



TIDES USA 2024

Novel TRiM™ Platform for Delivery of RNAi Therapeutics to Adipose Tissue

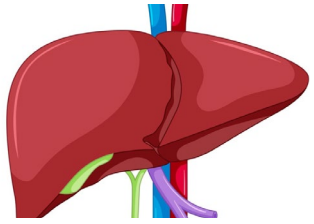
Tao Pei, Ph.D.

**Senior Vice President, Chemistry
Arrowhead Pharmaceuticals**

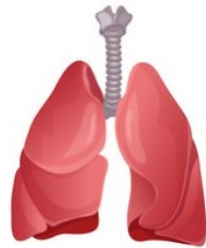
Safe Harbor Statement

This presentation contains forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995. These statements are based upon our current expectations and speak only as of the date hereof. Our actual results may differ materially and adversely from those expressed in any forward-looking statements as a result of various factors and uncertainties, including, without limitation, our developmental stage and limited operating history, our ability to successfully and timely develop products, enter into collaborations and achieve other projected milestones, rapid technological change in our markets, demand for our future products, legislative, regulatory and competitive developments and general economic conditions. Our Annual Report on Form 10-K, recent and forthcoming Quarterly Reports on Form 10-Q, recent Current Reports on Forms 8-K, and other SEC filings discuss some of the important risk factors that may affect our ability to achieve the anticipated results, as well as our business, results of operations and financial condition. Readers are cautioned not to place undue reliance on these forward-looking statements. Additionally, Arrowhead disclaims any intent to update these forward-looking statements to reflect subsequent developments.

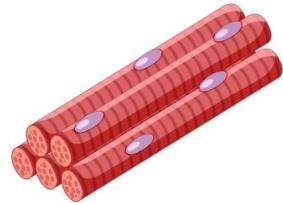
TRiM™ Platforms Drive Robust Pipeline for Multiple Tissue Types



