Scientific Sessions 2019

A Novel Short Interfering Ribonucleic Acid Shows Potent And Sustained Reduction Of Serum Lipoprotein(a) In Cynomolgus Monkeys

Saturday 16th November

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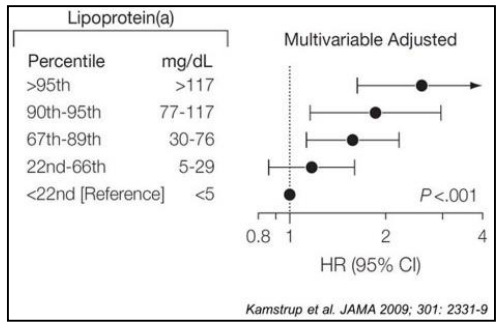
SILENCE THERAPEUTICS

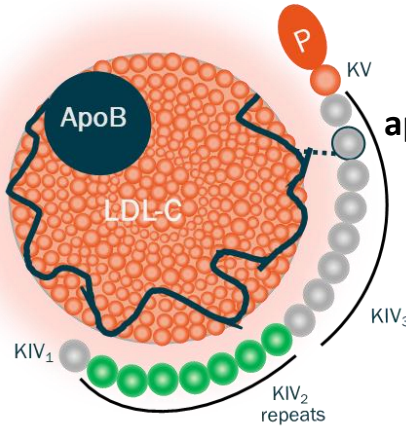
Lp(a) - an Independent Risk Factor for CVD

- **Lp(a) expressed predominantly in the liver**
  - Highly variable in size
  - Expression restricted to Human and NHP
- **Lp(a) levels are genetically defined**
  - Not modified through life style interventions
- **Considered to be pro-atherogenic, pro-thrombotic and pro-inflammatory**
- **Major untreated risk factor in CVD**
  - Currently approved therapies do not address Lp(a)
- **Higher levels of Lp(a) correlate with increased CVD risk**

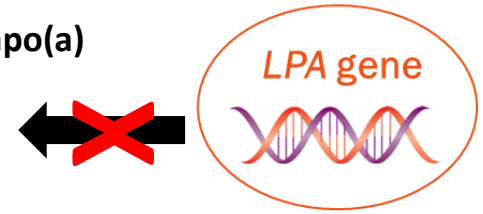


Increased MI risk

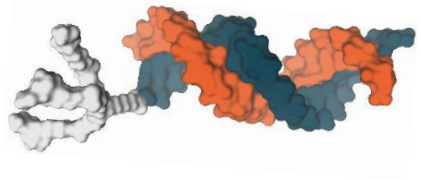
SLN360: a GalNAc siRNA against *LPA*



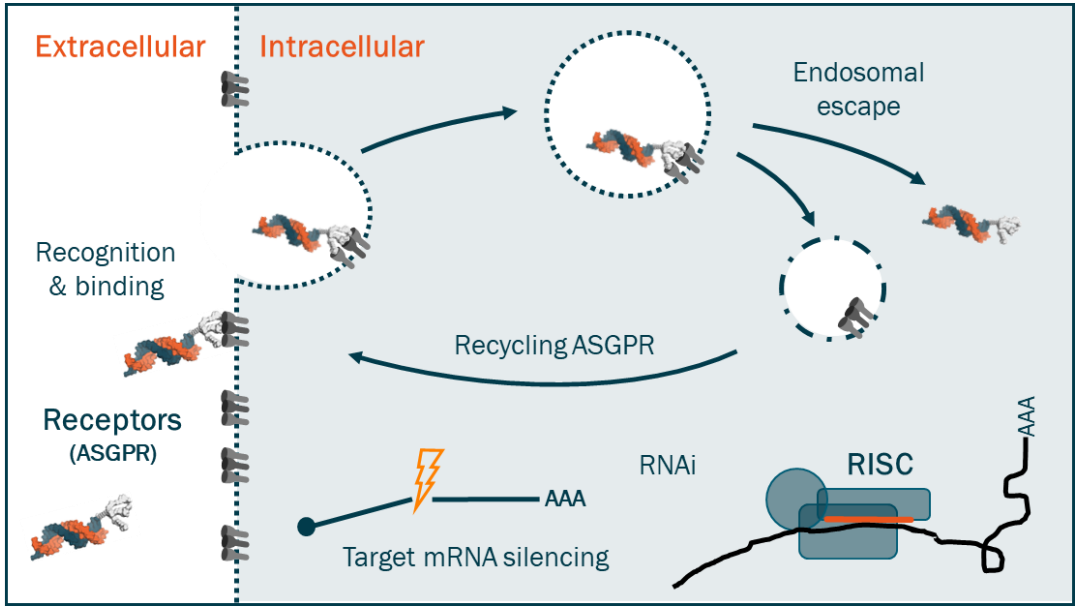
apo(a)



