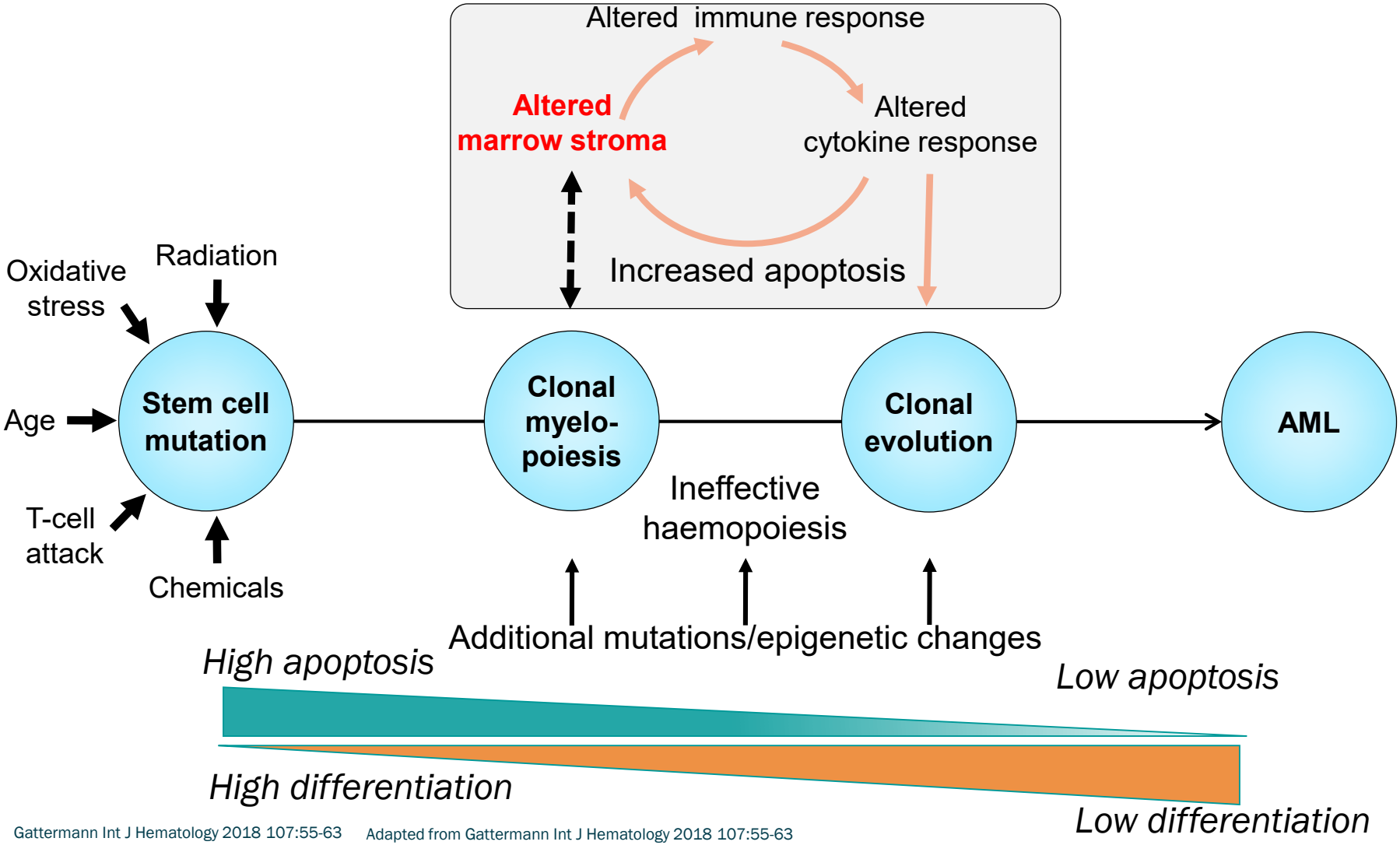
> Composite Scoring system from 0 to 4

> Categories: cytogenetics, bone marrow blast %, Hemoglobin, Platelets, Absolute neutrophil count

	No. patients	Very low	Low	Intermediate	High	Very high
Patients (%)	7012	19%	38%	20%	13%	10%
Survival***		8.8	5.3	3.0	1.6	0.8
AML/25%***		NR	10.8	3.2	1.4	0.7

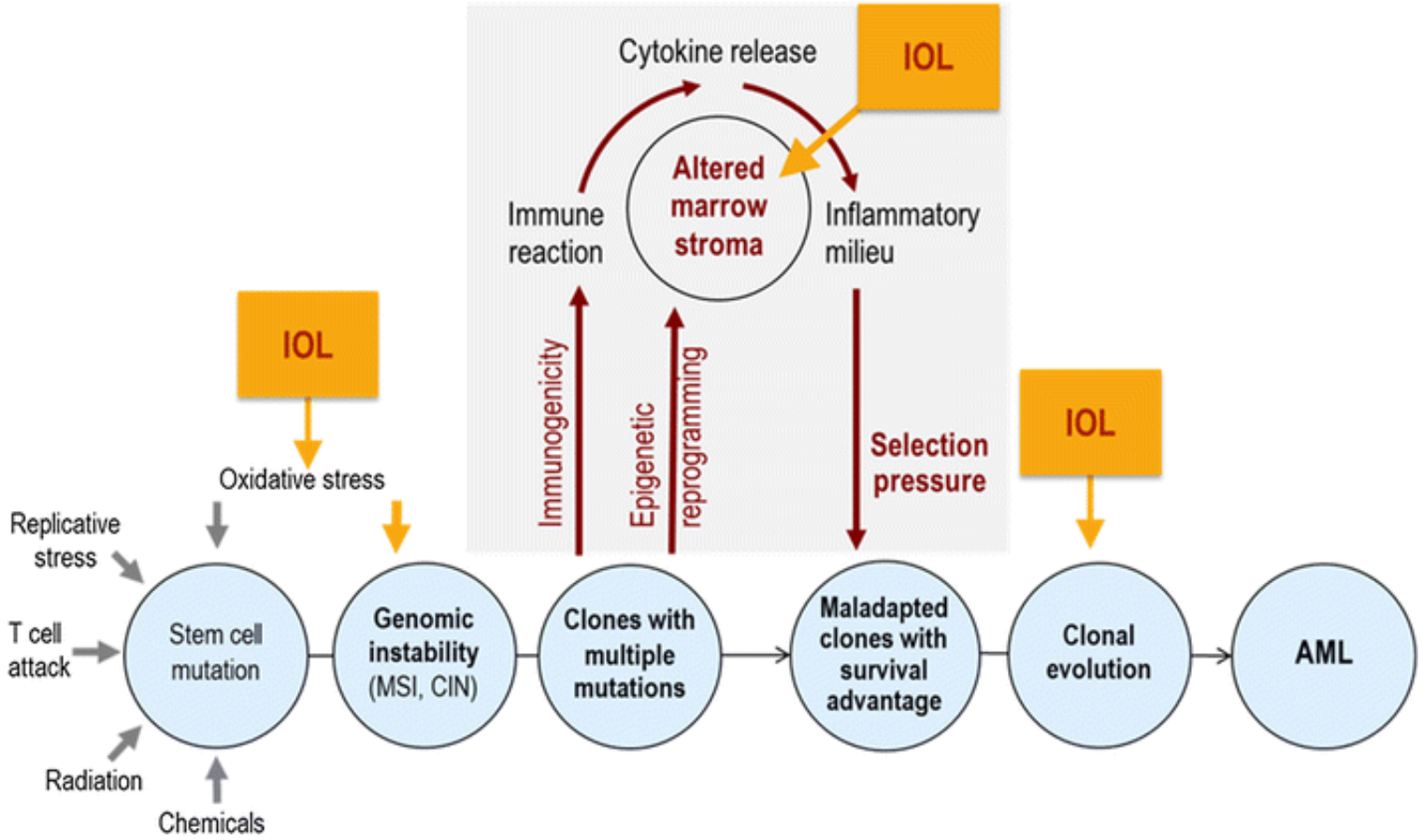
*Greenberg, et al, Revised International Prognostic Scoring System (IPSS-R) for MDS, Blood 120: 2454, 2012.
***Medians, years ^Median time to 25% AML evolution
**Schanz J et al, J Clin Oncology 2012; 30:820

Myelodysplastic Syndromes Etiology and of Progression to AML



Gattermann Int J Hematology 2018 107:55-63 Adapted from Gattermann Int J Hematology 2018 107:55-63

In MDS, Iron Overload Contributes to Ineffective Erythropoiesis, Stromal Dysfunction and Genetic Instability



In addition to its negative impact on erythropoiesis, iron overload aggravates oxidative stress and causes stromal dysfunction, potentially leading to faster clonal evolution towards leukemia

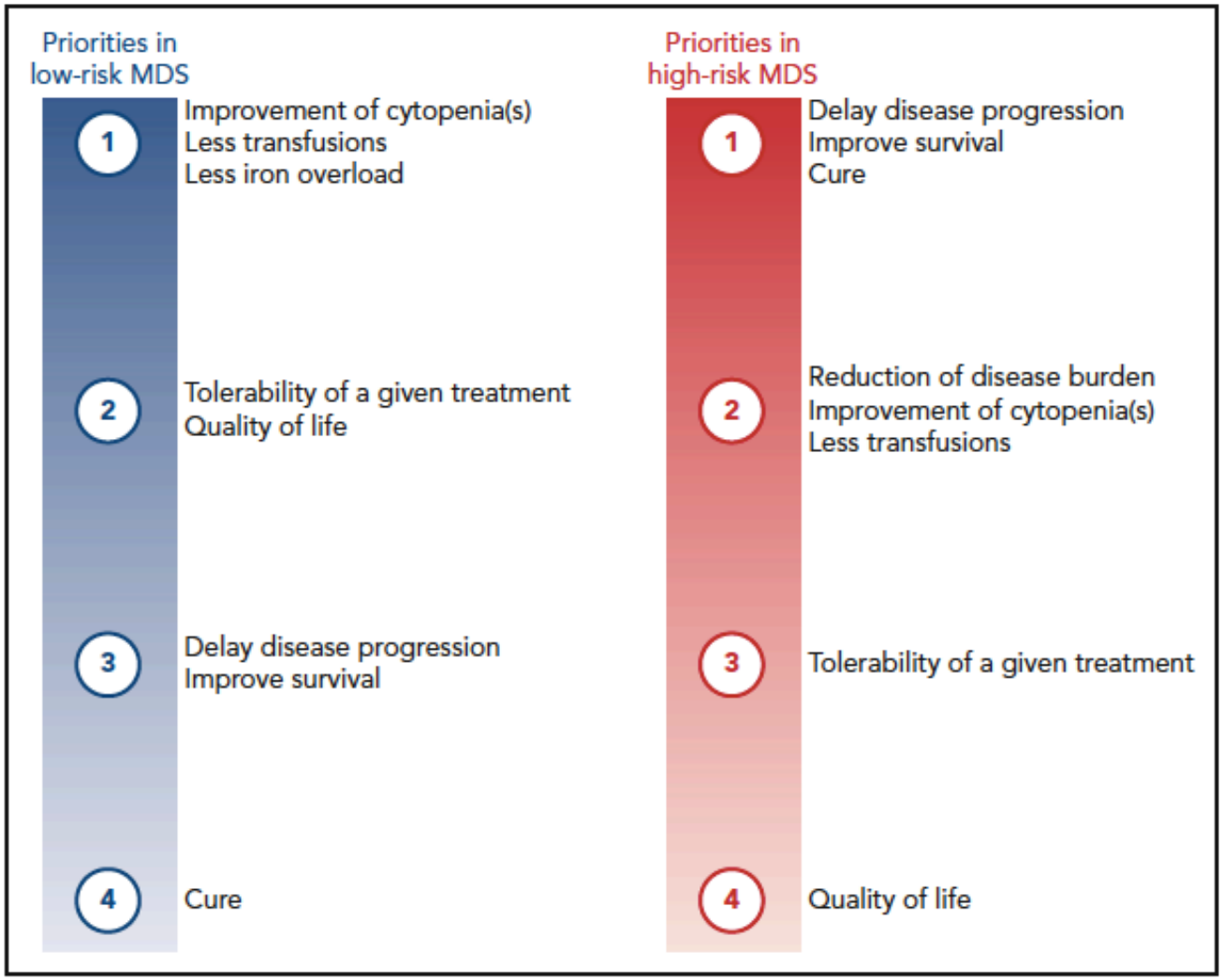
Gattermann Int J Hematology 2018 107:55-63

Treatment Options in MDS

Lower risk (IPSS Low, Int-1)	Higher risk (IPSS Int-2, High)
• EPO (ESAs) ± G-CSF	• Allo-SCT
• Immunosuppression – ATG ± cyclosporin	• HMAs: 5-azacitidine, decitabine
• Lenalidomide – del(5q)	• Intensive chemotherapy
• HMAs: 5-azacitidine, decitabine	
• Transfusion + Iron chelation	
• Platelet support	
• Allo-SCT	
• Novel Approaches	

IPSS, International Prognostic Scoring System; Int, intermediate; ATG, antithymocyte globulin; EPO, erythropoietin; G-CSF, granulocyte colony-stimulating factor; HDAC, histone deacetylase; SCT = stem cell transplantation

Therapeutic Priorities in Low *vs* High Risk MDS



Platzbecker, Blood 2019

Unmet Need in MDS

Limitations of ESAs & lenalidomide

> High refractory rate

> Only small subset of patients eligible

Limitations of iron chelators

> Adherence major issue - older population with polypharmacy/ low tolerance for side-effects

Anemia – a major clinical challenge

> **Anemia & transfusion dependency (TD) represent major issues for lower risk MDS**

- ~90% patients require RBC transfusion (~50% regular): all hospital admissions
- Severe anemia or TD associate with:
  ↑ cardiac complications, ↑ AML progression, ↓ survival[1]

[1]Hiwase et al., Am J Hematol 2017

Competitor Overview

	Product	Company	Highest Phase	Indications	MOA	Modality	Administration
EMA	Luspatercept	Celgene (Acceleron)	Registration	2L MDS – Reg TDT – Reg 1L MDS – Ph3 NTDT – Ph2	Erythroid maturation agent – TGFβ ligand trap	Fusion protein	SC, every 21 days
Hepcidin-Ferroportin Axis	LJPC-401	La Jolla Pharmaceutical	Phase 2	Cardiac IO in TDT – Ph2 HH – Ph2	Hepcidin mimetic	Synthetic peptide	SC, weekly
	PTG-300	Protagonist	Phase 2	TDT/NTDT – Ph2	Hepcidin mimetic	Synthetic peptide	SC, weekly
	IONIS TMPRSS6-LRX	IONIS	Phase I (complete)	NTDT expected	TMPRSS6 down regulation	Antisense oligonucleotide	SC, monthly
	VIT-2763	Vifor	Phase I (complete)	TBD	Ferroportin inhibitor	Small molecule	PO, BID
Gene Therapy	Lentiglobin (Zynteglo®)	Bluebird	Approved (EMA)	TDT – EMA approved	Gene therapy – β-globin addition	Ex vivo lentiviral vector	IV, Single administration
	CTX001	Vertex (CRISPR Therapeutics)	Phase I/2	TDT – Ph1/2 SCD – Ph1/2	Gene editing – HbF induction	Ex vivo CRISPR/Cas9	IV, Single administration
	ST-400	Sanofi (Sangamo)	Phase I/2	TDT – Ph1/2	Gene editing – HbF induction	Ex vivo – zinc finger nuclease	IV, Single administration

Summary of Clinical Stage Competitors

Luspatercept

> Launch expected in early 2020 in transfusion dependent β-Thalassemia and first-line MDS; expansion expected to NTDT (ongoing Phase 2) and second-line MDS (ongoing Phase 3)

> Majority of patients (60-80%) missed primary endpoint in Ph3s; potential to target non-responsive patient groups with SLN124

> Unfavorable 3-weekly schedule and potential safety concerns (back pain, fatigue, possible CVD risk)

Hepcidin-ferroportin axis

> Hepcidin mimetics (LJPC-401 and PTG-300) have an unfavorable profile – weekly dosing, high rates of injection site reactions, short half-life resulting in fluctuations in iron parameters

> Ferroportin inhibitor (VIT-2763) has an unfavorable profile – fluctuations in iron parameters even with BID dosing, high rates of TEAE but limited details

> Antisense oligonucleotide targeting TMPRSS6 – siRNA approach is potentially safer and Phase Ib in patients presents opportunity to fast track development

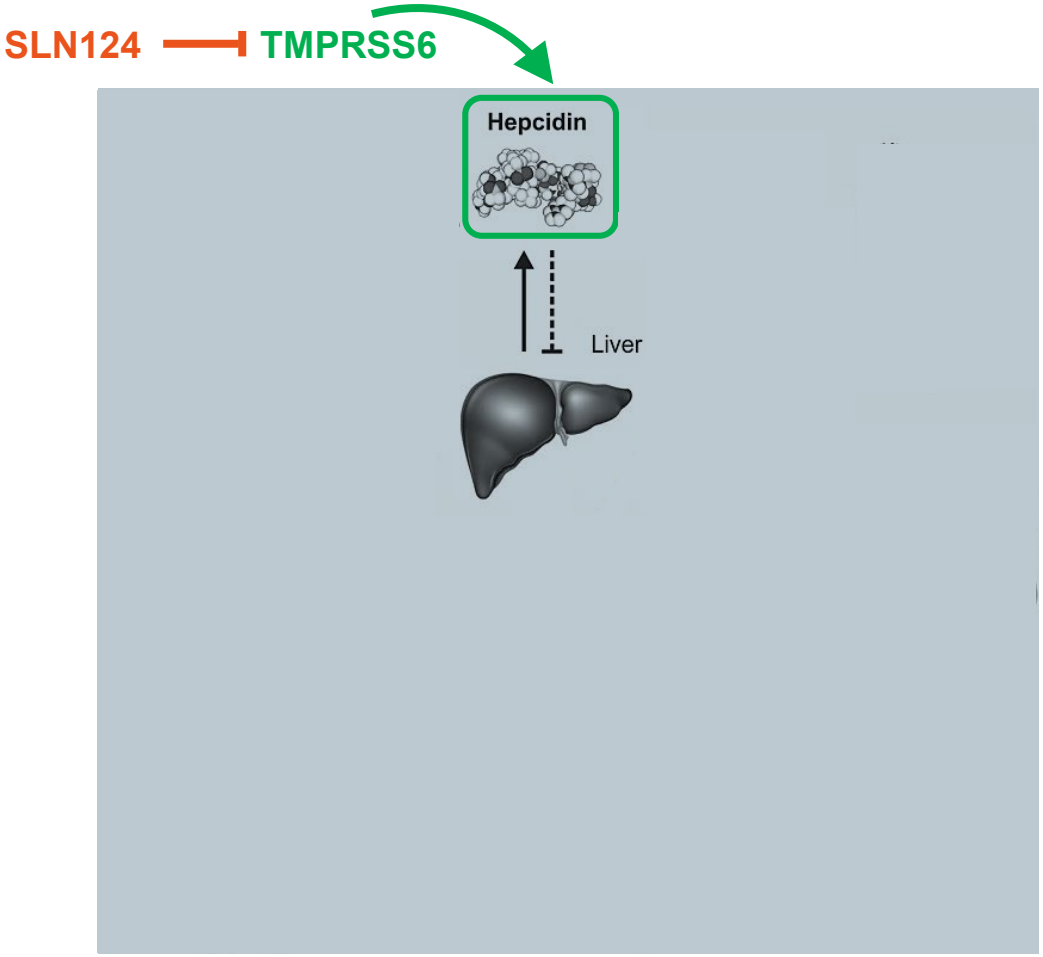
Gene therapy

> Will be limited to TDT patients who are eligible for SCT – myeloablative conditioning carries significant risk

> Complexity of procedure/manufacturing, PRMA challenges and infrastructure requirements expected to further limit use to a small subset of patients

Hepcidin, Iron Balance and Erythropoiesis

Hepcidin – The Regulator of Plasma Iron



- Hepatic-derived primary regulator of iron homeostasis
- Controls plasma iron by regulating
  - intestinal absorption
  - iron recycling from macrophages
- Hepcidin deficiency leads to iron toxicity/iron overload
  - Iron loading anemias – inherited (β-Thalassemia)/ acquired (MDS)

Adapted from Anderson & Frazer, Am J Clin Nutr 2017

Iron Restriction as a Therapeutic Tool?