9
Clinical
Programs



3
Clinical
Programs



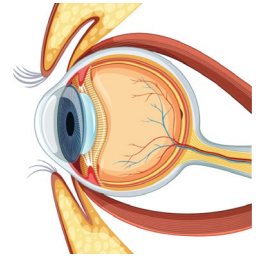
2
Pre/Clinical
Programs



1
Preclinical
Program

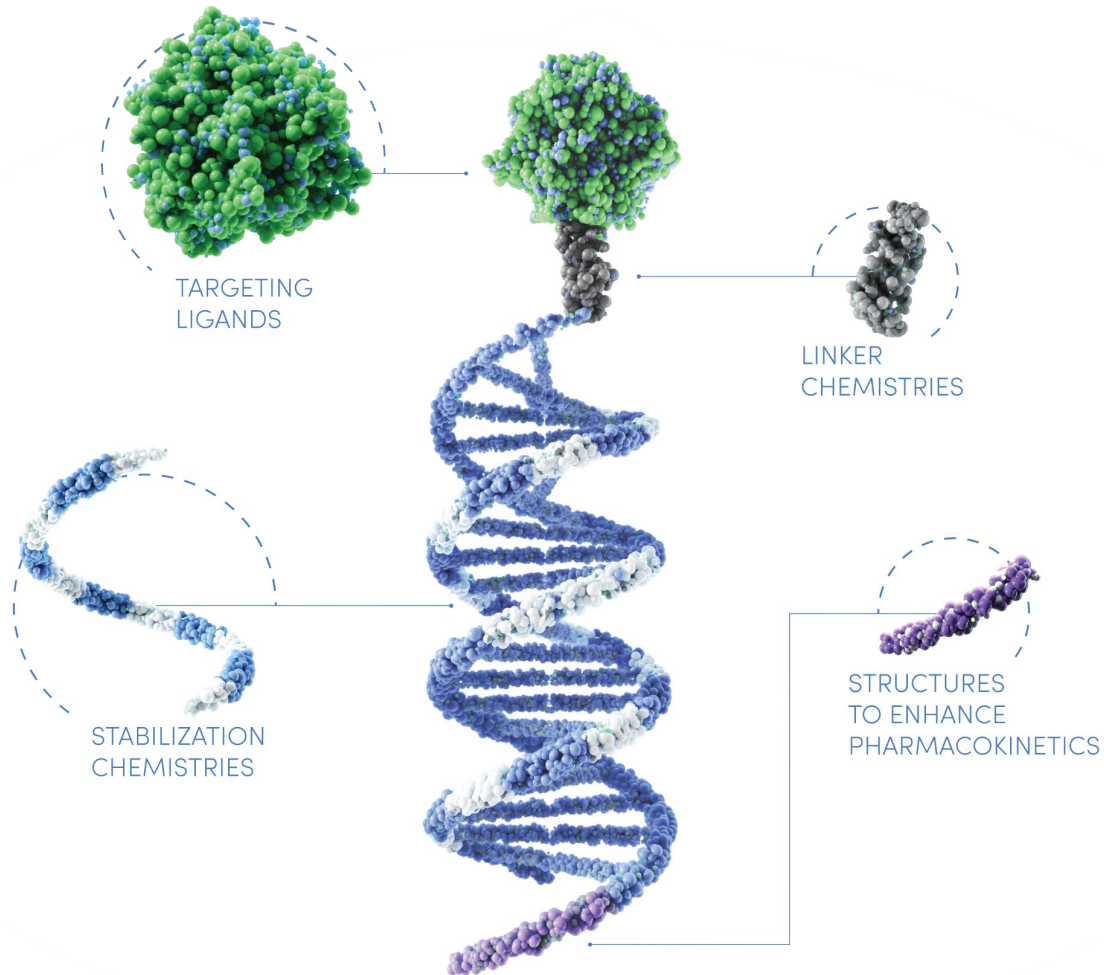


1
Preclinical
Program



1
Preclinical
Program

TRiM™ Platform: Targeted RNAi Molecule



A modular system with:

- ❖ Unique RNAi chemistry insights and expertise
- ❖ Powerful platform technology to maximize activity and stability employing:
 - ❖ Algorithmic approach to sequence selection and design
 - ❖ Stabilization chemistry
 - ❖ Targeting ligand
 - ❖ Linker chemistry
 - ❖ PK and PD enhancers

Agenda

- ❖ TRiM™ Adipose Platform
 - ❖ Platform development
 - ❖ Platform efficacy in mouse and NHP
 - ❖ Tissue selectivity and distribution profile
 - ❖ Safety profile

Adipose Tissue Is Therapeutically Relevant to Metabolic Diseases

- Largest endocrine organ in the body
- Produces/secretates numerous adipokines (messengers) which regulate numerous physiological functions
- Adipose dysfunction has been associated with:
 - Insulin resistance
 - Type 2 diabetes (T2D)
 - Dyslipidemia
 - Hyperinsulinemia
 - Cardiovascular disease
 - Cancers
- Adipose tissue-related research has greatly increased over the last 10 years as a result of its roles in regulating metabolic functions