GalNAc



Double stranded RNA



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

SLN360 selection process

Design and screen of 250 siRNAs

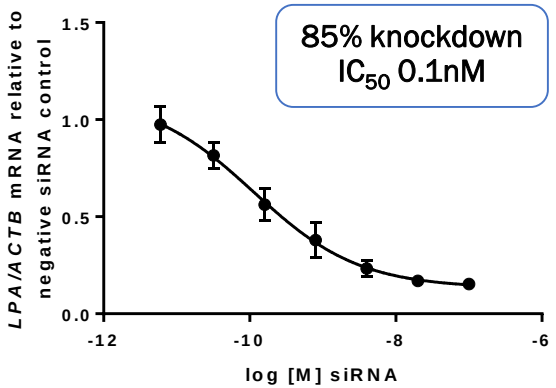
Synthesis of GalNAc-conjugated siRNA molecules

Potency in human & cynomolgus 1° hepatocytes

Pharmacodynamic / Proof of Mechanism studies in vivo (NHP)

Pre-clinical Development

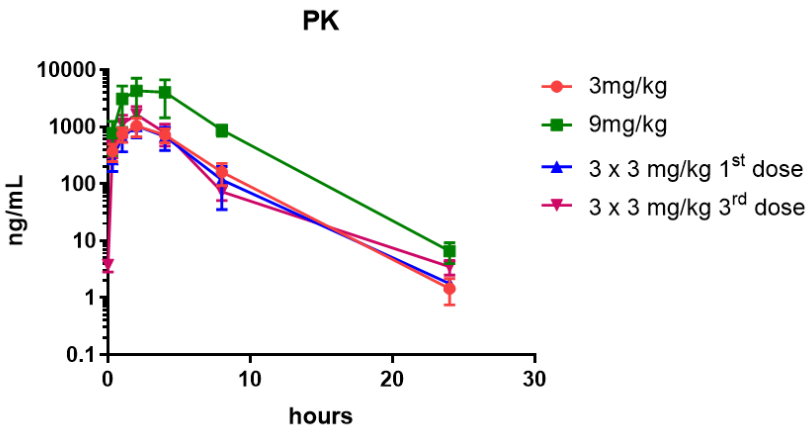
IND H2 2020



Robust long-term Lp(a) reduction observed

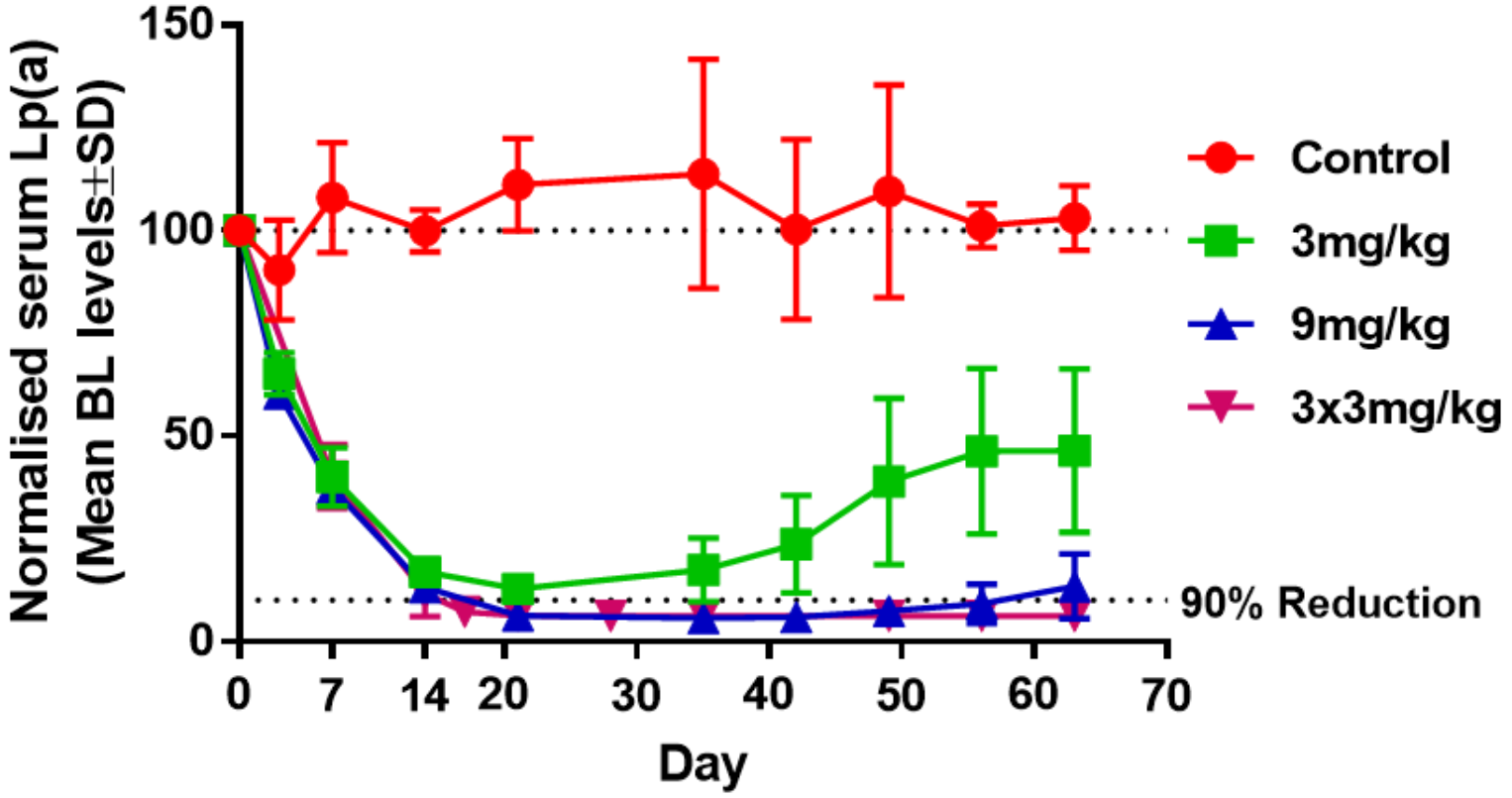
Typical short siRNA PK observed

No serum accumulation



- Median pre-treatment Lp(a) 117.4nmol/L (range 37.6-176.1)
- Disconnected serum PK/liver PD relationship