Iron restriction is a physiological adaptation in anemia of chronic disease

- Hepcidin induced reduction in transferrin saturation
- Iron restriction as a therapeutic tool?

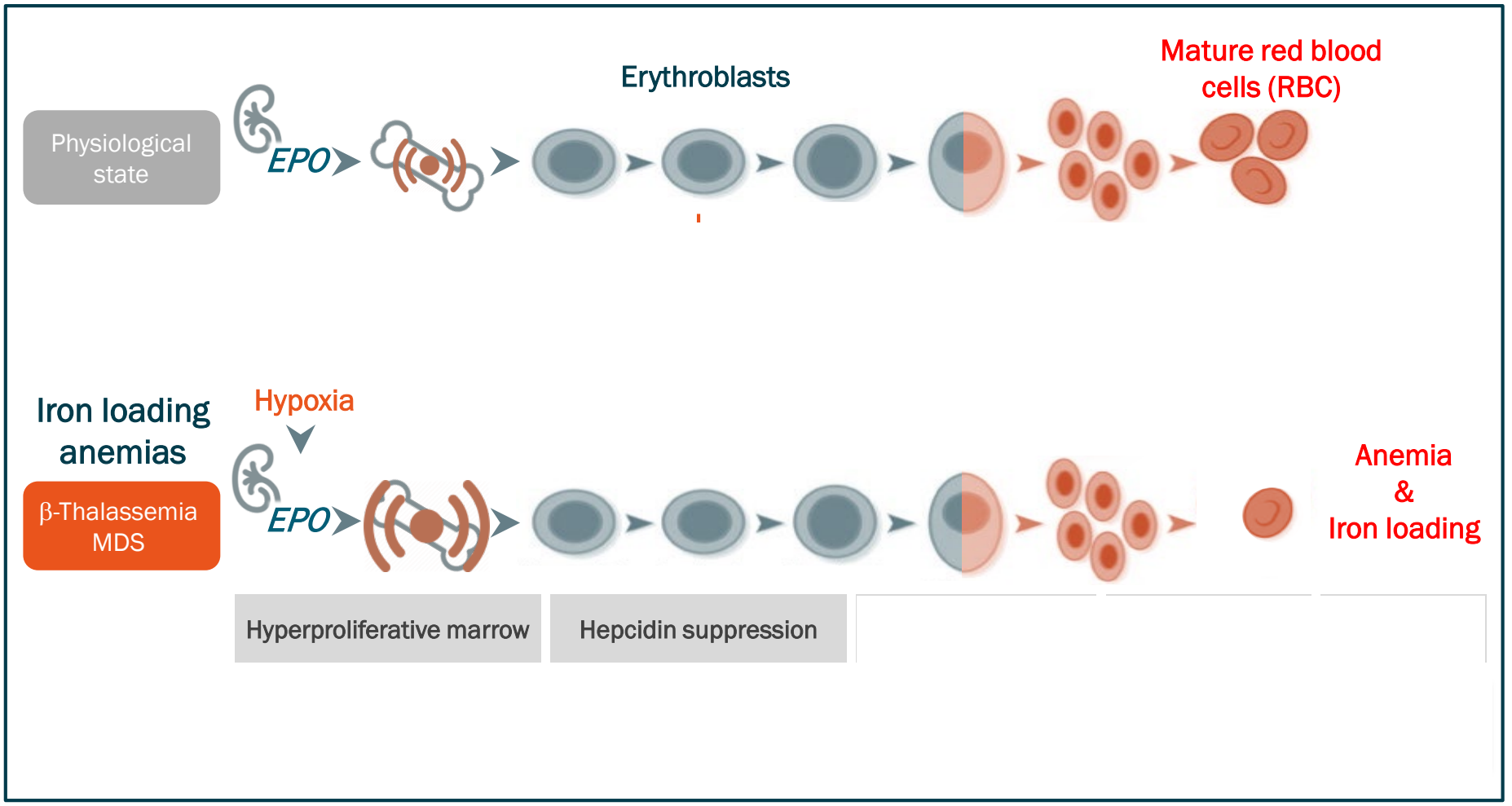
Approaches to iron restriction to modulate ineffective erythropoiesis

- By transferrin treatment
- By hepcidin mimetics
- By ferroportin inhibitors
- By increasing hepcidin synthesis, e.g. with SLN124

Iron restriction by TMPRSS6 inhibitors

- Gene ablation, siRNA or ASO techniques inhibit TMPRSS6 expression to stimulate endogenous hepcidin production
- Data from preclinical mouse models of β-Thalassemia demonstrate improvements in
  - anemia,
  - reduction of ineffective erythropoiesis,
  - splenomegaly,
  - iron overload.

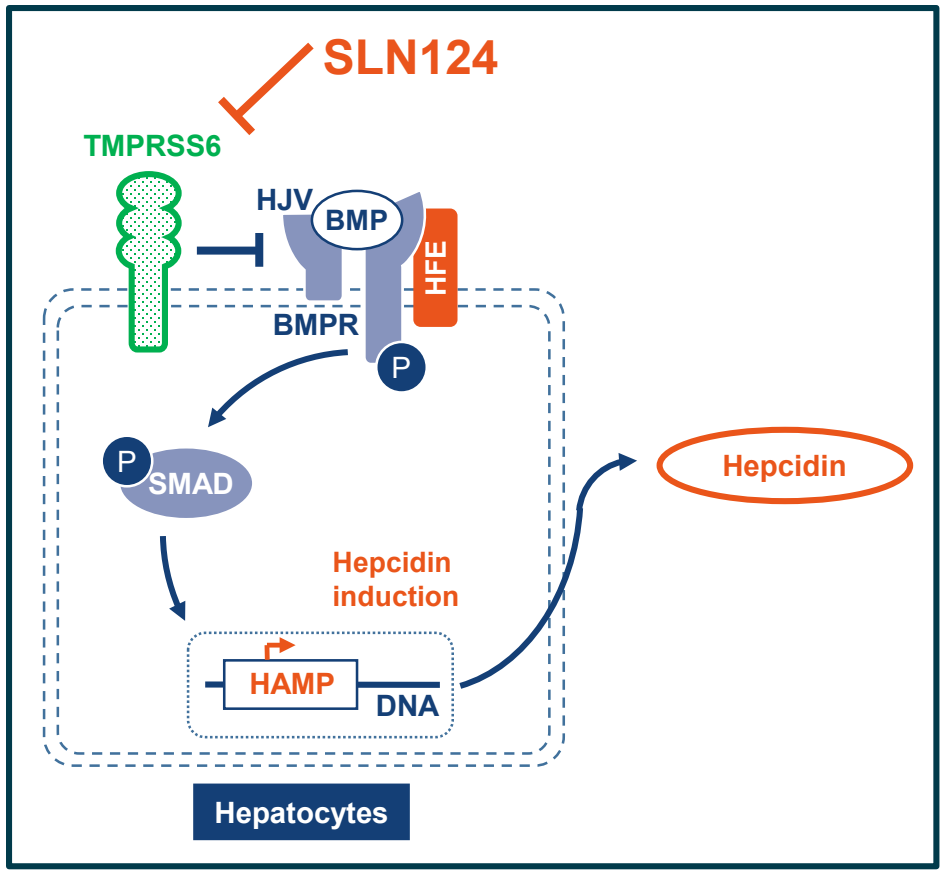
Persistent Ineffective Erythropoiesis Suppresses Hepcidin to Promote Iron Toxicity and Anemia



β-Thal =β-Thalassemia; MDS = Myelodysplastic syndromes; HBB = β-globin; HSC = Hematopoietic stem cell; ROS = reactive oxygen species

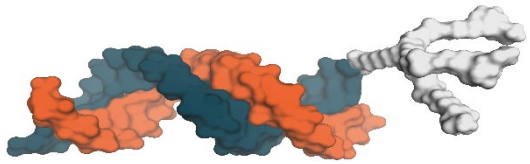
SLN124: TMPRSS6 as a Target for Drug Action

Rationale for Targeting TMPRSS6 in Iron Overload Disorders



- **Hepcidin is the master regulator of iron homeostasis**
  - Reduces dietary iron absorption and controls release of iron from storage cells
  - Hepcidin levels are low in patients with iron-loading anemias
- **TMPRSS6** (Transmembrane Protease Serine 6) is a negative regulator of the BMP/SMAD pathway
- Activation of the pathway induces hepcidin expression
- **Therapeutic hypothesis:** inhibition of TMPRSS6 expression in the liver will raise hepcidin, reduce iron absorption and improve erythropoiesis

SLN124 - a GalNAc conjugated siRNA approach



Loss of TMPRSS6 is Well Characterized in Animal Models

In iron-loading conditions

> Ablation of TMPRSS6 expression in murine models for β-Thalassemia or hereditary hemochromatosis[1,2]

- Improves hematopoiesis, ameliorates anemia, corrects splenomegaly
- Normalizes transferrin saturation, corrects iron overload

In the absence of iron-loading conditions

> Deletion of TMPRSS6 gene in mice

- impairs iron absorption, restricts iron availability leading to **IRIDA** phenotype with microcytic anemia[3,4,5]

[1]Nai et al., Blood 2012; [2]Finberg et al., Blood 2012; [3]Du, Science 2008; [4]Willemetz et al., Blood 2014; [5]Bartnikas et al., Haematologica 2013; Folgueras et al., Blood 2008

Relevant Animal Disease Models to Study Iron-Loading Anemia and Hepcidin Deficiency

β-Thalassemia intermedia

> $Hbb^{th3/+}$ mice
> Beta globin gene defect causes β-Thalassemia
> Prototypical iron-loading anemia with 2° hepcidin deficiency

Collaboration with
Dr. J. Vadolas & Dr. G. Grigoriadis HUDSON INSTITUTE OF MEDICAL RESEARCH
Monash Medical Centre/Melbourne, Australia

Hereditary Hemochromatosis type 1

> $HFE^{-/-}$ mice
> HFE defective in 80% of HH patients
> IOL due to 1° genetic hepcidin deficiency

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

MDS

> Genetic complexity challenging for development of translatable animal models[1,2]
> No model of *spontaneous* IOL due to IE-mediated hepcidin suppression[3,4]
> Due to a final common pathway of hepcidin deficiency driving IOL, findings from above models translatable for the strategy to enhance hepcidin in MDS

[1]Komeno et al., J Cell Physiol 2009; [2]Wegrzyn et al., Leuk Res 2011; [3]Zhou et al., Blood 2015; [4]Jin et al., Haematologica 2018

SLN124 in Non-Clinical Models

SLN124 Reduces Transferrin Saturation in β-Thalassemic Mice

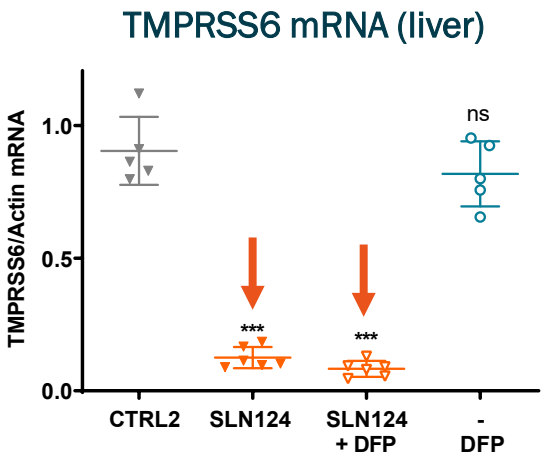
Study design

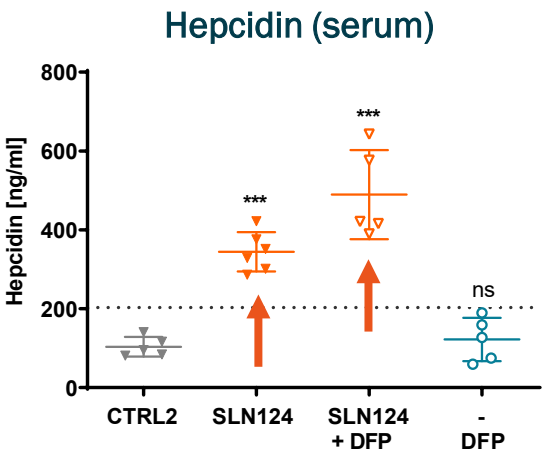
$Hbb^{th3/+}$ mice, 2-4 m, n=5-8
2x 3mg/kg SLN124 s.c.
1.25 mg/ml deferiprone in drinking water

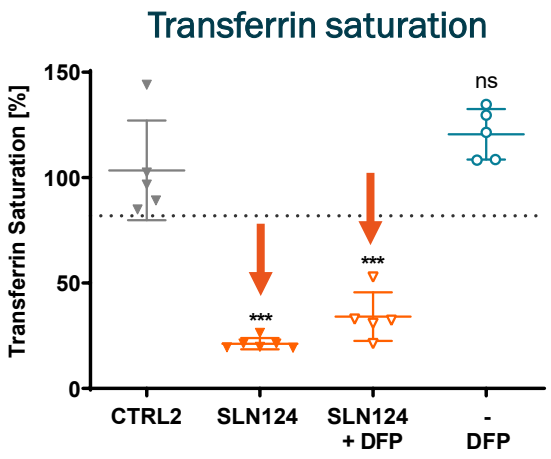


Collaboration with
Dr. J. Vadolas & Dr. G. Grigoriadis
Monash Medical Centre/Melbourne, Australia

HUDSON INSTITUTE OF MEDICAL RESEARCH







DFP = Deferiprone; CTRL2 = control siRNA

Levels of PBS-treated wild-type mice

> SLN124 raises hepcidin levels and reduces transferrin saturation
> No effect by oral DFP
> Robust reduction of Tsat is maintained in the presence of iron chelation

SLN124 Reduces ROS, Improves RBC Maturation and Raises RBC Count in Circulation 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

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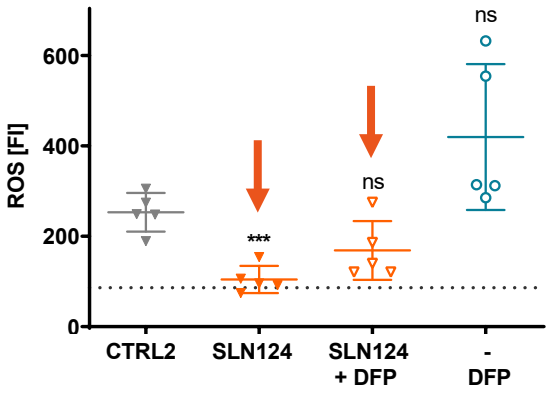
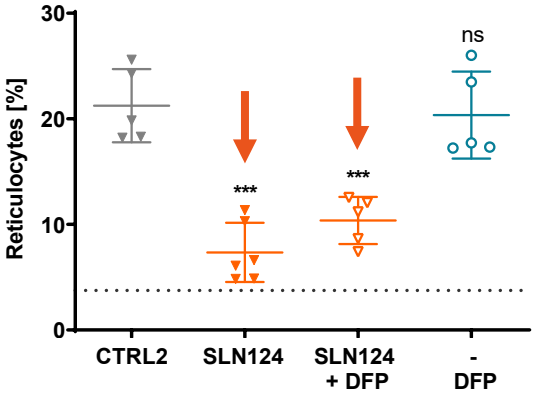
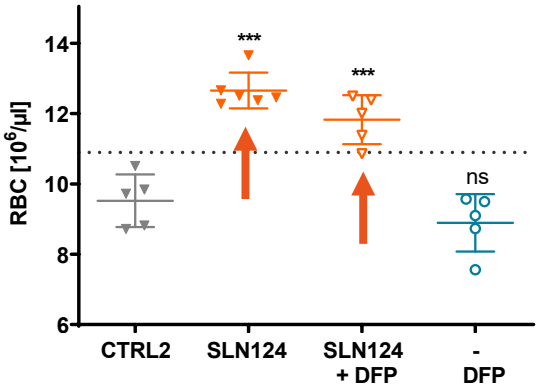
Reactive Oxygen Species (ROS)



Reticulocytes



Red Blood Cell Count



DFP = Deferiprone; CTRL2 = control siRNA

Levels of PBS-treated wild-type mice

- > SLN124 reduces iron toxicity as shown by ROS reduction
- > SLN124 improves red blood cell maturation as demonstrated by ↓ reticulocyte proportion
- > No effect by DFP alone
- > Combination with iron chelator does not impact SLN124 MOA

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

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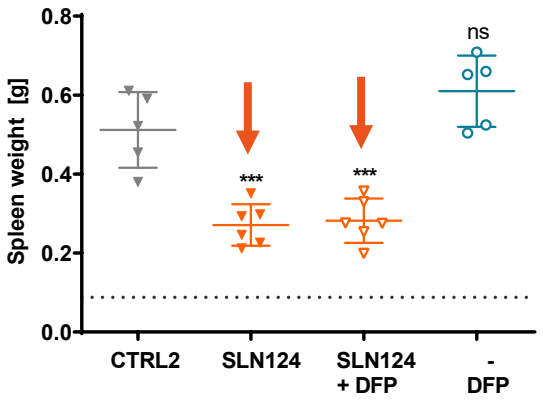

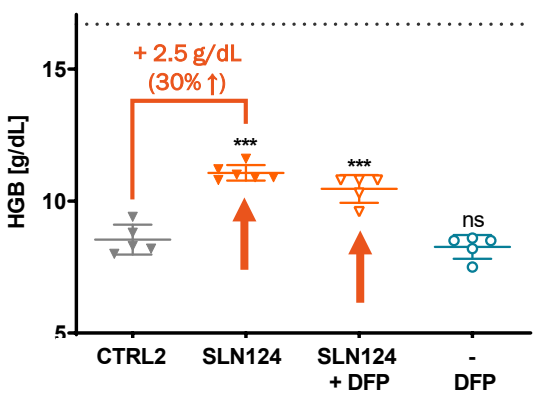

DFP = Deferiprone; CTRL2 = control siRNA

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 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

SLN124 Reduces Liver Iron Levels and Restores Normal Spleen Architecture 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