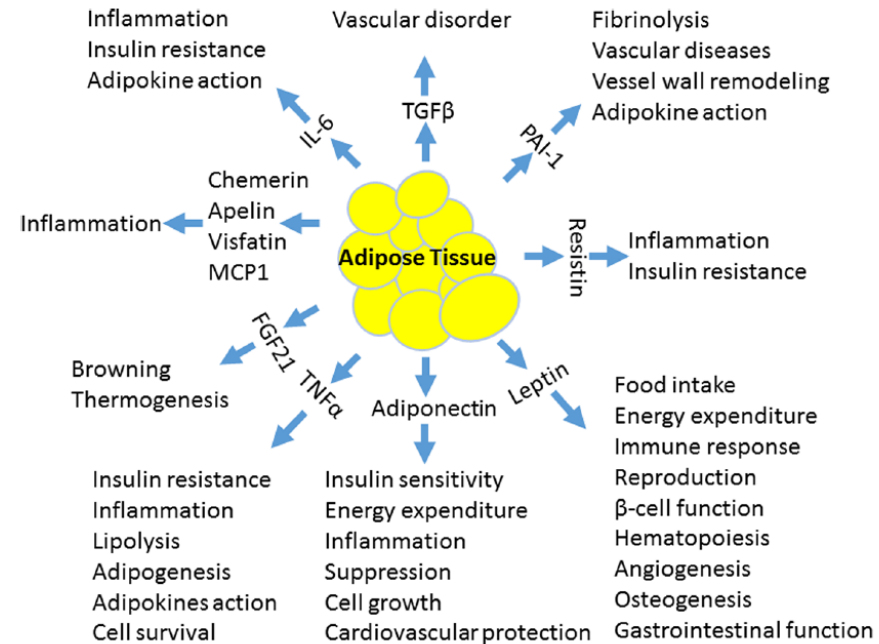


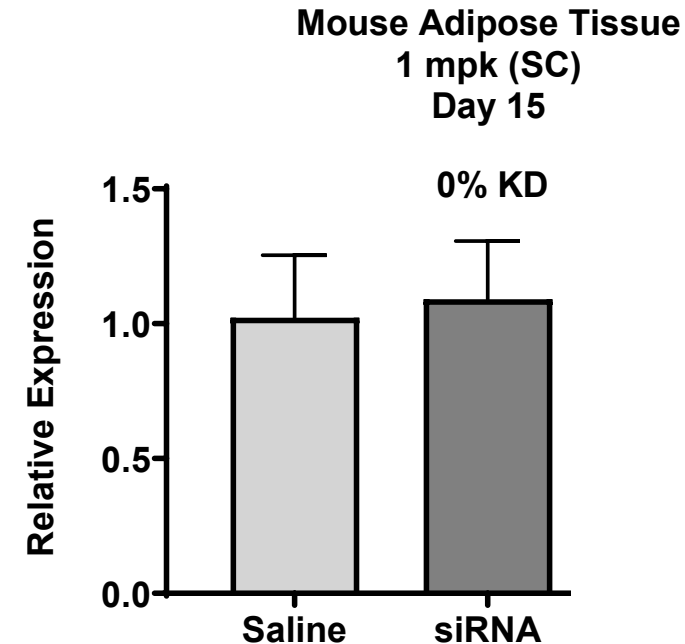
Figure 2
The physiological functions of adipokines. Adipokines, the cytokines derived from adipose tissue, act to regulate insulin sensitivity, inflammation, cardiovascular function, behaviour and cell growth, resulting in the development of obesity-induced metabolic diseases. ASP, acylating simulation protein; FGF21, fibroblast growth factor 21; IL6, interleukin 6; MCP1, monocyte chemoattractant protein 1; PAI1, plasminogen activator inhibitor 1; TNFα, tumour necrosis factor alpha.

Luo, L. & Liu, M. (2016). Adipose tissue in control of metabolism. *Journal of Endocrinology*, 231. R77-R99.