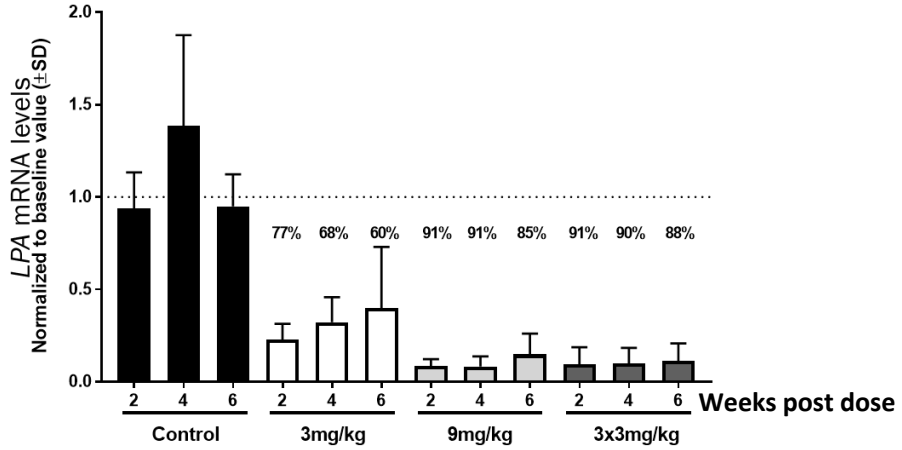
Prolonged serum Lp(a) reduction



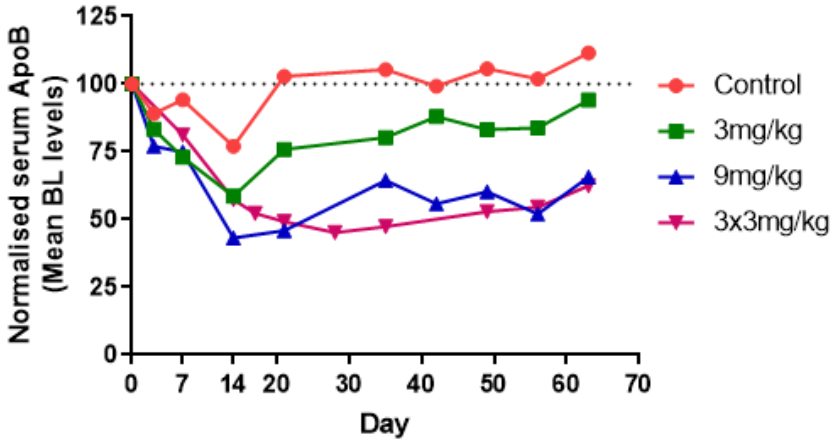
>95% reduction achieved

Lp(a) reduction leads to reduced serum ApoB in NHP

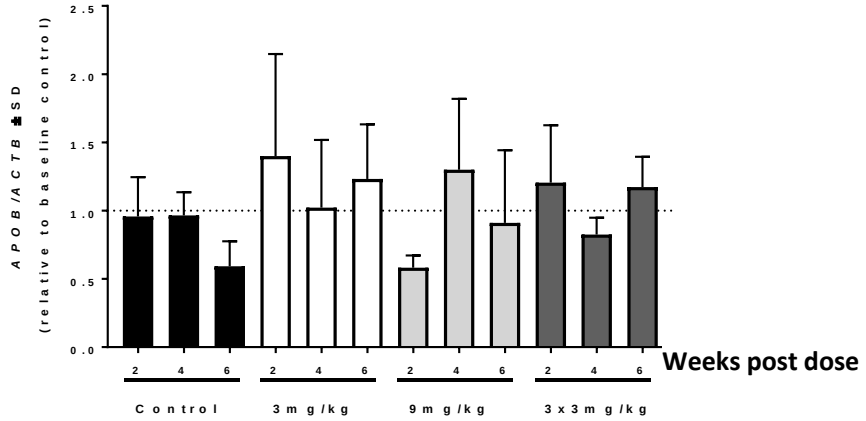
LPA mRNA reduction for >6 weeks



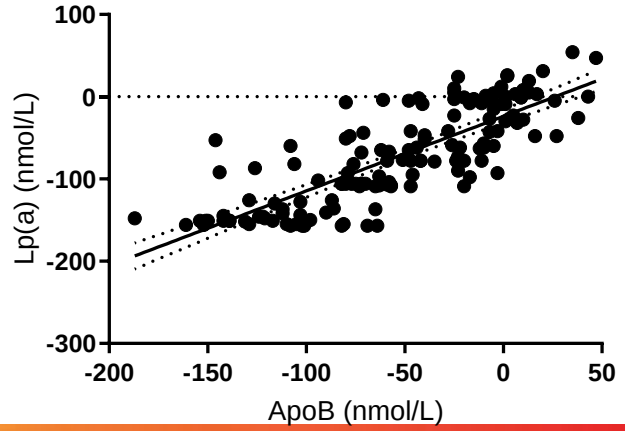
ApoB serum reduction



No reduction in liver *APOB* mRNA



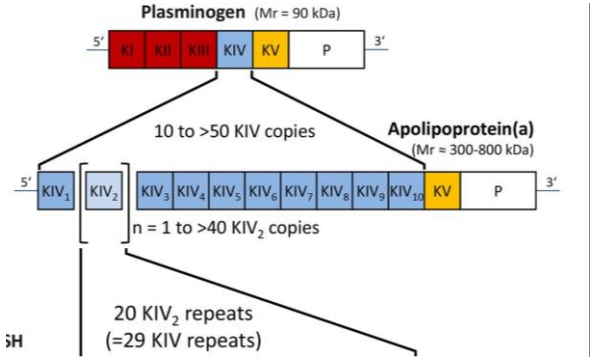
Linear reduction in apoB and Lp(a)



- No additional ApoB reduction
- In line with other Lp(a) lowering modalities

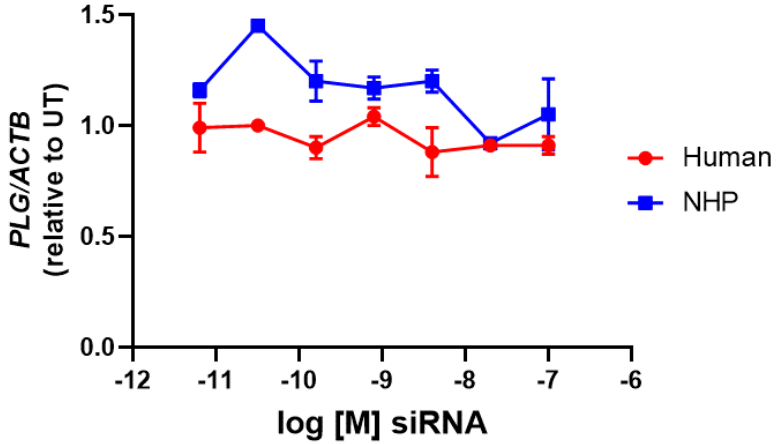
No reduction in *PLG* expression in vitro or in vivo