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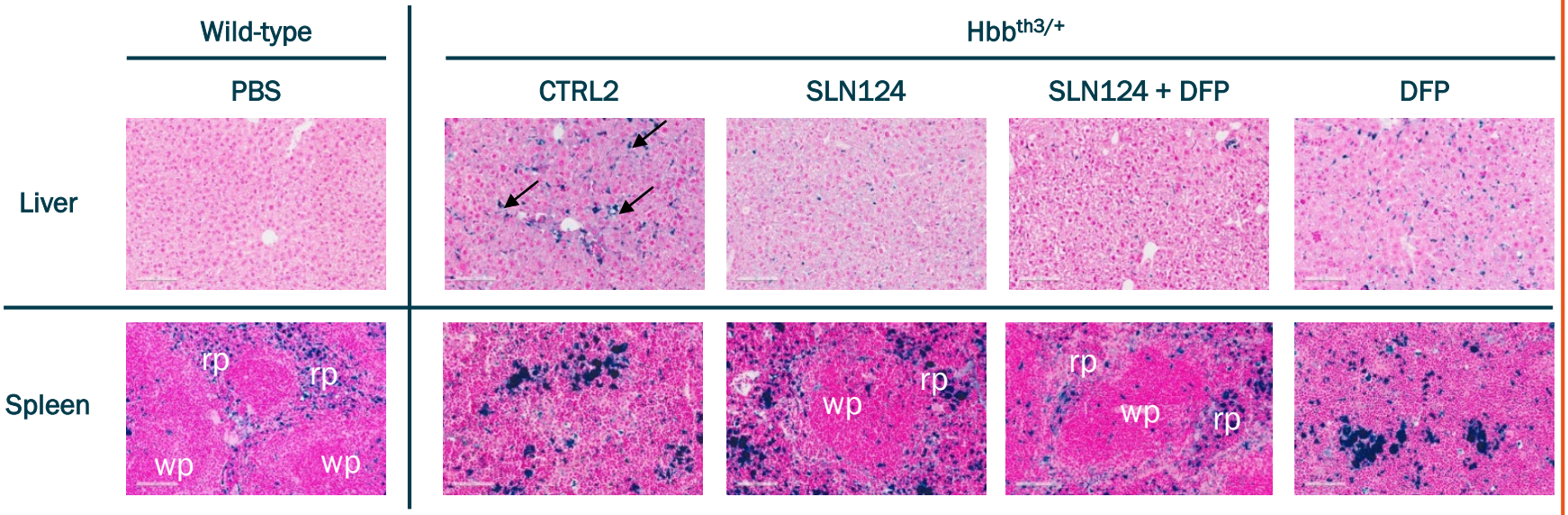
Iron detection in tissue sections (visualized by Pearl's Prussian Blue)



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

In a Hereditary Hemochromatosis model with Established Iron Overload, SLN124 Enhances Reduction of Tissue Iron Levels by Deferiprone

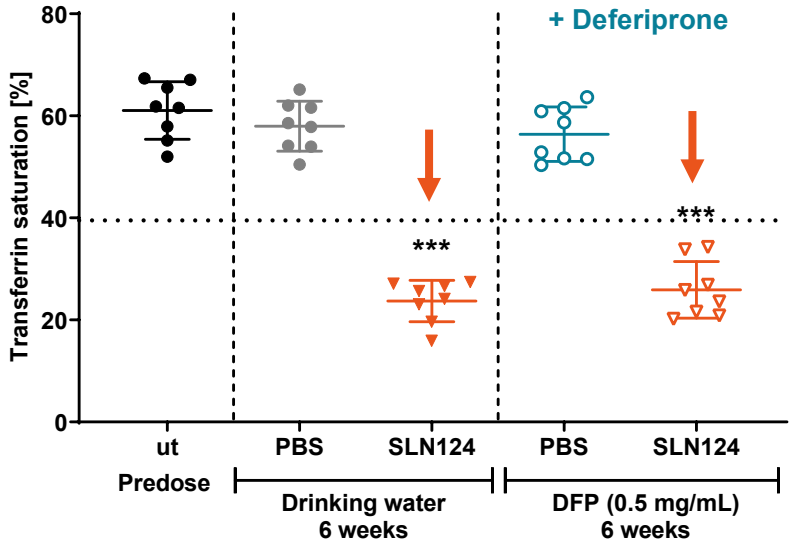
Study design

HFE$^{-/-}$ mice, females, 3 m, n=8
1 or 2x 3mg/kg SLN124 s.c.
+/- 0.5 mg/mL DFP in drinking water

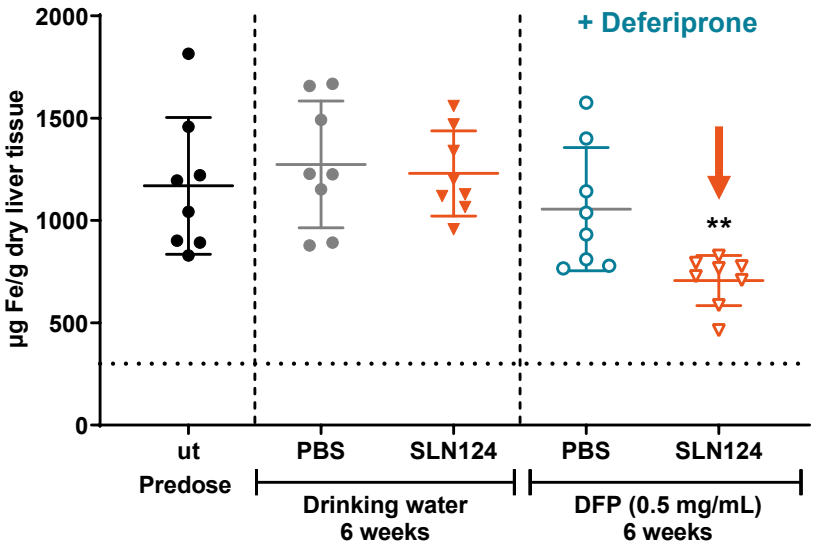


Collaboration with
Prof. Dr. Martina Muckenthaler
Heidelberg University, Germany

Transferrin Saturation



Liver Iron Content



DFP = Deferiprone; CTRL2 = control siRNA

····· Levels of PBS-treated wild-type mice

> SLN124 reduces Tsat

> SLN124 effectively enhances the reduction of iron overload by chelation

Summary

- β thalassemia and MDS are both marked by anemia characterized by ineffective erythropoiesis and increased iron-loading
- Although these diseases have distinct etiologies and affect different patient populations both display dyserythropoiesis and dysregulation of iron metabolism through low hepcidin
- Standards of care (blood transfusion, ESA, iron chelators) have greatly improved natural history of the diseases but have their own liabilities and do not address dysregulated iron homeostasis
- Multiple new approaches are in development including red cell differentiation agents– however response rates and magnitude are limited and durability still needs to be shown
- Restoration of iron homeostasis by SLN124 offers the prospect of dealing with both ineffective erythropoiesis and iron overload as shown by results in relevant animal models
- This approach is complementary (to SoC, e.g. chelators) meaning that combination treatment feasible
- The long duration of action of siRNA, with good safety profile, are likely to be key to ensuring compliance and optimizing therapeutic benefit

SILENCE THERAPEUTICS

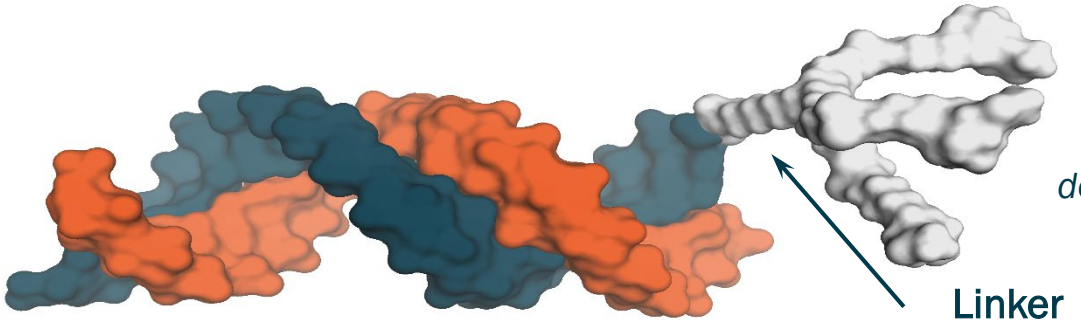
R&D Day, September 12 2019

SLN124 for the Treatment of Iron Loading Anemias

Dr Giles Campion
Head of R&D, Chief Medical Officer

SLN124 – Molecular Design

Chemical modifications
Increase stability



GalNAc (N-Acetyl Galactosamine)
Mediates targeted delivery to hepatocytes

Linker
Connects siRNA sense strand to GalNAc

Target-specific siRNA
Mediates TMPRSS6 gene silencing

GalNAc conjugation is becoming a well established strategy to direct siRNA to hepatocytes in a safe and specific manner

- GalNAc targets therapeutic siRNA molecules to hepatocytes
- siRNA highly specific for targeting a single gene
- Proprietary siRNA design algorithm to reduce the risk for off-target effects
- Short systemic exposure but long PD effects due to siRNA stabilization technology
- Requires infrequent subcutaneous administration
- High safety margin and expected favorable tolerability

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TMPRSS6 is a Well-Validated Target in Humans



> Hepcidin key regulator of iron metabolism[1]

> In humans, loss-of-function mutations in TMPRSS6 gene cause **iron-refractory iron deficiency anemia (IRIDA)**[2,3,4,5]

- Symptoms more pronounced during childhood/adolescence
- Generally normal growth and development[6]
- Major pathophysiological characteristics in blood
  - Low transferrin saturation, low ferritin levels with inappropriate high levels of hepcidin
  - Congenital hypochromic microcytic anemia
  - Refractory or only partially responsive to oral or i.v. iron supplementation
- **All features due to iron deficiency**

[1]Folgueras et al., Blood 2008; [2]Finberg et al., Nat Genetics 2008; [3]Heeney & Finberg, Hematol Oncol Clin 2014; [4]Donker et al., Am J Hematol 2016; [5]Weinstein DA et al., Blood 2002; [6]De Falco et al., Haematologica 2016

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Favorable Non-Clinical Safety Profile

- 29-day GLP toxicology studies in mice and NHP - no observations of overt signs of toxicity at any dose level (NOAEL 83.3 mg/kg/week, highest dose tested)
  - Some events considered platform-wide toxicological responses for GalNAc-siRNA conjugates independent of molecular target[1]
  - Doses 27- to 83-fold greater than the efficacious pharmacologic dose, applying an aggressive weekly treatment schedule in mice and NHPs, respectively
  - Relevant pharmacodynamic effect achieved in these healthy animals:
    - reduced hepatic TMPRSS6 mRNA expression in all SLN124 dosed groups
    - significant decreases in serum iron and transferrin saturation

[1]Janas et al., Toxicol Pathol 2018

NOAEL = Non-Observed Adverse Effect Level

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Potential Significant Benefits of SLN124

Patient care

> Differentiated MoA to ↑ hepcidin

> Combination with chelators or ESAs

> Provide much needed option for treating ESA failure

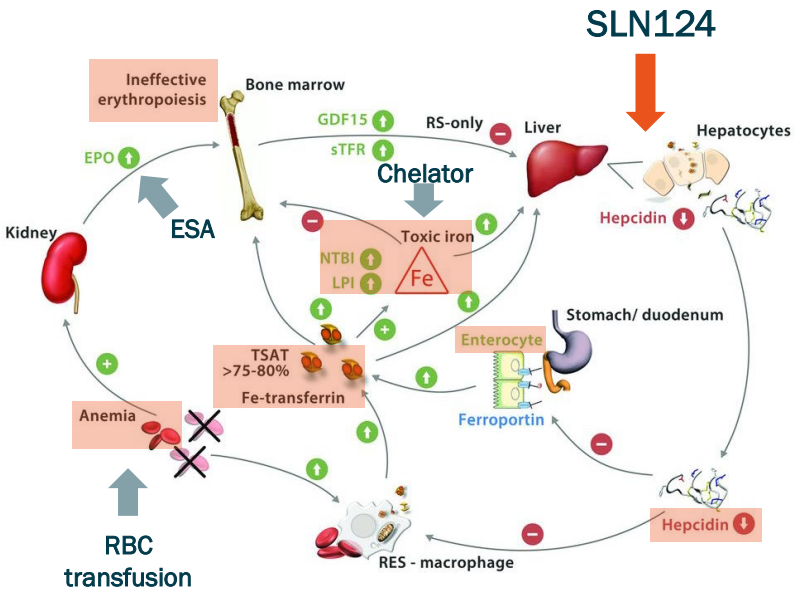
> Long duration of action: ≥ monthly s.c. dosing

Improved safety over existing therapies

> Highly targeted approach & high safety margin

> Better tolerability profile vs. chelators

Targets affected by SLN124



Modified from de Swart et al., Haematologica 2018

ESA = Erythropoietin Stimulating Agent

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SLN124 Has the Potential to Address an Unmet Medical Need by Improving Anemia and Restoring Iron Homeostasis

SLN124 vs. approved therapies to treat chronic anemia and iron overload

Therapy goal	SLN124	RBC transfusion	Iron chelators	ESAs[a]
Reduce systemic iron levels[b]	✓	✗	✓	+/-
Improve erythropoiesis[b]	✓	✗	✗	+/-
Ameliorate anemia[b]	✓	✓	✗	+/-
Reduce requirement for blood transfusions	✓	✗	✗	+/-
Prevent tissue iron overload[b]	✓	✗	✓	+/-

a = Efficacious in a subset of low risk MDS patients only; responders refractory within ~2 years

b = effects demonstrated in non-clinical animal models

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Phase Ib Clinical Trial Overview – SLN124

2-part first-in-human, single-blind, multicenter, randomized placebo-controlled single ascending and multiple dose study to assess the preliminary safety, tolerability, PD and PK of SLN124 administered subcutaneously for the treatment of Non-transfusion-dependent (NTD) β-Thalassemia and low or very low risk MDS

> The Investigators and participants will be blinded to study drug, but Silence and its representatives will be unblinded.

Part A – Single Ascending Dose (SAD) in patients with NTD β-Thalassemia or compound heterozygous hemoglobin E/β-Thalassemia

Part B – Multiple Dose (MD) study in patients with NTD β-Thalassemia or compound heterozygous hemoglobin E/β-Thalassemia and low or very low risk MDS

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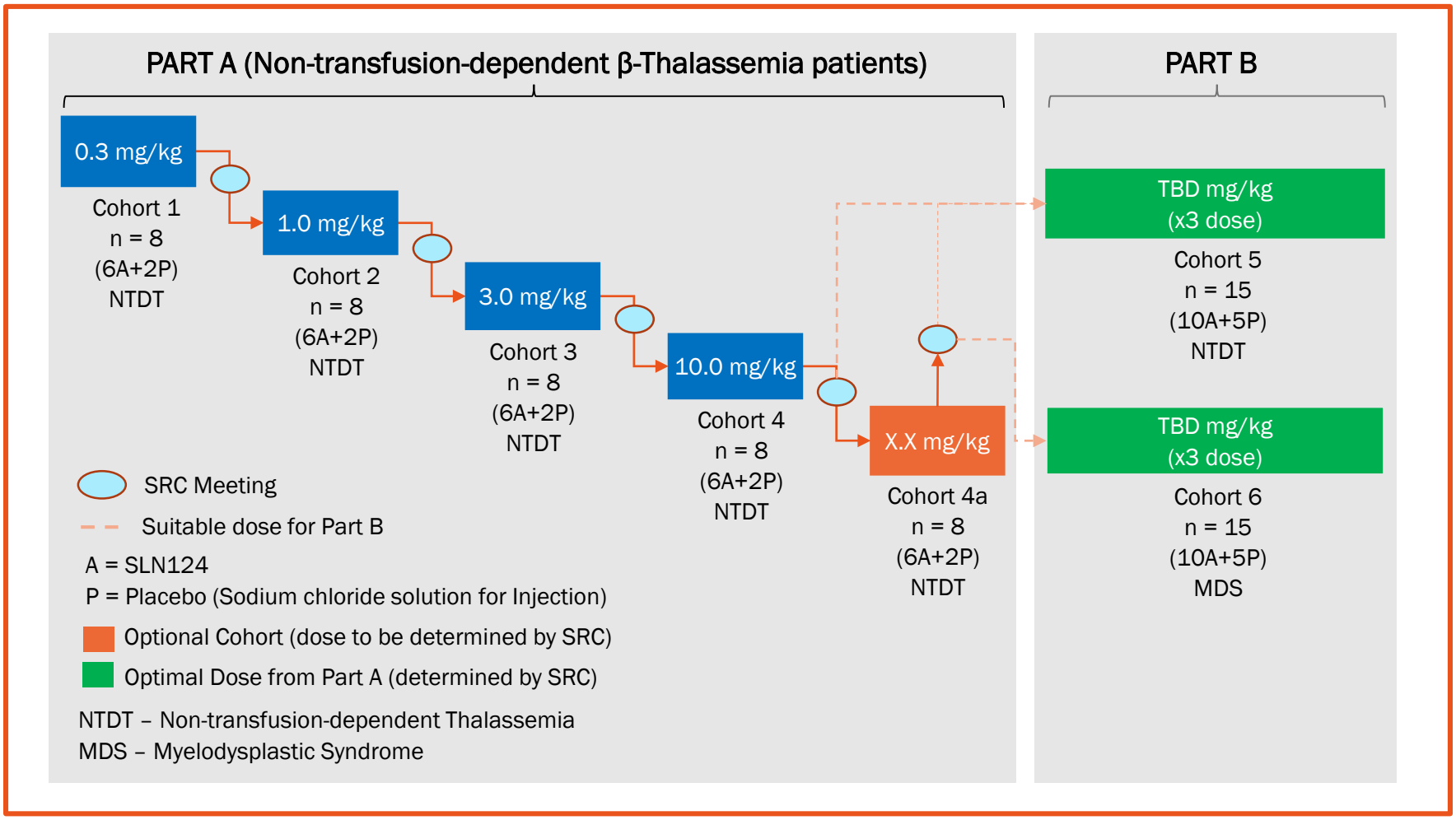
Phase Ib Study Parts A and B – SLN124



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Phase Ib Study Objectives – SLN124

- Safety and tolerability
- Pharmacokinetics
- Determine impact of single and multiple doses of SLN124 on pharmacodynamic and clinical markers of efficacy
  - Serum Fe
  - Ferritin
  - Transferrin
  - Transferrin Saturation (Tsat)
  - Non-transferrin bound iron

  → Iron overload

  - Reticulocyte count
  - Hb

  → Ineffective erythropoiesis
- Confirm in humans the positive pre-clinical data observed to date

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Phase Ib Patient Population – SLN124

- Patients selected vs. Healthy Volunteers (HV) due to the risk of causing anemia in HVs through SLN124 MoA
- Patients with NTD β-Thalassemia and low/very low risk MDS with clear evidence of biochemical iron overloading
- NTD β-Thalassemia selected with no or limited transfusion requirement
- MDS with very low, or low risk category with ring sideroblast (MDS-RS)[1]

[1] portion of early red blood cells are **ring sideroblasts** (cells that contain rings of iron deposits around the nucleus).