Adipose Tissue Is Therapeutically Relevant to Metabolic Diseases

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Target Gene mRNA Expression

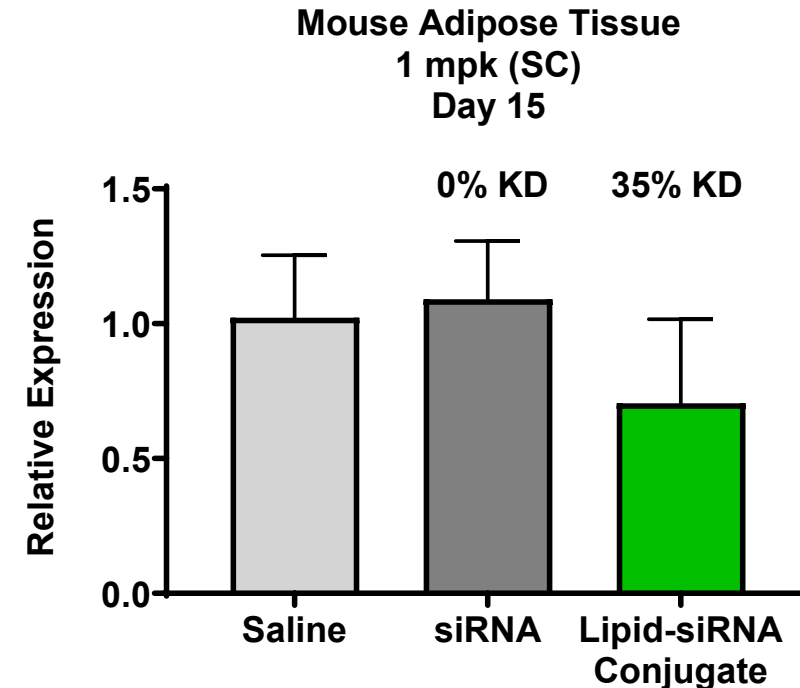


- Platform development strategy: targeting Adiponectin (i.e. Adipoq) gene, exclusively expressed in adipocytes
- **No target gene knockdown (KD) observed via siRNA alone**

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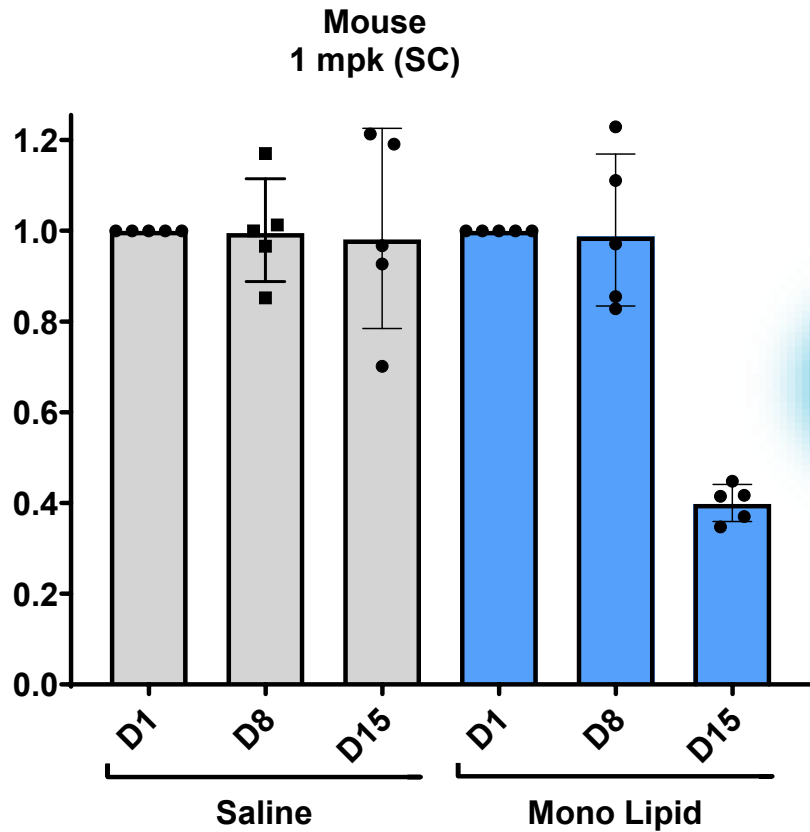
Target Gene mRNA Expression



- Given nature of adipose as lipid storage, lipids chosen to target siRNA to desired tissue
- **Lipid-siRNA conjugate shown to enable knockdown (KD) of target gene**