Plasminogen and apo(a) homology

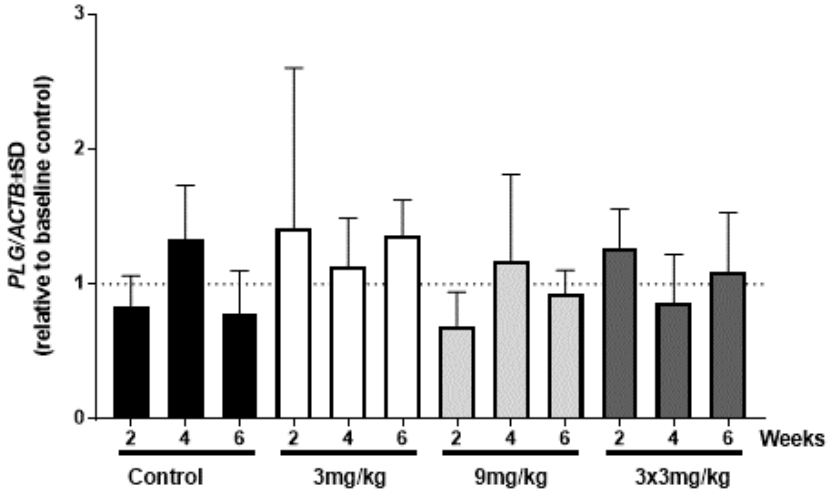


Konrad Schmidt et al. J. Lipid Res. 2016;57:1339-1359

In vitro – primary hepatocytes



In vivo - NHP



Thrombosis risk due to inadvertent *PLG* reduction is not a concern

Summary

- 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,
  - 95% reduction achieved
- Expression of closely related *PLG* is not affected

SLN360 on target for IND in H2 2020

Acknowledgements

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- Mona Eisermann
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Thank you!

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