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Phase Ib Inclusion Criteria – SLN124

Evidence of biochemical iron overload and anemia

> Tsat, ferritin, hemoglobin

- Mean ferritin level > 300 µg/L
- Transferrin saturation > 45%
- Mean Hb 10 g/L

>Stable chelator use permitted

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SLN124 European Regulatory Interactions

Scientific advice

> Clinical and Quality with MHRA - June 2018 and January 2019

> Quality with BfArM - December 2018

EU orphan drug designation for β-Thalassemia

> Decision adopted for SLN124 - January 2019

First-in-human trial of SLN124 in MDS and β-Thalassemia

> CTA approved in the EU (UK) - May 2019

> Design allows SAD in β-Thalassemia to inform MD in MDS

- Rationale - β-Thalassemia and MDS both iron-loading anemias[1]
- Share core pathophysiological sequence of ineffective erythropoiesis, low hepcidin, excessive iron absorption and secondary iron overload[2]

[1]Camaschella & Nai, *Br J Haematol* 2016; [2]Sebastiani et al., *Front Pharmacol* 2016

MHRA = Medicines and Healthcare products Regulatory Agency; BfArM = Bundesinstitut für Arzneimittel und Medizinprodukte

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SLN124 Summary

Hepcidin deficiency - key pathophysiological mechanism linking anemia and iron overload in β-Thalassemia and MDS

- Differentiated MoA specifically targeting key iron regulator - hepcidin
- Robust Hb response in prototypical model of ineffective erythropoiesis
- Consistent ↓ in plasma iron and tissue iron overload
- Highly targeted approach (GalNAc conjugated siRNA) with high safety margin and expected favorable tolerability
- Long duration of action permitting ≥ monthly s.c. dosing: stable effects on iron overload/hemoglobin

Significant benefit to patients

- Potential to address both anemia (ineffective erythropoiesis) & iron toxicity/overload
- Potential to fulfill criteria for major Hb response - ↓ transfusion need & iron burden
- Synergy with chelators - ↓ their toxicity/side-effect burden; ↑ adherence

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SILENCE THERAPEUTICS

R&D Day, September 12 2019

Questions & Answers

SILENCE THERAPEUTICS

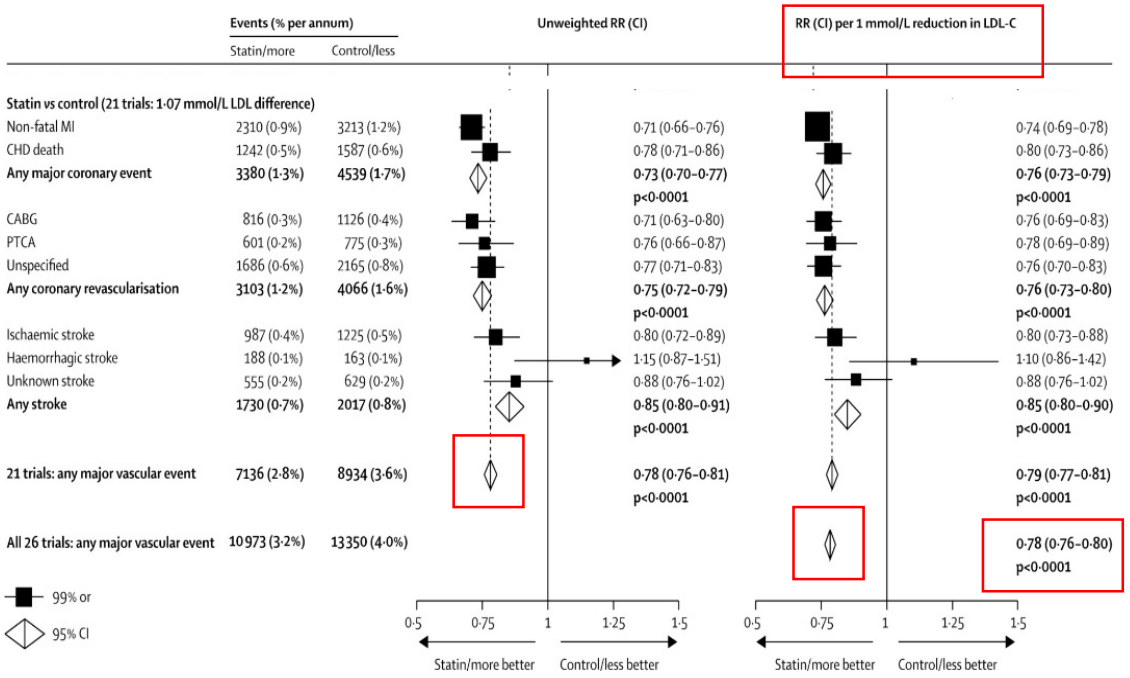


R&D Day, September 12 2019

Elevated Lp(a) and Cardiovascular Disease

Henry Ginsberg MD
Irving Professor of Medicine
Vagelos College of Physicians and Surgeons
Columbia University

Lowering LDL has Transformed the Natural History of Atherosclerotic Cardiovascular Disease



The Lancet 376 (9753)1670

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However, Rates of ASCVD Remain Elevated in High-Risk Patients Even After Dramatic Lowering of LDL-C: Why?



- Statin intolerance
- Inadequate dosing
- Inadequate use of combination therapies
- Compliance

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What Can We Do?

> Treat Statin Intolerance

> Improve Compliance

> Convince Doctors to Use Optimal Doses

> Add second drugs:

- Ezetimibe
- PCSK9 Inhibitors

But diminishing returns on LDL-C lowering and increasing problems regarding compliance

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More Importantly:
There are Non-LDL-C Causes of ASCVD



Residual risk

> Hypertension

> Smoking

> Diabetes/Insulin Resistance

> High Triglycerides

> Low HDL-C

> **LIPOPROTEIN (a)**

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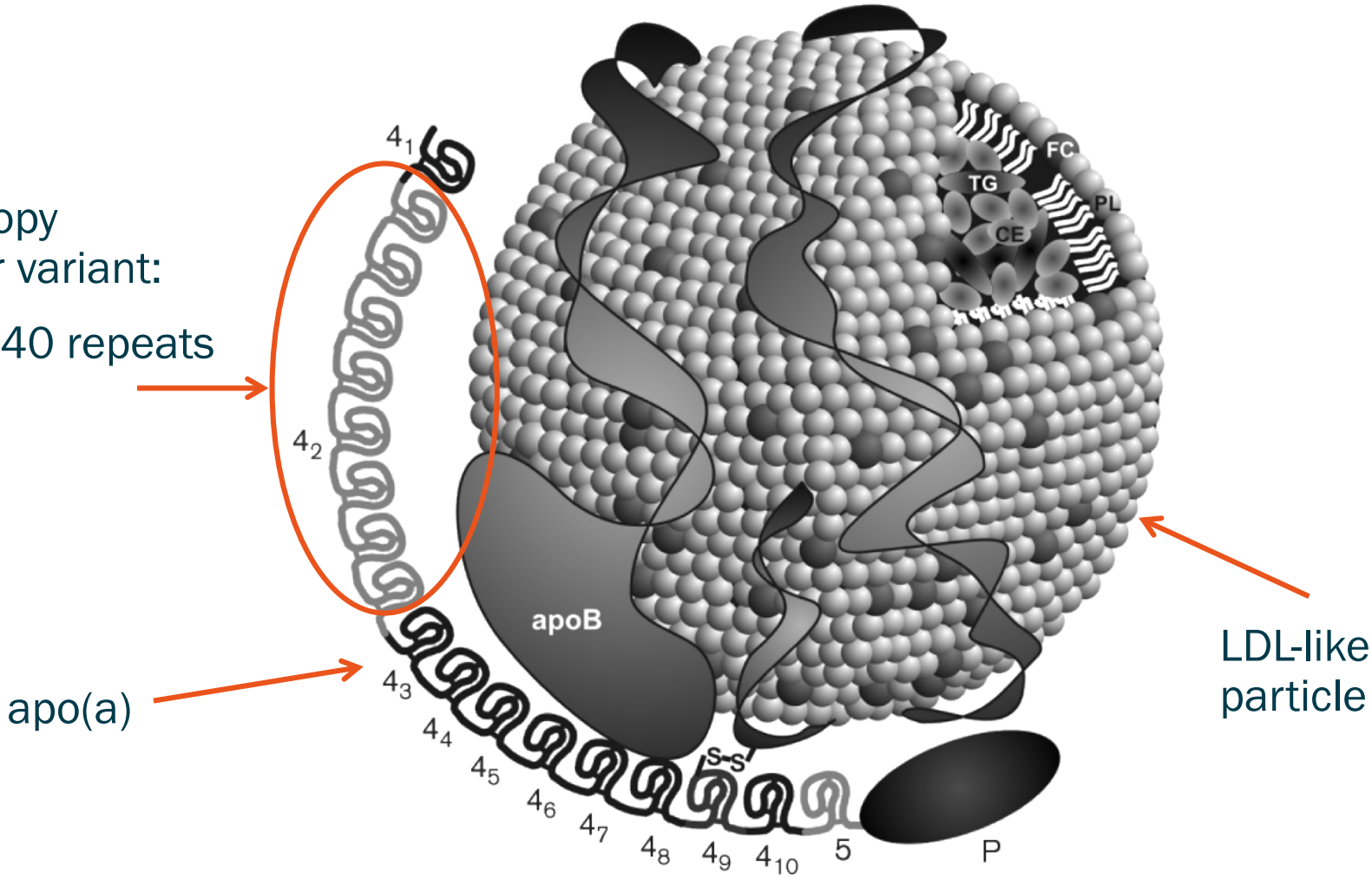
Lipoprotein(a)

KIV-2 copy number variant:

> 2 to >40 repeats



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

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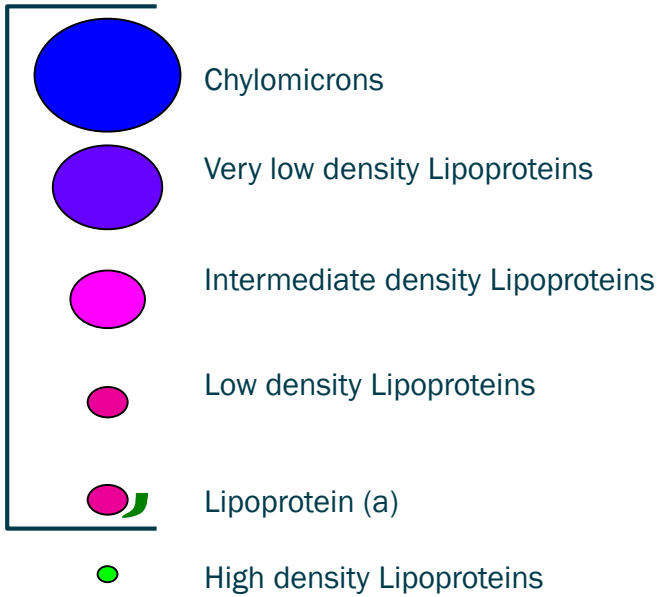
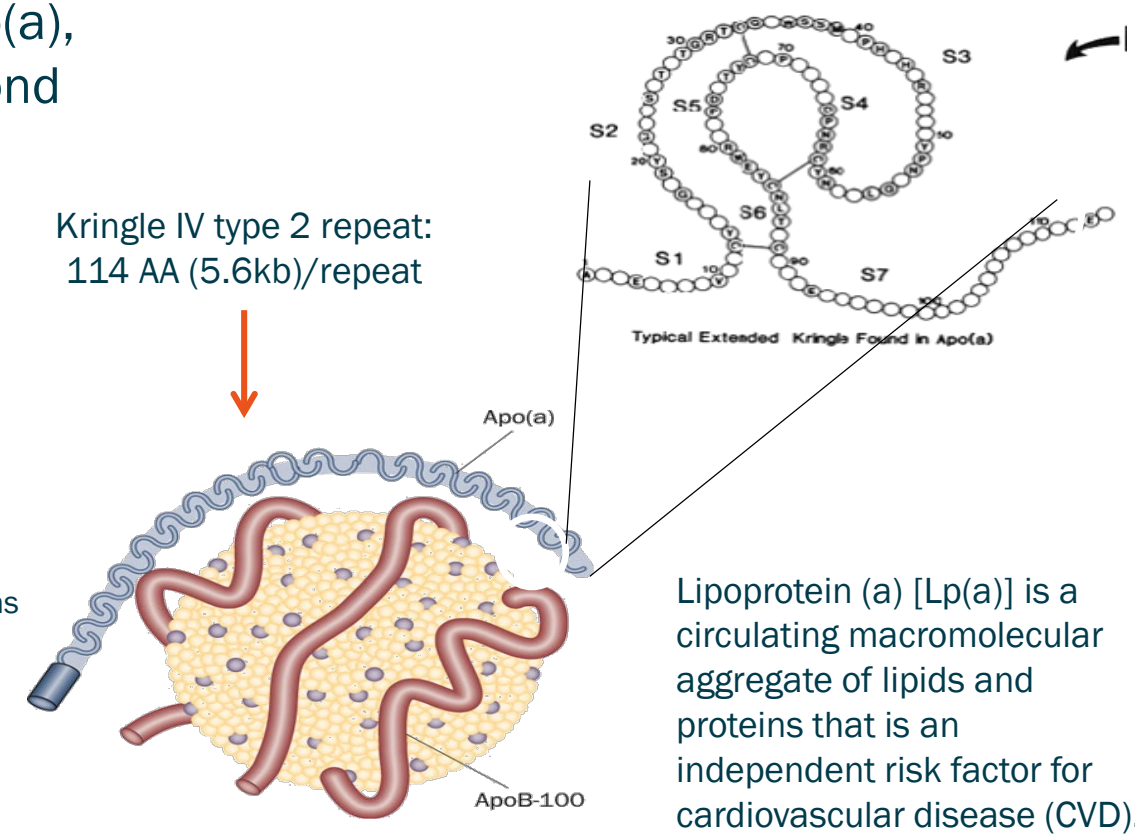
Lipoprotein(a)

Lp(a) is an LDL-like particle covalently bound to a glycoprotein, apo(a), through a single disulfide bond

Non-HDL Cholesterol



Kringle IV type 2 repeat:
114 AA (5.6kb)/repeat



Lipoprotein (a) [Lp(a)] is a circulating macromolecular aggregate of lipids and proteins that is an independent risk factor for cardiovascular disease (CVD).

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1963: Geneticist Kare Berg



- **Goal**: define lipoprotein differences between individual human sera.
- **Discovery**: Through immunological investigations of human serum he discovered a new antigen that was associated with low density lipoproteins (LDL).

He shortly showed that this new antigen was a genetic trait and proposed it be called Lp(a)

Lp: refers to lipoprotein,

"a": the accepted terminology at that time for naming antigens in human immunogenetics.

Berg K. 1963. A new serum type system in man–the LP system. Acta Pathol. Microbiol. Scand. 59: 369–382

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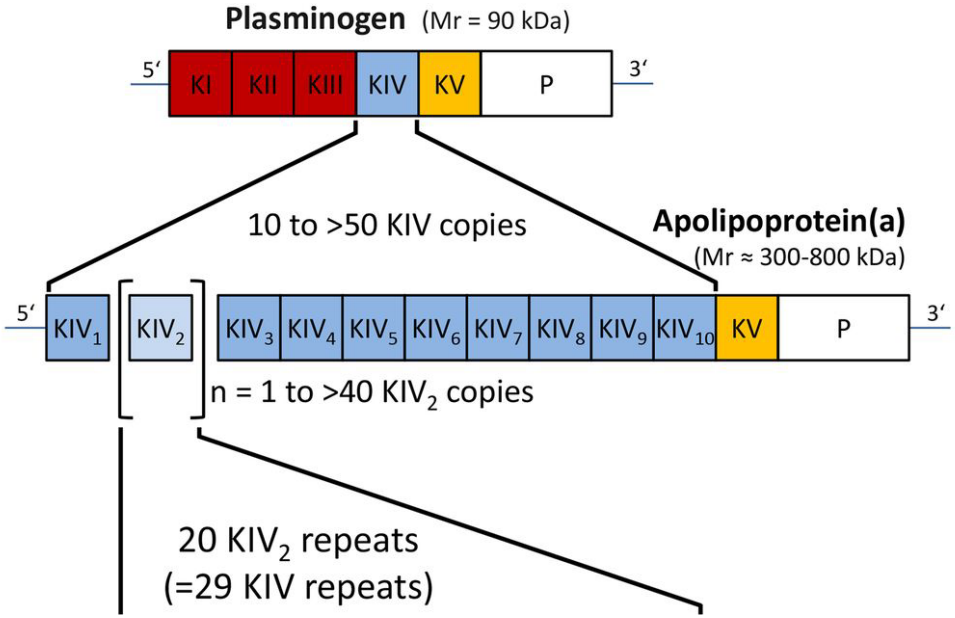
Schematic Illustration of the Structural Homology Between PLG and Apo(a)



Konrad Schmidt et al. J. Lipid Res. 2016;57:1339-1359

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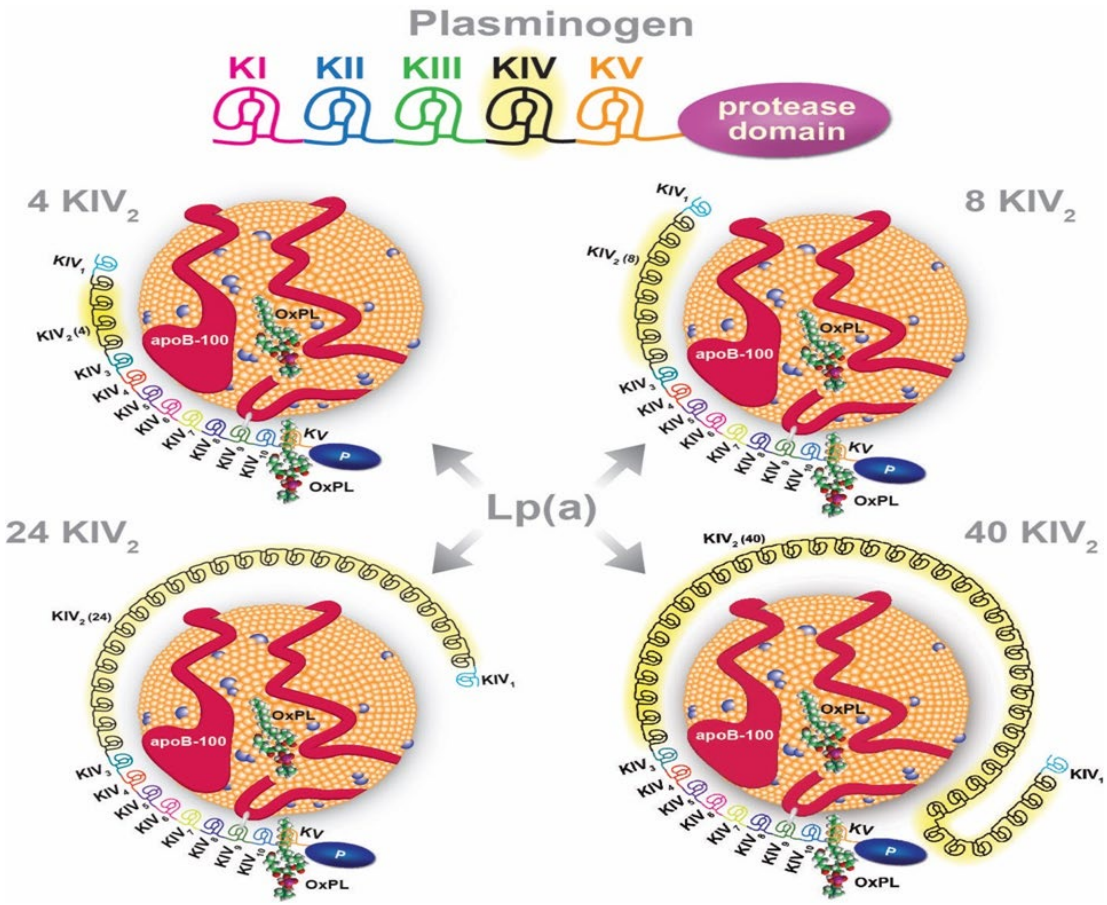
Lp(a): Particle Heterogeneity