Dual Lipid Platform Outperforms Mono Lipid in Mouse

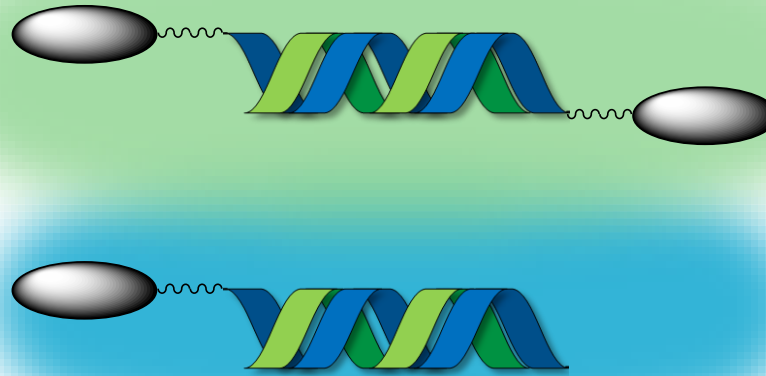
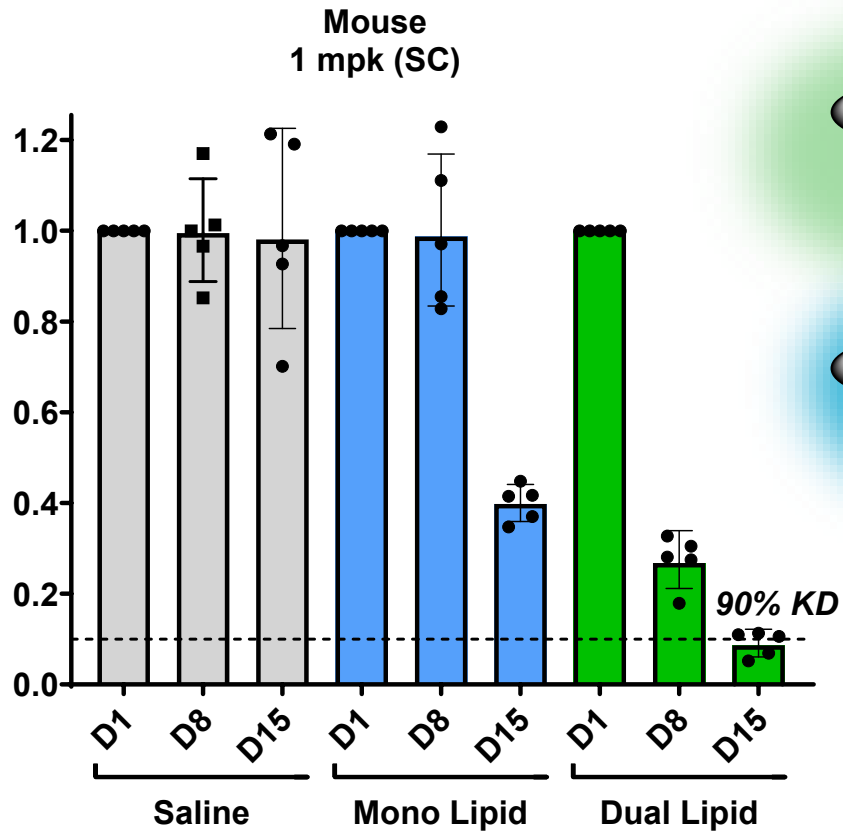
Serum Adipoq Protein Expression



- Mono lipid conjugate able to achieve good KD (~60%)