Tsimikas, JACC, 2017, 69:692

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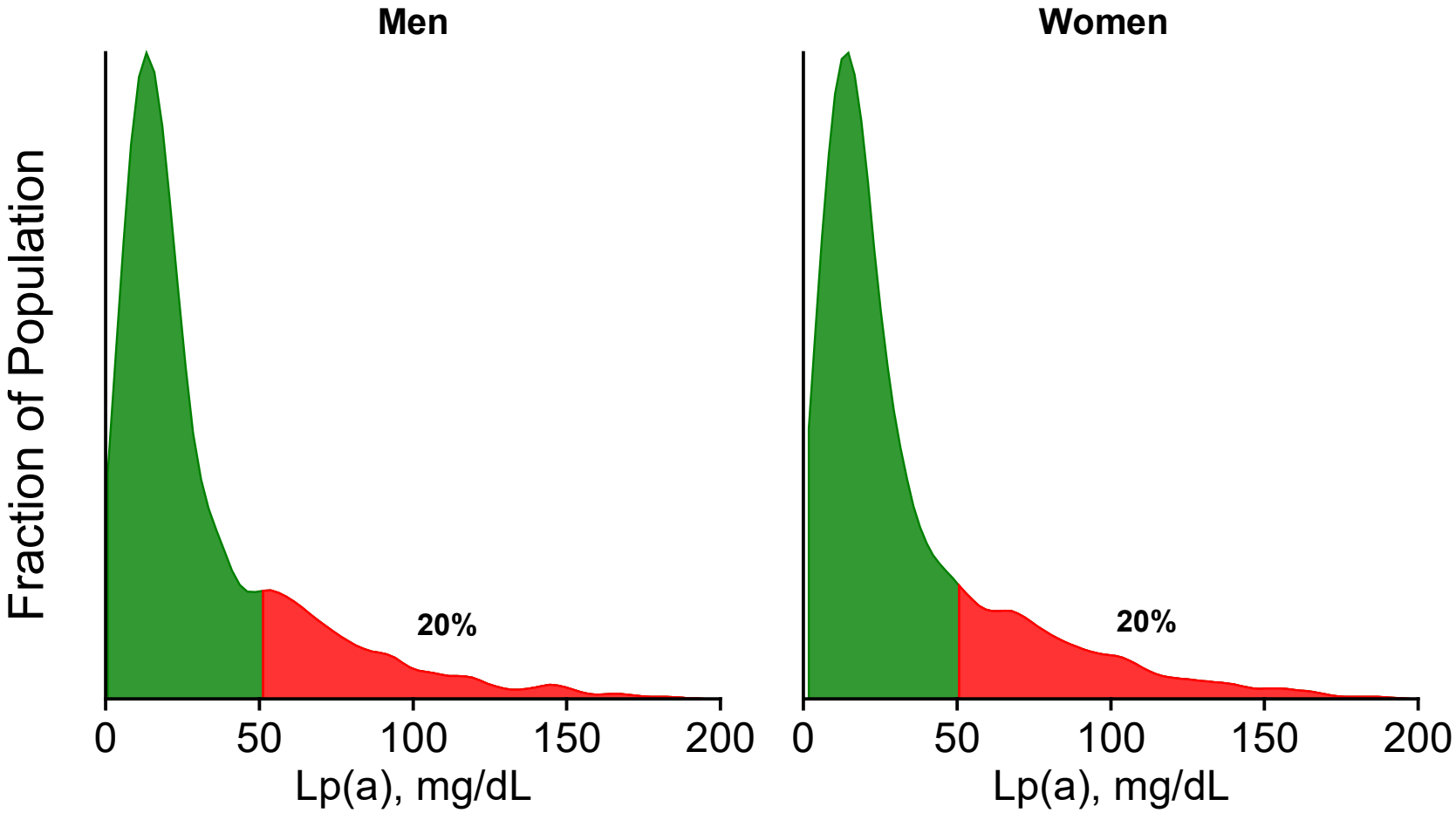
Copenhagen General Population (n=6000)



Nordestgaard B Eur Heart J: 2010 31:2844-53.

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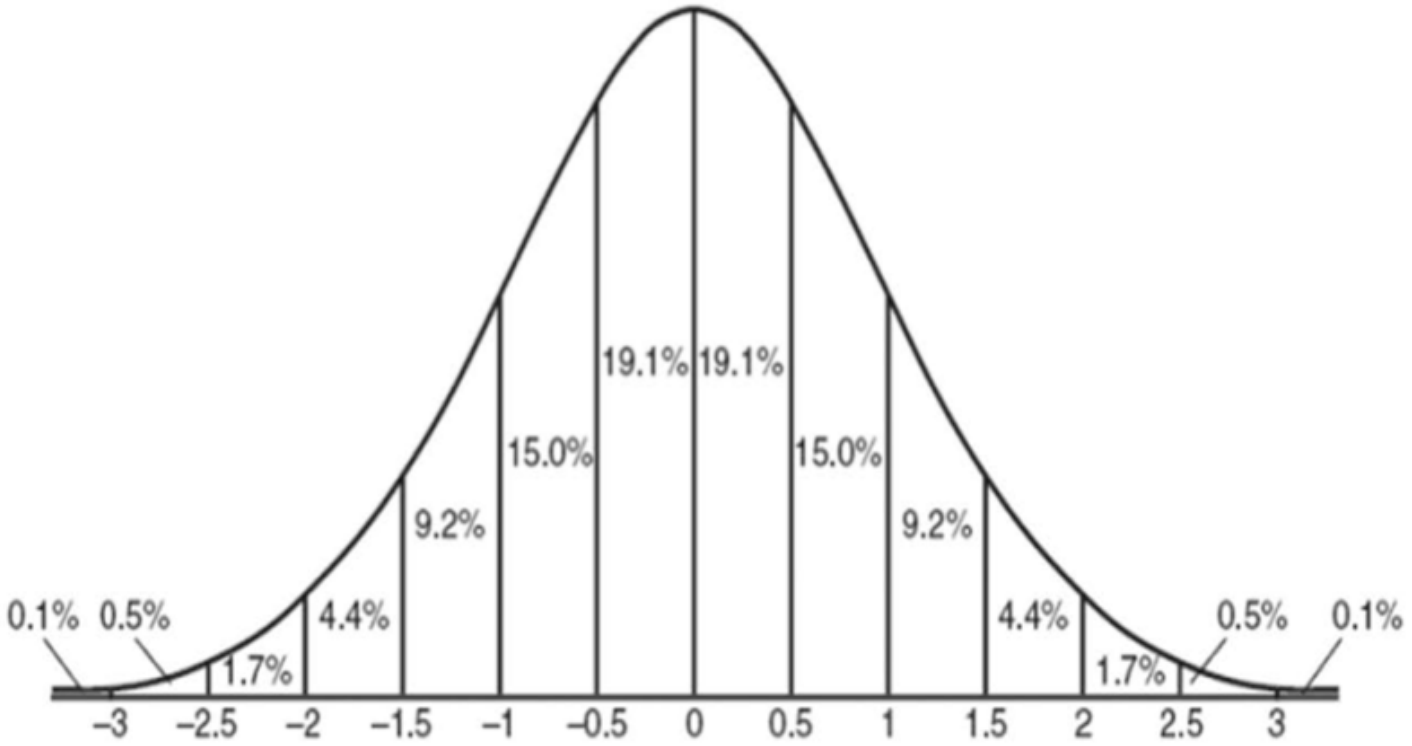
4. The bell-shaped curve shown below illustrates a Standard Normal Distribution. Vertical lines have been drawn for every ½ standard deviation away from the mean. Illustrate the calculations you performed in question 3:
[a] draw a vertical line that divides "borderline high" and "high" cholesterol levels for this population,
[b] lightly shade the area representing "borderline high" cholesterol levels for this population, and
[c] darkly shade the area representing "high" cholesterol levels for this population.



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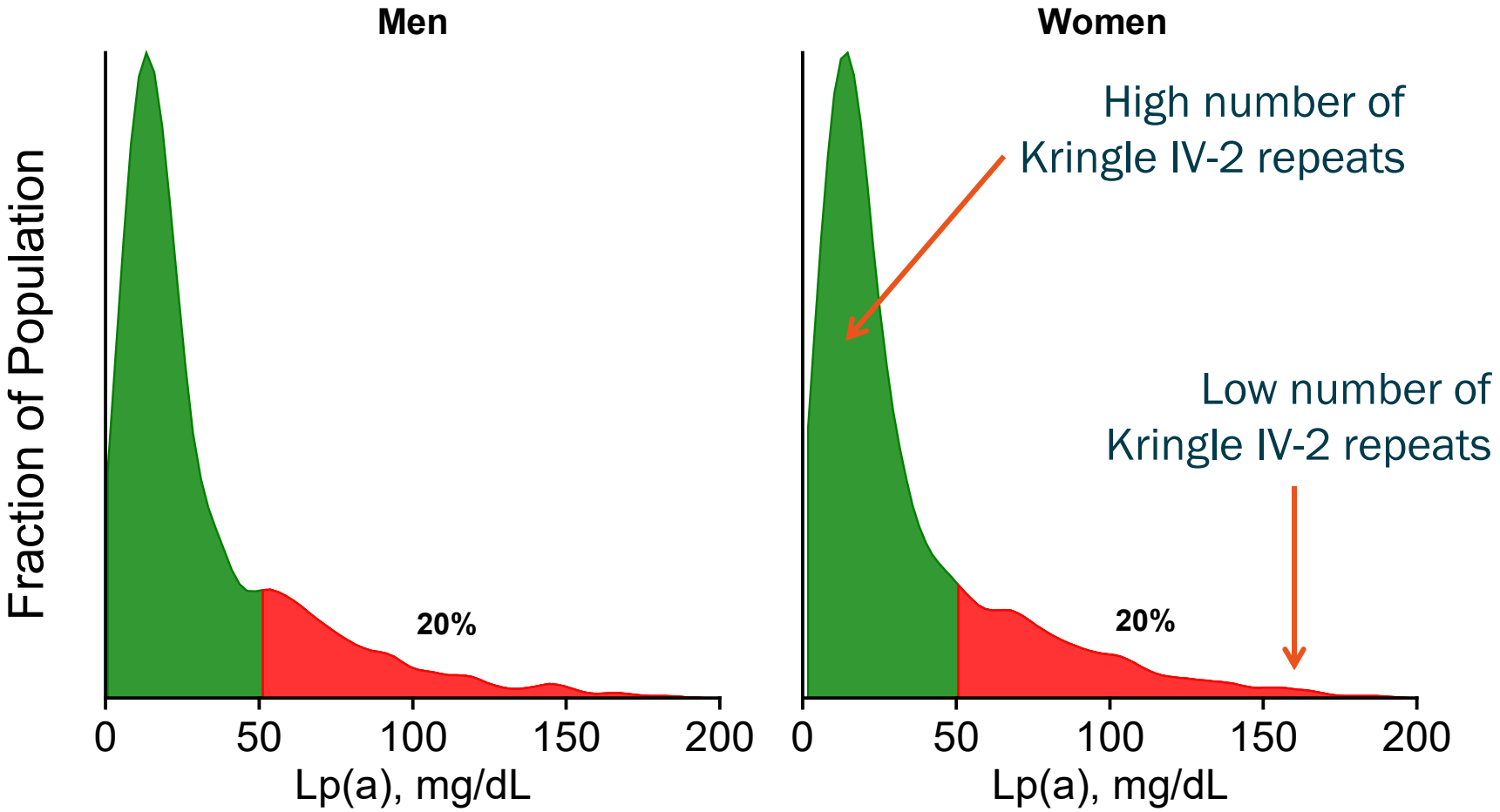
Copenhagen General Population (n=6000)
Lp(a) Levels are About 90% Genetically Determined



Nordestgaard et al, EHJ, 2010, 31:2844

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Prevalence of Elevated Lp(a): US and Globally

Prevalence	20%	10%	5%	1%
Lp(a) Level	60 mg/dL	90 mg/dL	116 mg/dL	180 mg/dL
Number (USA)	64 million	30 million	16 million	3.2 million
Number (EU)	150 million	75 million	37.5 million	7.5 million
Number Globally	**1.4 billion**	700 million	350 million	7 million

Arterioscler Thromb Vasc Biol. 2016;36:2239-2245 and adapted from Tsimikas

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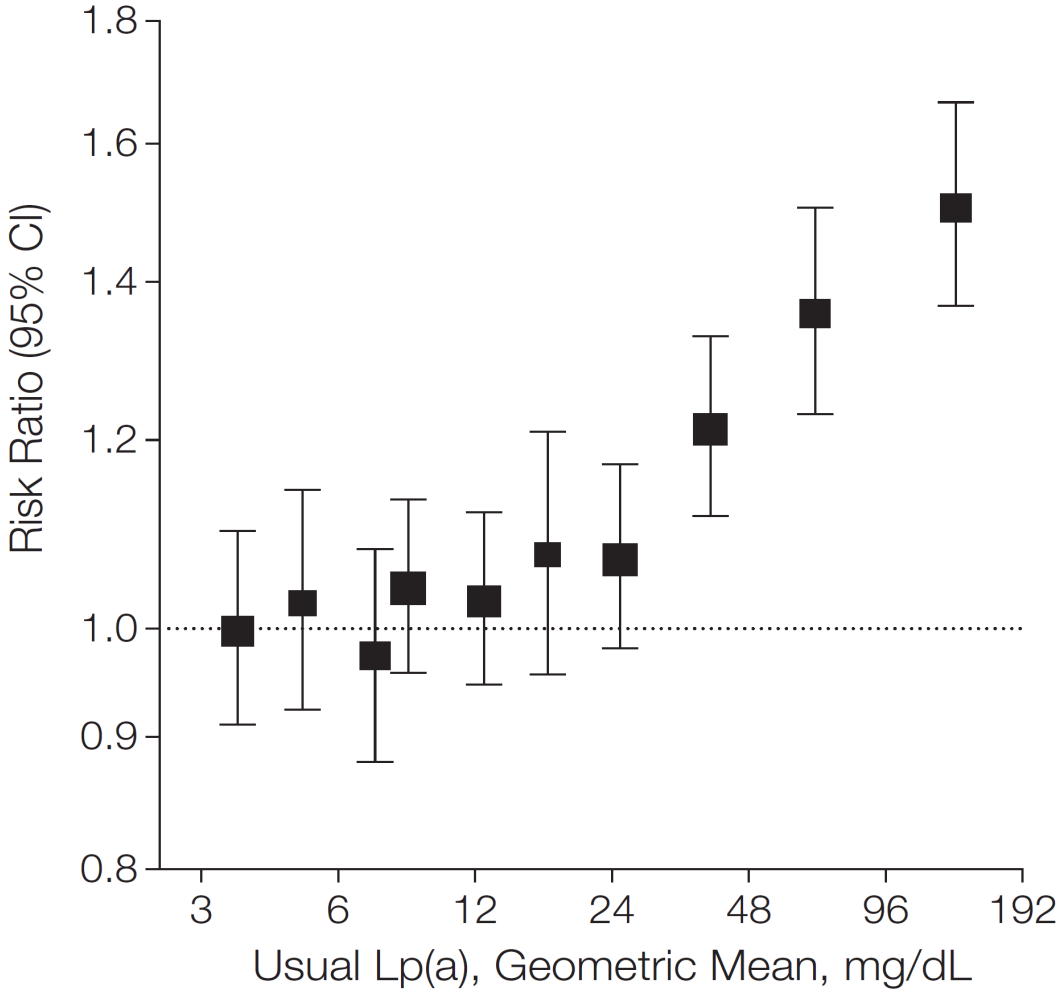
Nonfatal MI and Coronary Death (9318 Cases)



Emerging Risk Factor Collaboration. JAMA 2009; 302: 412-23

MI = Myocardial infarction

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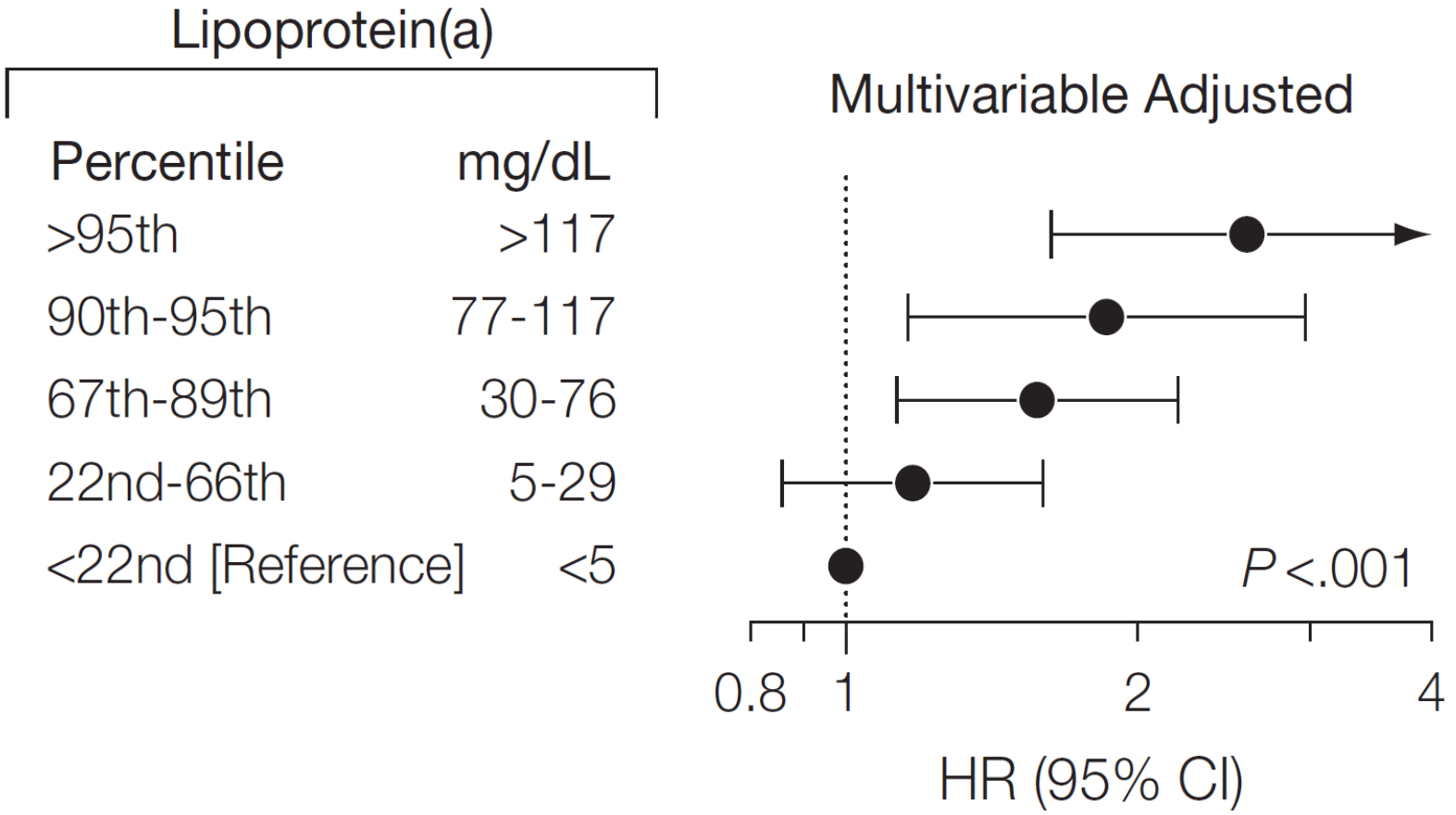
Risk of MI as a Function of Lp(a) Levels in the General Population: Copenhagen City Heart Study



Kamstrup et al. JAMA 2009; 301: 2331-9

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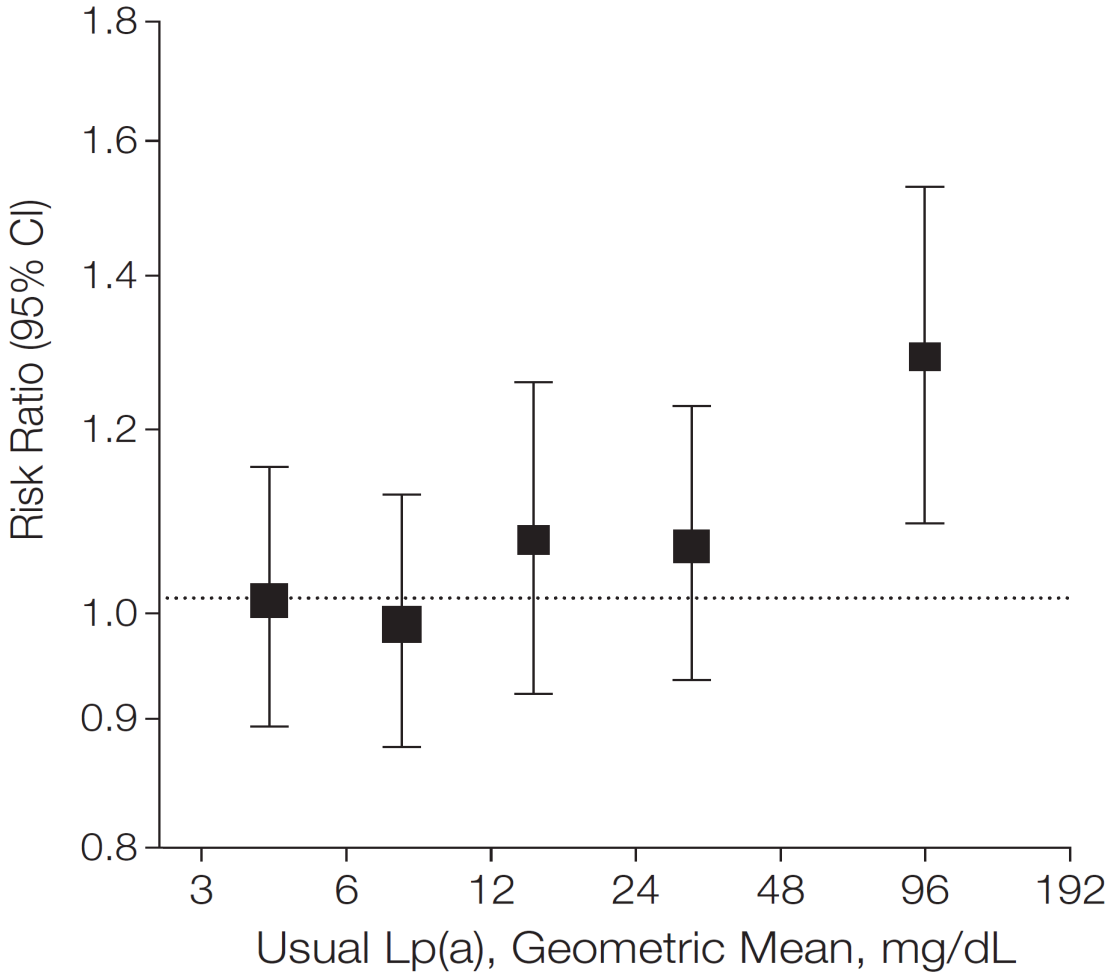
Ischemic Stroke (1890 Cases)



Emerging Risk Factor Collaboration. JAMA 2009; 302: 412-23

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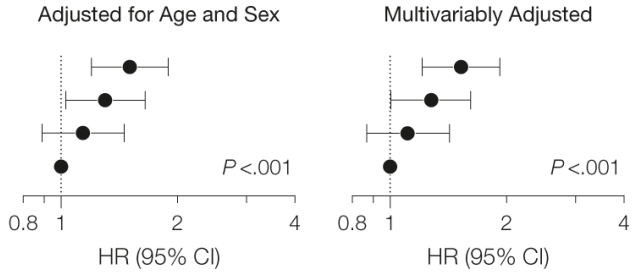
Lp(a): a Genetically Validated Target

CCHS

KIV-2 Repeats

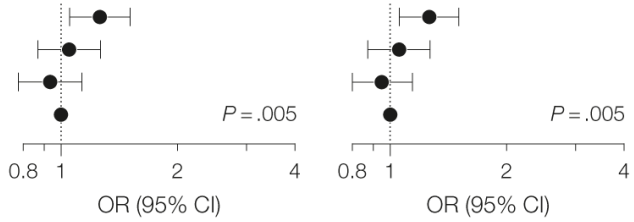
Quartile	No. of Repeats	Participants, No.	Events, No.
1	6-30	2160	181
2	31-35	2159	158
3	36-40	2159	137
4 [Reference]	41-99	2159	123



CGPS

KIV-2 Repeats

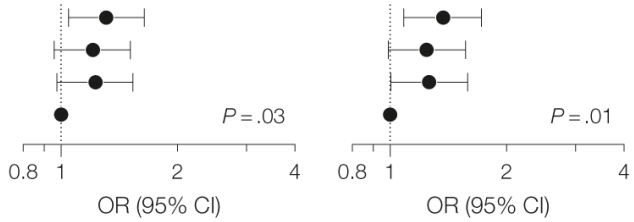
Quartile	No. of Repeats	Controls, No.	Cases, No.
1	6-30	7016	287
2	31-35	7064	246
3	36-40	7095	219
4 [Reference]	41-99	7076	234



CIHDS

KIV-2 Repeats

Quartile	No. of Repeats	Controls, No.	Cases, No.
1	13-30	291	325
2	31-35	304	311
3	36-40	302	313
4 [Reference]	41-96	333	282



Kamstrup PR, et al. JAMA. 2009;301(22):2331-2339

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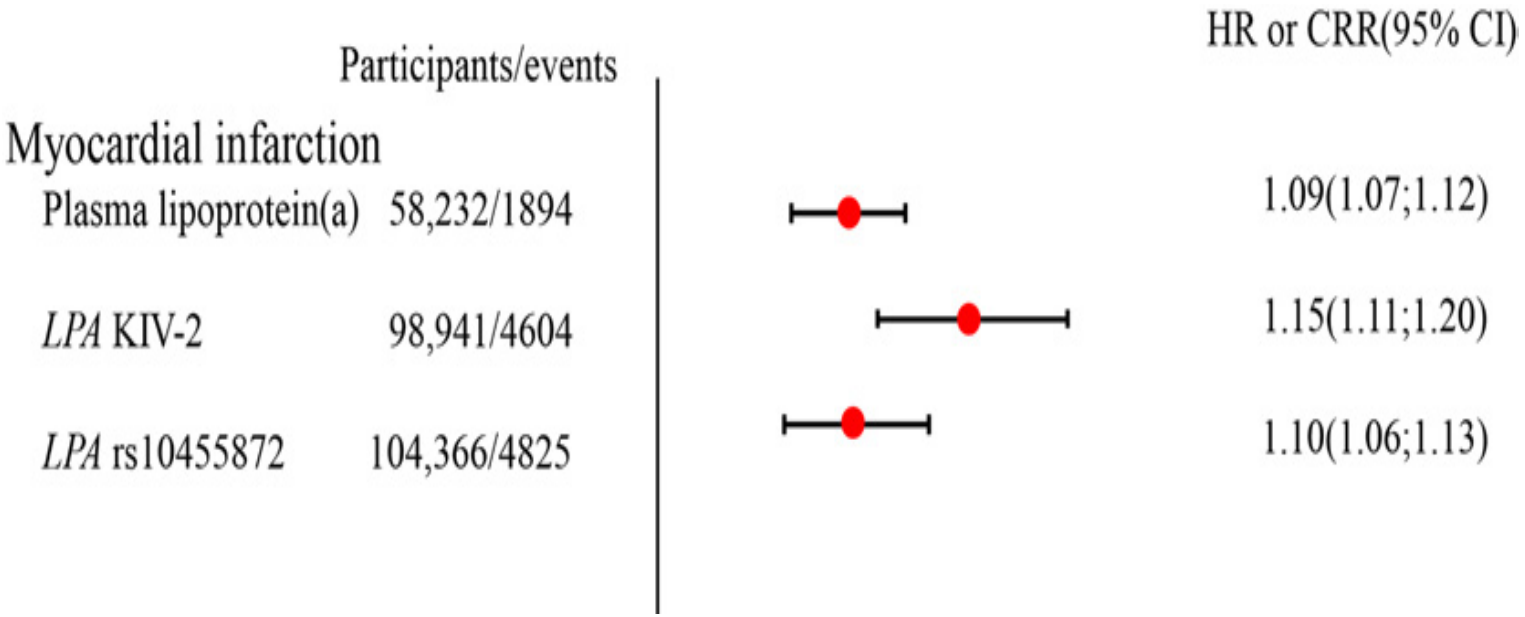
Lp(a): a Genetically Validated Target



Nordestgaard and Langsted J. Lipid Res. 2016. 57: 1953–1975

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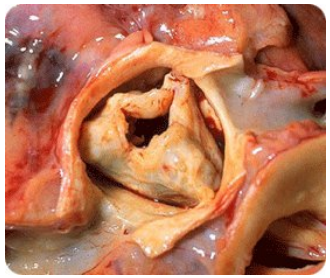
Lp(a) and Aortic Stenosis

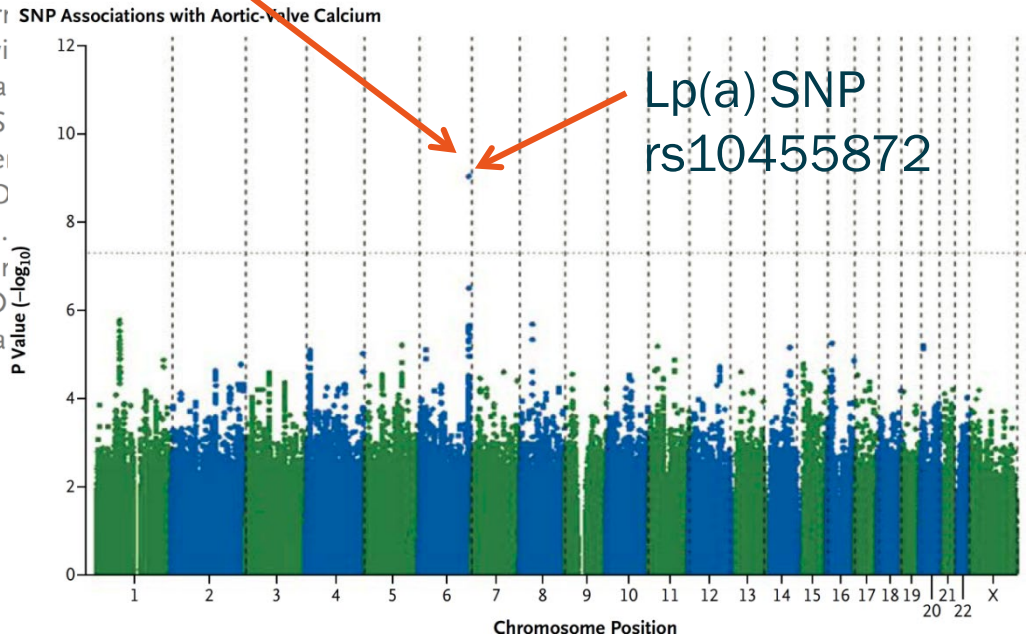
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 7, 2013 VOL. 368 NO. 6



Genetic Associations with Valvular Calcification and Aortic Stenosis

George Thanassoulis, M.D., Catherine Y. Campbell, M.D., David S. Owens, M.D., J. Gustav Smith, M.D., Ph.D., Albert V. Smith, Ph.D., Gina M. Peloso, Ph.D., Kathleen F. Ker Tamara B. Harris, M.D., Rajeev Malhotra, M.D., Kevi Børge G. Nordestgaard, M.D., D.M.Sc., Anne Tybjaerg-Ha Thor Aspelund, Ph.D., Michael H. Criqui, M.D., M.P.H., S Yongmei Liu, Ph.D., Marketa Sjogren, Ph.D., Jespe Thomas W. Mühleisen, Ph.D., Markus M. Nöthen, M.D Emanuele Di Angelantonio, M.D., Ph.D., John Danesh, F.R. Quenna Wong, M.S., Raimund Erbel, M.D., Sekar Vilmundur Gudnason, M.D., Ph.D., Christopher J. O for the CHARGE Extracorona



Relative risk of aortic valve per allele

Calcification	2.05 (1.63-2.57)
Stenosis Sweden	1.68 (1.32-2.15)
Stenosis Denmark	1.60 (1.12-2.28)

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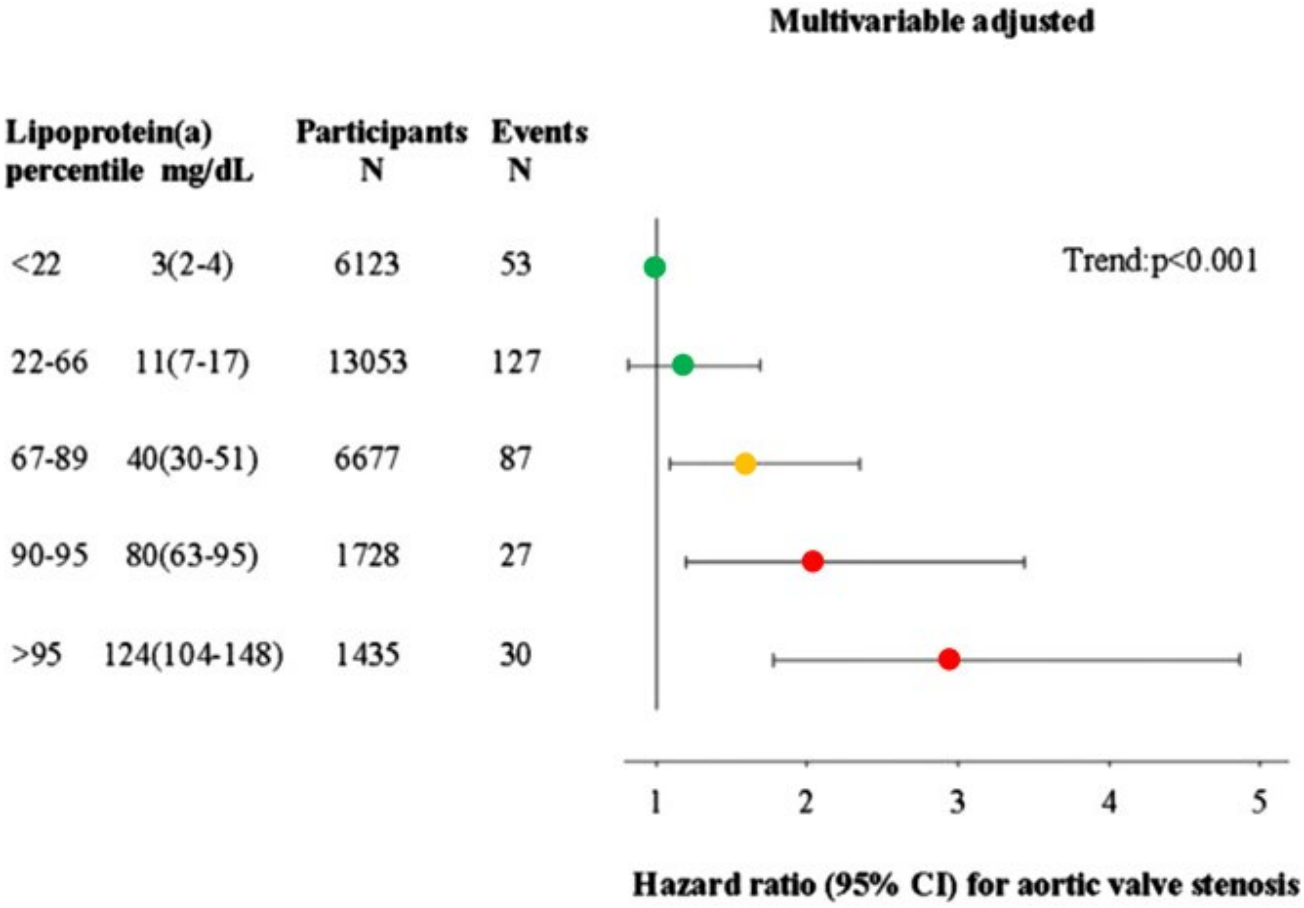
Lp(a) and Aortic Stenosis



Nordestgaard and Langsted J. Lipid Res. 2016. 57: 1953–1975

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- This is all very interesting but does it mean that there is an unmet need to treat Lp(a)?
- Why not just treat LDL more aggressively?

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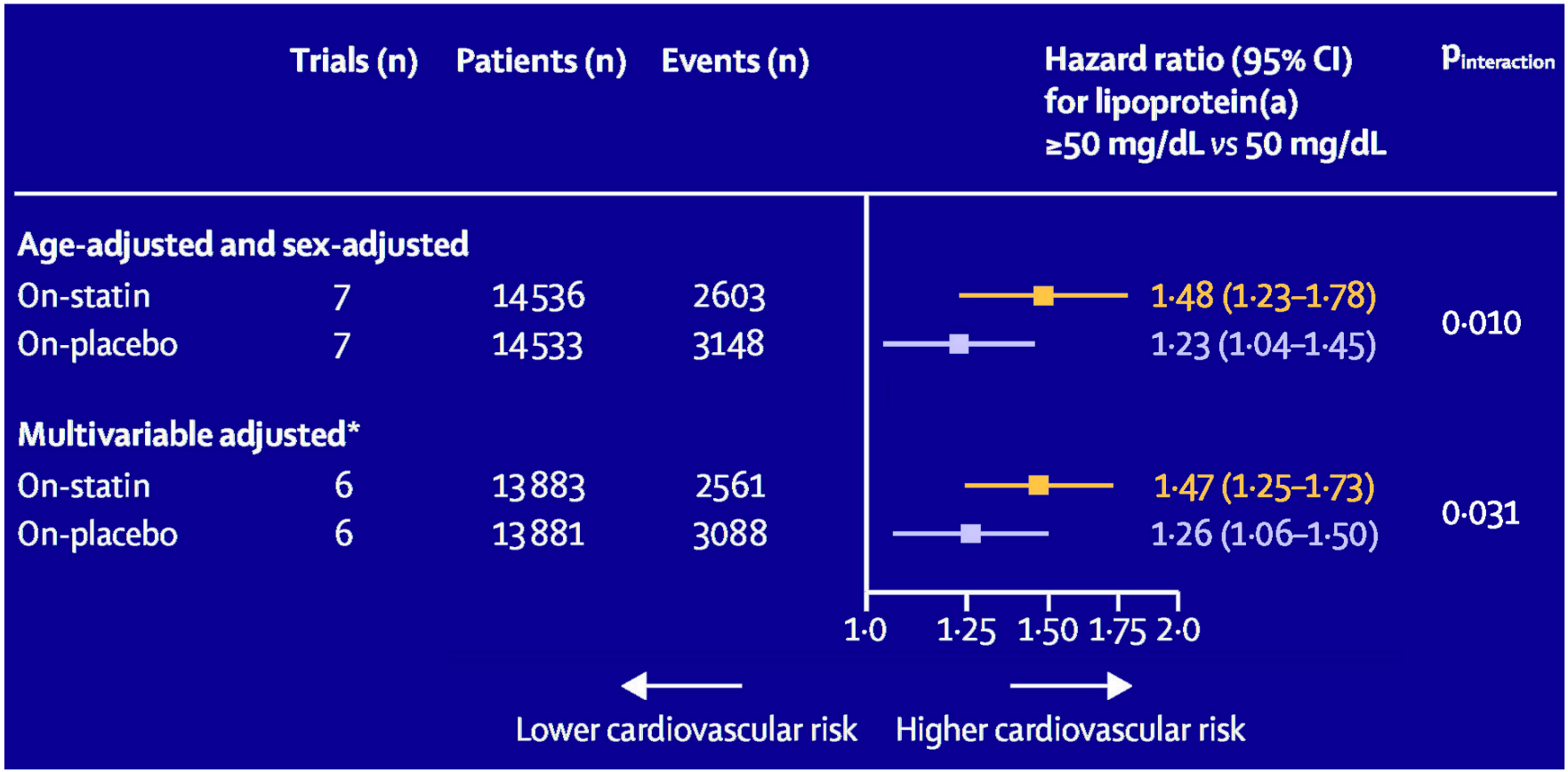
Statin Treatment and CV Risk of Lp(a)

Patient-level meta-analysis of placebo-controlled statin trials



Lancet 2018; 392: 1311–20

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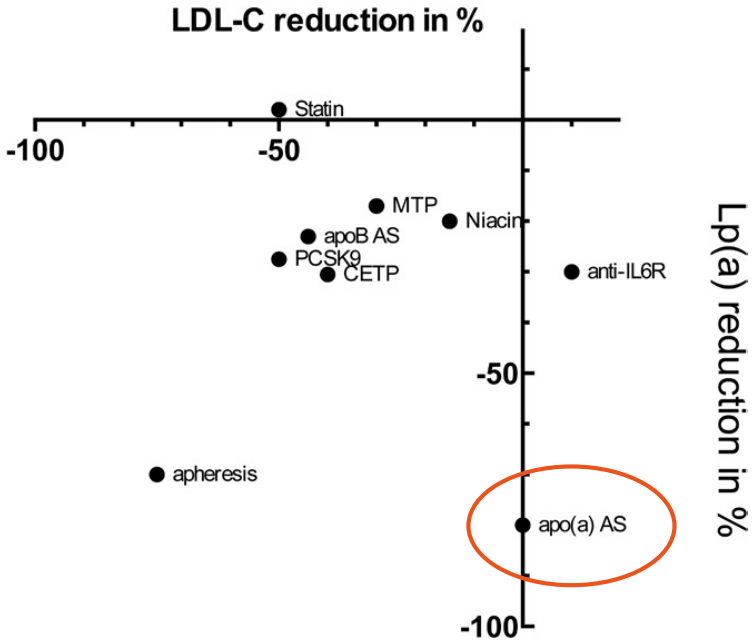
Lp(a) Largely Poorly Managed by Current Therapies

- No clinical trial investigating the effect of specifically lowering Lp(a) on prevention of CVD conducted so far – **no specific guidelines for targeting Lp(a).**
- **Cholesterol lowering drugs** (e.g. statins etc) are used to reduce additional risk factors, however **effect on Lp(a) levels is minimal.**
- **PCSK9 antibodies reduce Lp(a) by up to 30%** but is currently unclear whether this is enough to reduce risk associated with Lp(a).
- **Niacin** also lowers Lp(a) by 20-30% but is difficult to take and is associated with several significant adverse side-effects.
- **Apheresis is the only approach that can reduce Lp(a)** levels by a large amount, however is **invasive and burdensome**



- Experts agree that 100mg/dl reduction in Lp(a) is needed for 20% risk reduction[1]

RNA modalities will provide a stronger and specific way to reduce Lp(a) levels

Capelleveen et al 2016

1 https://www.tctmd.com/news/unlocking-lpa-baseline-levels-matter-so-too-does-absolute-reduction

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Benefit of Reduction

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FOURIER Trial

- Elevated baseline Lp(a) concentration was independently associated with an increased risk of coronary events
- Patients with elevated baseline Lp(a) levels derived greater absolute reduction in Lp(a) and tended to derive greater clinical benefit from PCSK9 inhibition
- Clinical benefit of Lp(a) lowering may predominantly occur in patients with elevated baseline levels

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ODYSSEY Outcomes Trial

- Baseline Lp(a) predicts MACE in patients with recent ACS.
- The contribution of Lp(a) lowering to event reduction with alirocumab increases with higher baseline Lp(a) levels, and becomes clinically meaningful in patients with elevated baseline Lp(a) levels.

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Changes in Lp(a) and LDL-C With Equivalent Effects on CVD

1.0 mmol/L (39 mg/dl cholesterol) lifetime lower LDL-C

50% reduction in ***lifetime*** risk of CHD

0.4 - 101.5 mg/dl (30-40 mg/dl cholesterol) lifetime lower Lp(a)

Burgess SB, Ference BA, et al. 2018; JAMA Cardiology doi: 10.1001/jamacardio.2018.1470

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Desired Profile of New Therapeutic to Lower Lp(a)

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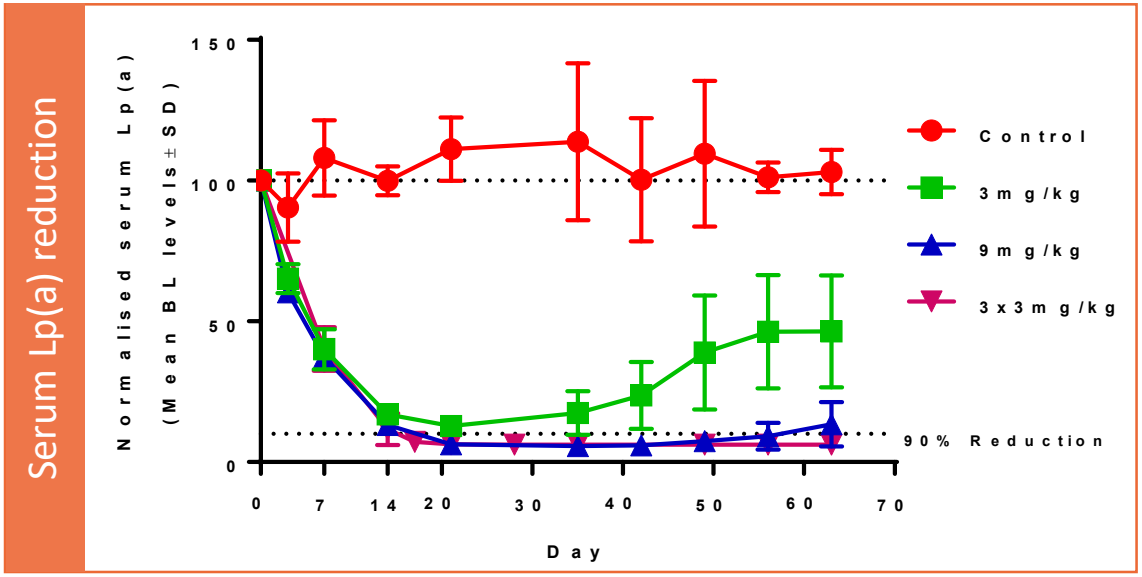
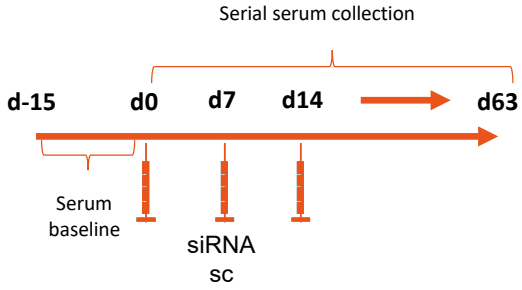
siRNA Knockdown





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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Summary

- Elevated Lp(a) a potent risk factor for cardiovascular disease but is underappreciated in management guidelines
- Usual life-style changes and currently approved therapeutics not effective
- New agents required that lower Lp(a) by up to 80%
- Compliance a potent factor in reducing the effectiveness of risk reducing therapeutics
- Safety, long duration of action and potent effect key to managing Lp(a) associated CV risk

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SILENCE THERAPEUTICS

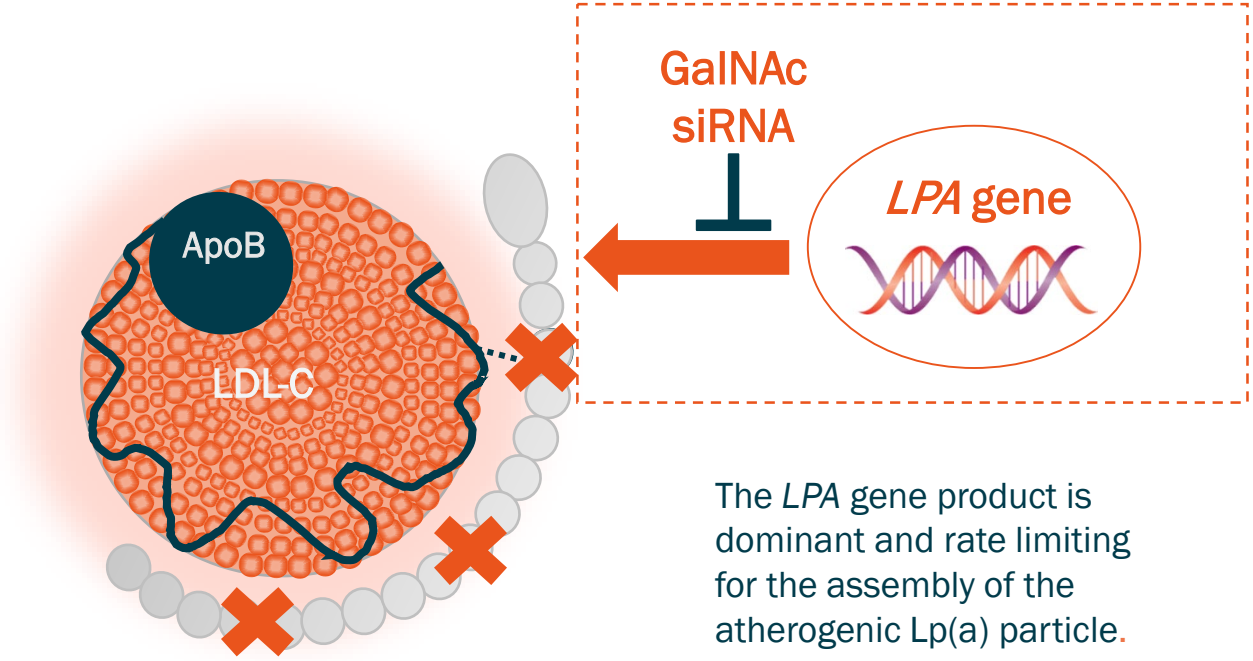
R&D Day, September 12 2019

SLN360 for the Treatment of Cardiovascular Disease Associated With High Lp(a)

Dr Giles Campion
Head of R&D, Chief Medical Officer

Lp(a) as a Target for SLN360

The Lp(a) complex is composed of two different proteins encoded by the *LPA* and the *APOB* genes and a lipid particle, both expressed in hepatocytes:



The *LPA* gene product is dominant and rate limiting for the assembly of the atherogenic Lp(a) particle.

> *LPA* loss of function mutations protective effect against coronary heart diseases
(Lim et al. PLoS Genet 10(7): e1004494)

> Gain of function mutations in *LPA* lead to increased risk of coronary heart disease
(Emdin et al., J Am Coll Cardiol. 2016;68,2761-2772)

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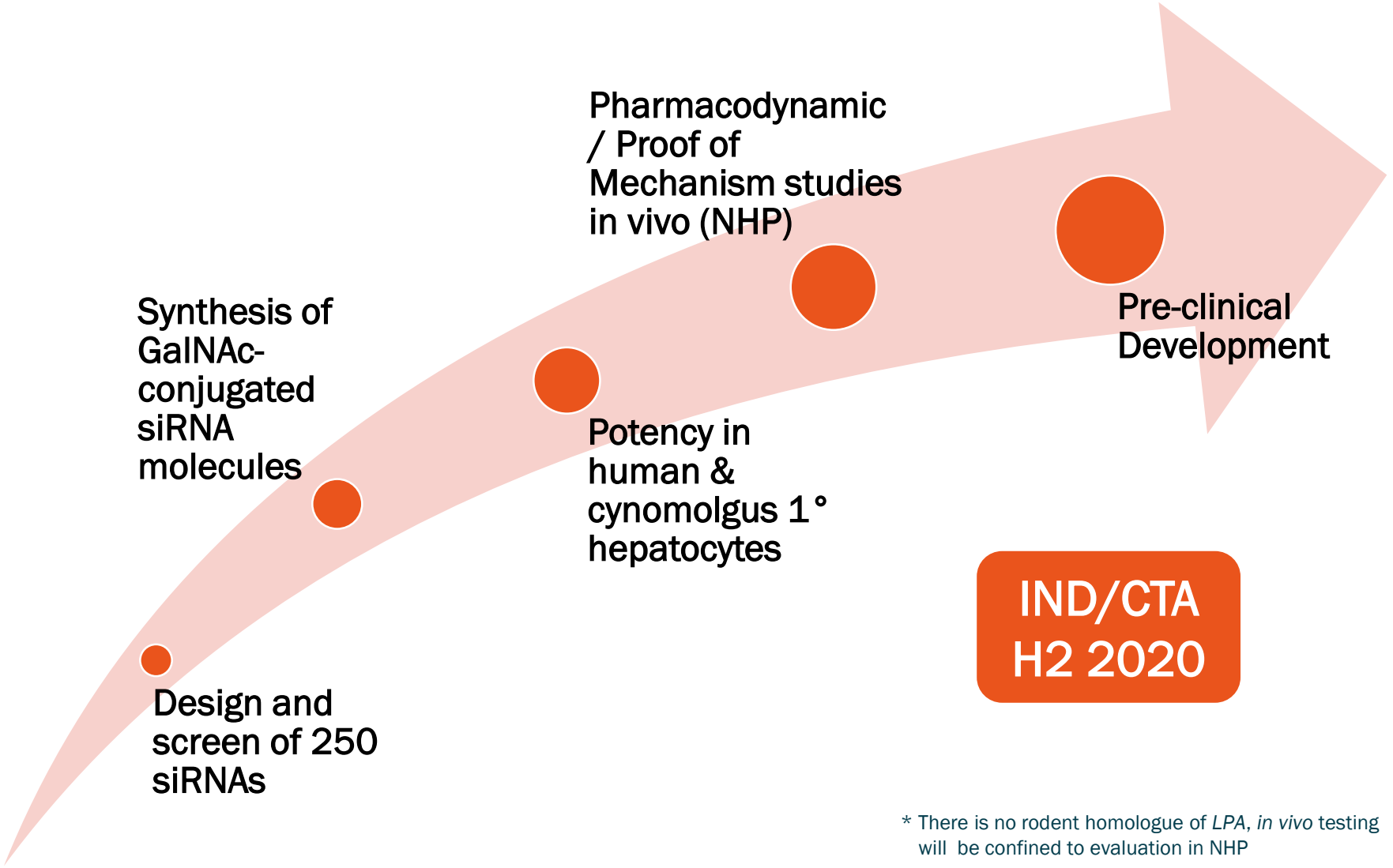
Lead and Lead Selection



* There is no rodent homologue of *LPA*, *in vivo* testing will be confined to evaluation in NHP

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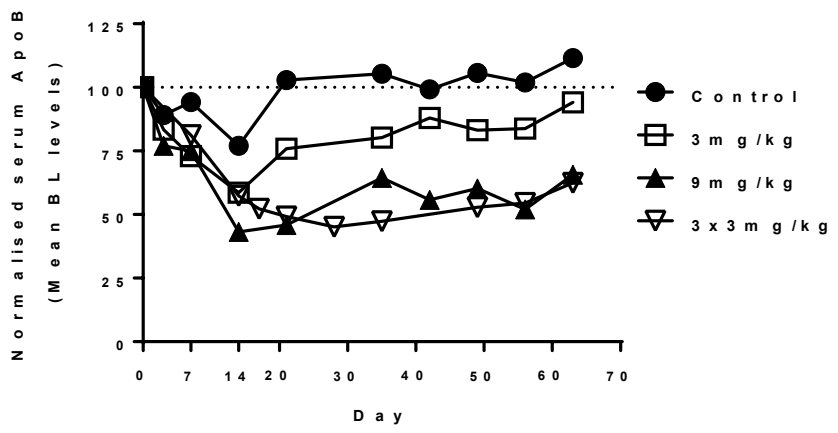
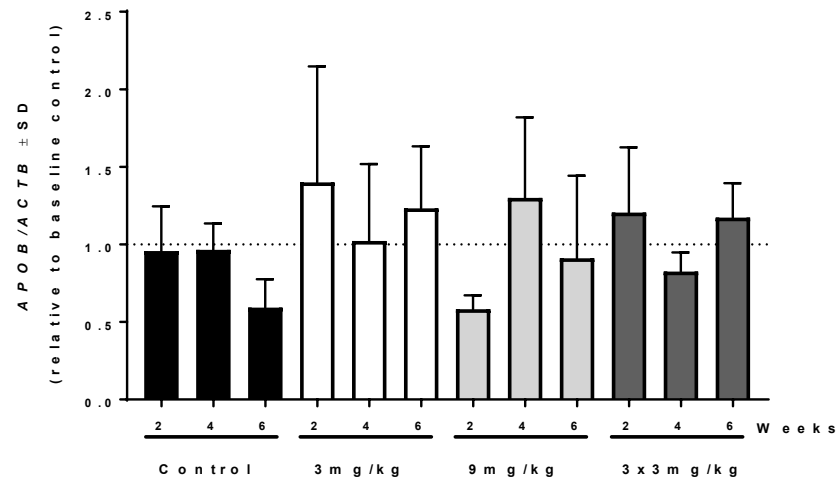
Additional Lowering of ApoB

PROTEIN



RNA



Lp(a) reduction leads to significant lowering of the disease-relevant biomarker ApoB

> Dose-dependent reduction in ApoB serum levels

> ~ 50% reduction in ApoB with both single 9mg/kg and 3x3mg/kg

> No effect on *APOB* gene expression

> No clear effect on any of the additional lipid parameters (e.g. LDL-C)

> No effect on a panel of 5 genes sensitive to lipid changes in the liver

- *LDLR, FASN, SCD1, HMGCR, CYP7A1*

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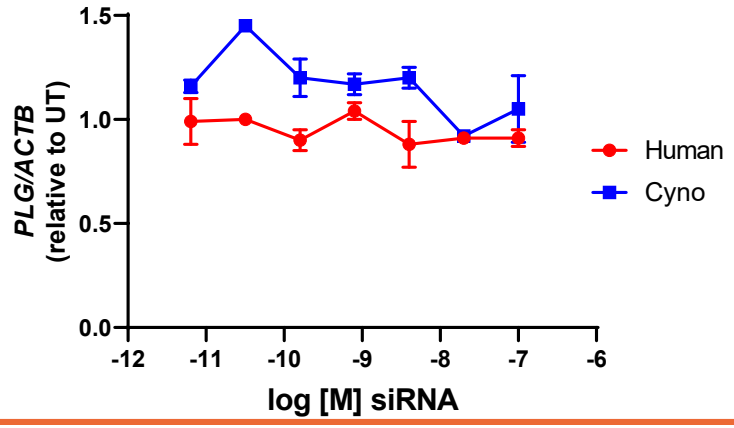
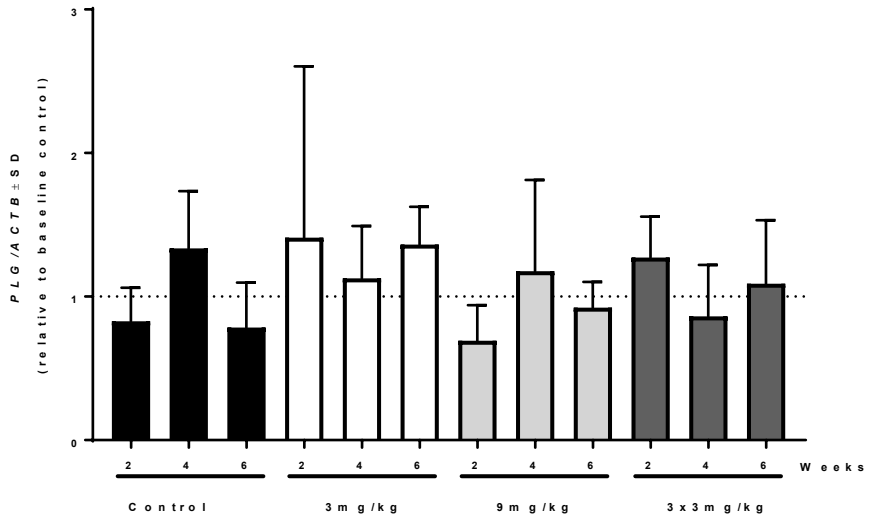
No Downregulation of Plasminogen mRNA

In vitro



In vivo



> Plasminogen protein has high homology to apo(a)

> SLN360 sequence shows several mismatches to *PLG* sequence

In vitro

> No dose-dependent alterations in *PLG* levels in primary human and cyno hepatocytes

In vivo

> No dose- or time-dependent alterations in *PLG* levels in primary cyno liver mRNA levels

PLG mRNA knockdown is absent in vitro and in vivo

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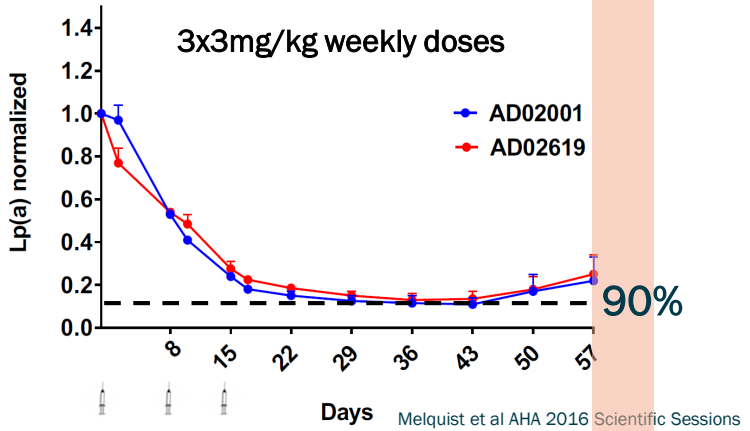
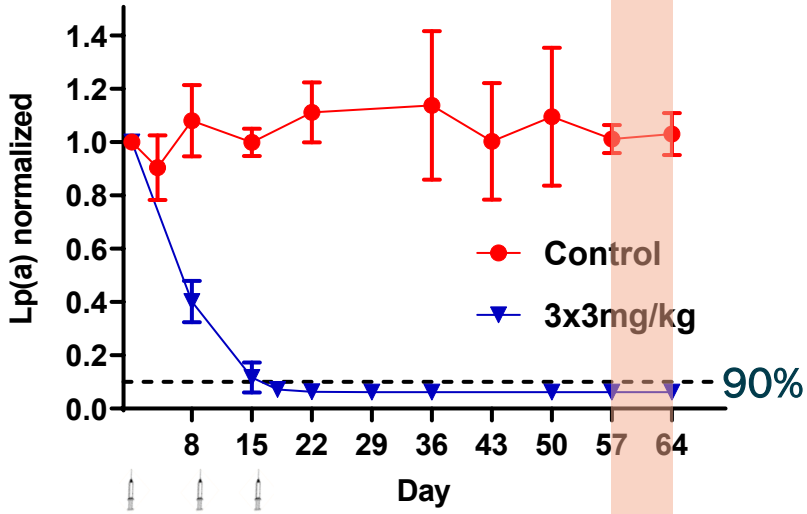
Clinical-Stage Competition – Amgen (Phase I)

Amgen/Arrowhead



Melquist et al AHA 2016 Scientific Sessions

SLN360



- Amgen (Arrowhead molecule) – GalNac siRNA
- Amgen: peak inhibition D29-43
- **SLN360: peak inhibition D17-21**
- Amgen: 90% reduction at peak inhibition
- **SLN360 >90% reduction: not detectable in any animal after D28**
- Amgen: ~75% 6 weeks after last dose
- **SLN360: >90% for at least 7 weeks after last dose**

Our SLN360 program is competitive with the Amgen/Arrowhead program

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Clinical-Stage Competitors Targeting Lp(a)

Correct as of Aug 2019

Product	Company	Highest Phase	Indications	MOA	Modality	Administration
AMG-890	Arrowhead/ Amgen	Phase I	CVD with high Lp(a)	Apo(a) inhibition	siRNA	SC, N/A
AKCEA-apo(a)-LRx (TQJ230)	Akcea (Novartis)	Phase 2 (completed)	CVD with high Lp(a)	Apo(a) inhibition	Antisense	SC, weekly or monthly

> Inclisiran, an siRNA in Phase 3 for hypercholesterolemia and ASCVD, has shown limited impact on Lp(a) levels

SLN360 has best-in-class potential, as suggested by the increased potency and longer duration of action compared to competition. Other drugs further along in development likely to validate the field: acceptance of Lp(a) as a risk factor and increase in patient screening.

CVD- Cardiovascular Disease; *SC*- subcutaneous, *ASCVD*- Atherosclerotic Cardiovascular Disease

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SLN360 Summary

Rationale

> Lp(a) is a low-density lipoprotein 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.

SLN360

> 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 competitive performance.

> IND/CTA filing is planned for H2 2020

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SILENCE THERAPEUTICS

R&D Day, September 12 2019

SLN500 for the Treatment of Complement-Mediated Diseases

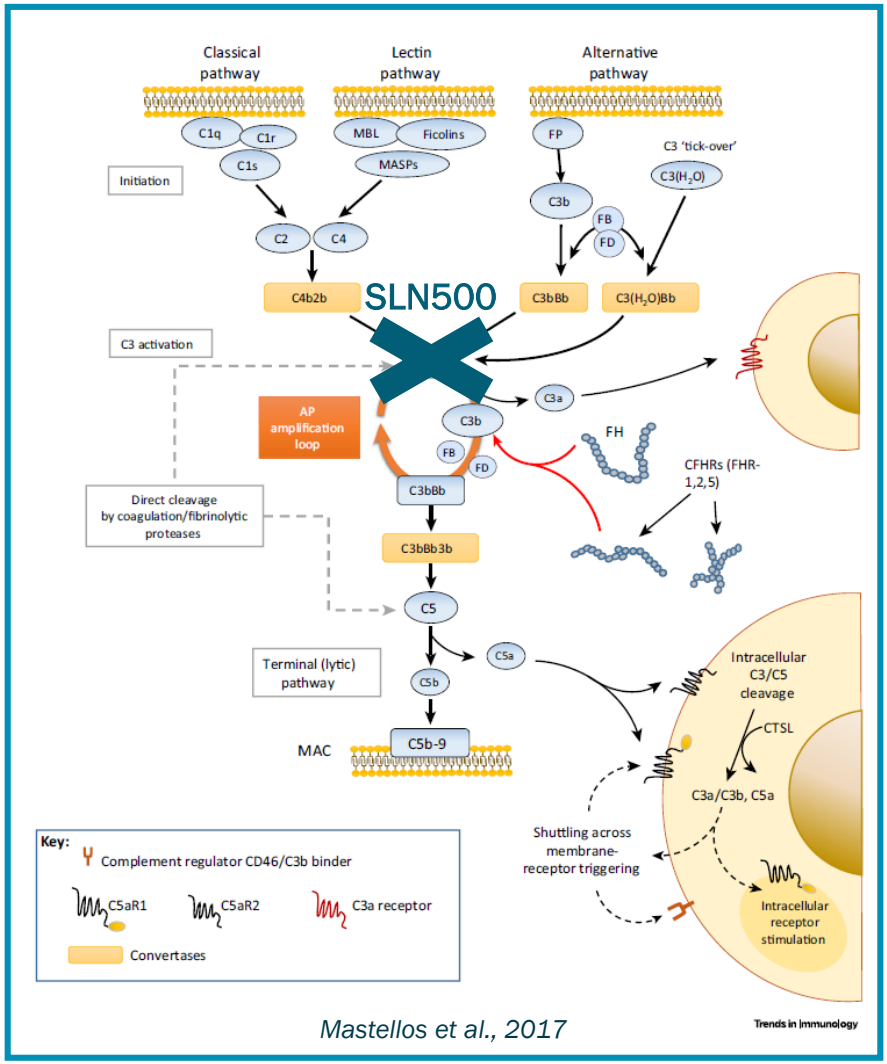
Dr Giles Campion
Head of R&D, Chief Medical Officer

Complement as a Target Cascade

C3 - Hub of the complement cascade

- Complement belongs to the innate immune system
- >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



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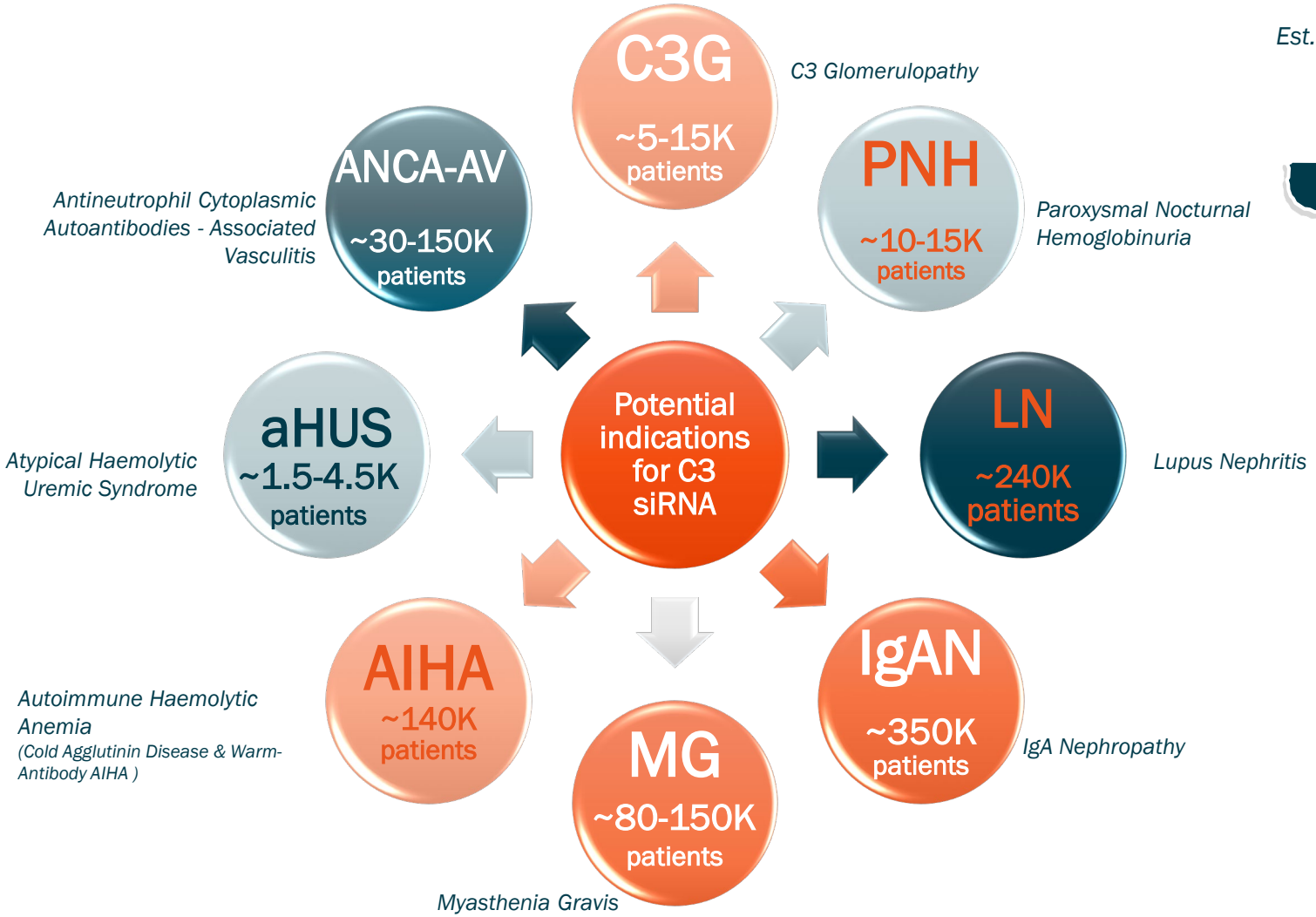
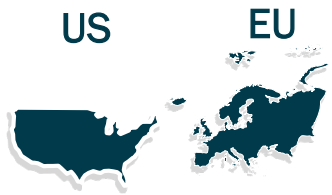
MAC: Membrane attack complex

Attractive market size
Combined opportunity in multiple orphan indications



Est. combined prevalence



...and others

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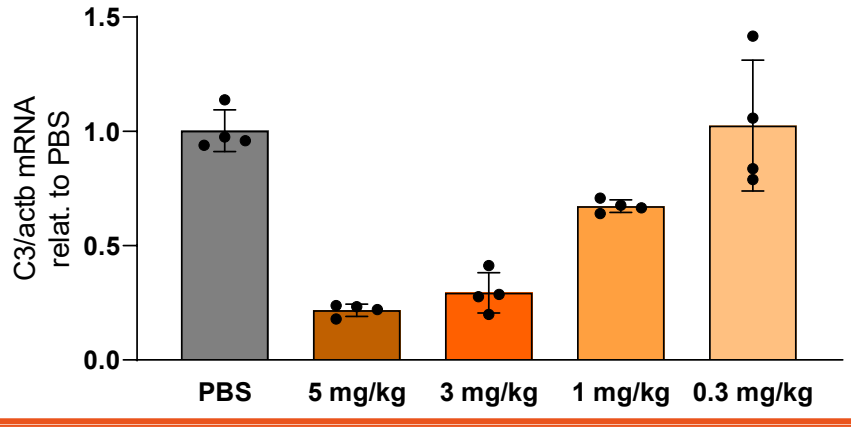
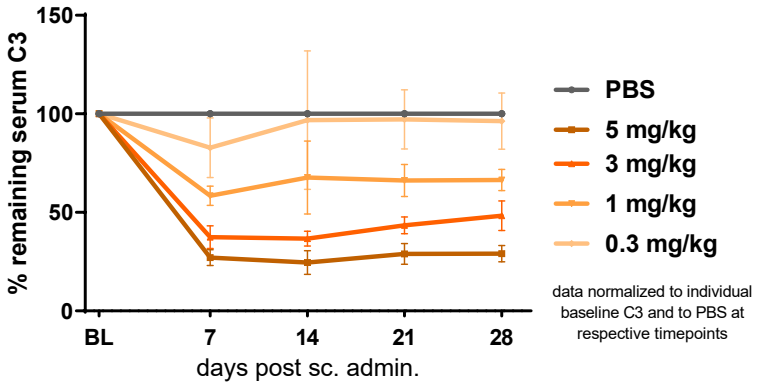
SLN500 Proof of Mechanism Data

Dose response study with SLN500 in healthy mice

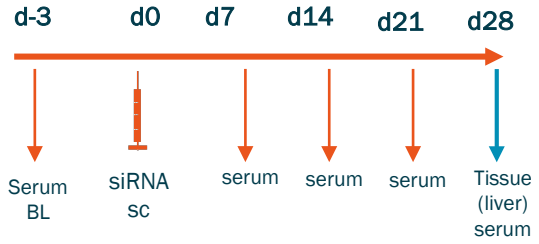
RNA DAY 28



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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Clinical Stage Drugs Targeting C3

Correct as of Aug 2019

Product	Company	Highest Phase	Indications	MOA	Modality	Administration
APL-2	Apellis	Phase 3	Nephropathies (C3G), GA, PNH, CAD, WAHA	C3 inhibition	Synthetic peptide	SQ, daily
AMY-101	Amyndas	Phase I	C3G, PNH, periodontitis, kidney transplant	C3 inhibition	Synthetic peptide	SQ or IV, unclear dosing but likely QD or several injections/week

SLN500 is the only known siRNA targeting C3 – 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

GA- Geographic Atrophy; PNH- Paroxysmal Nocturnal Hemoglobinuria; *CAD*- Cold Agglutinin Disease; *WAHA*- Warm Antibody Autoimmune Haemolytic Anemia; *SC*- subcutaneous; *IV*- Intravenous;

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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

> A potent lead sequence has been selected and tested in vivo in mice. Studies in non human primates are currently ongoing

> 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

R&D Day, September 12 2019

Questions & Answers

SILENCE THERAPEUTICS

R&D Day, September 12 2019

Closing Remarks

Dr. David Horn Solomon
Chief Executive Officer

Silence Therapeutics' Summary

Valuable Platform	> Reproducible, proprietary gene silencing (RNAi) therapeutics platform, rapidly generating internal pipeline and out-licensing options. Platform validated through recently announced collaboration with Mallinckrodt
Growing Clinical Pipeline	> SLN124 (β-Thalassemia and MDS[1]). Phase Ib trial to start in H2 2019. SLN360 (LPa) IND/CTA in 2020. SLN500 (C3) IND/CTA in 2021.
Strong Experienced Team	> Pioneers in siRNA for over 18 years, growing clinical team, and experienced biopharma management team
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. Cash position recently strengthened by Mallinckrodt collaboration ($25m in upfronts[3])

HQ in London



R&D in Berlin



Approx. 45 employees across both sites

Notes:
[1] MDS = Myelodysplastic syndrome
[2] As of 31st Aug 2019 and £=$1.22
[3] $20 upfront and $5m equity investment

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Outlook

SLN124

> SLN124 Phase Ib commences soon with interim results for the Part A (Single Ascending Dose) expected in 2020

> Phase Ib trial is expected to fully readout in H2 2021

SLN360

> IND and/or CTA expected to be filed in H2 2020

> Phase I trial to start shortly thereafter and funding this program is a key priority for us

SLN500

> Fully funded (directly or through milestones) by Mallinckrodt. IND and/or CTA targeted in H1 2021

Earlier stage, as yet undisclosed, proprietary programs

> At least two Discovery programs ready to enter IND-enabling studies during 2020

Extra-hepatic delivery

> Numerous collaborations being explored. This is a key priority

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