Dual Lipid Platform Outperforms Mono Lipid in Mouse

Serum Adipoq Protein Expression



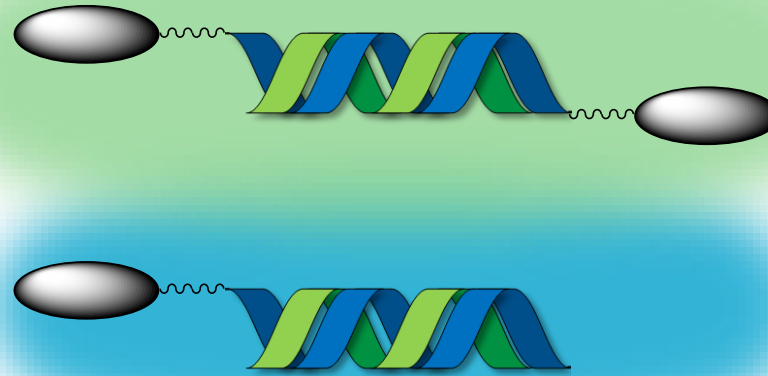
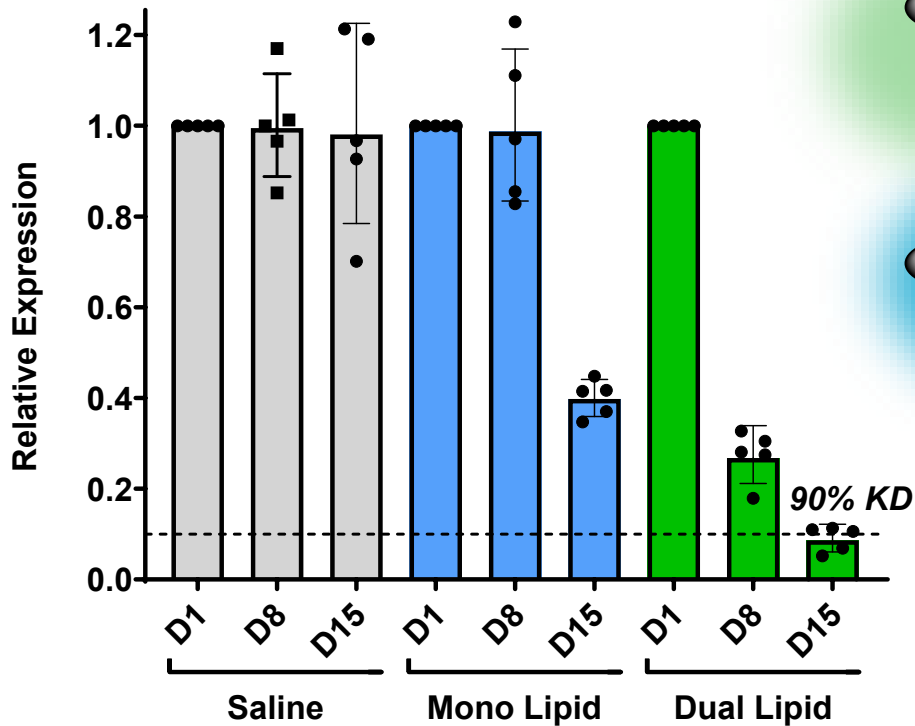
- Dual lipid conjugate found to improve KD efficacy

Dual Lipid Platform Outperforms Mono Lipid in Mouse

Serum Adipoq Protein Expression

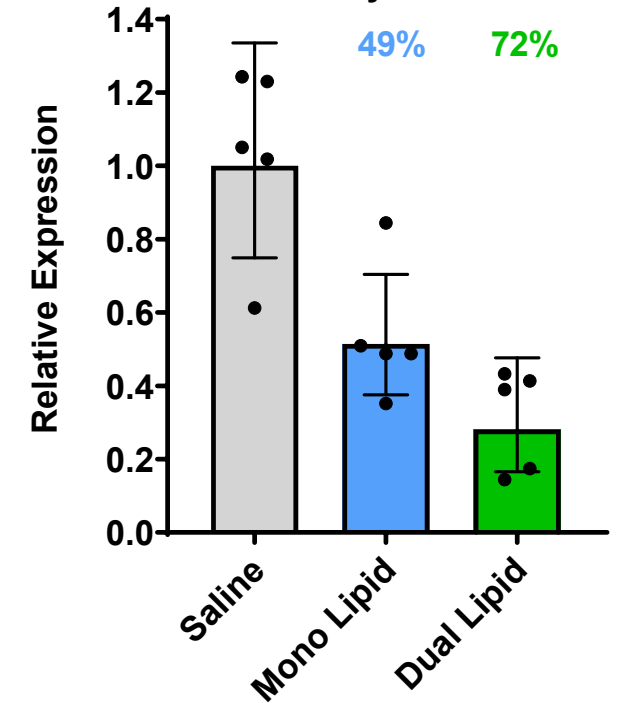
Tissue Adipoq mRNA Expression

Mouse
1 mpk (SC)



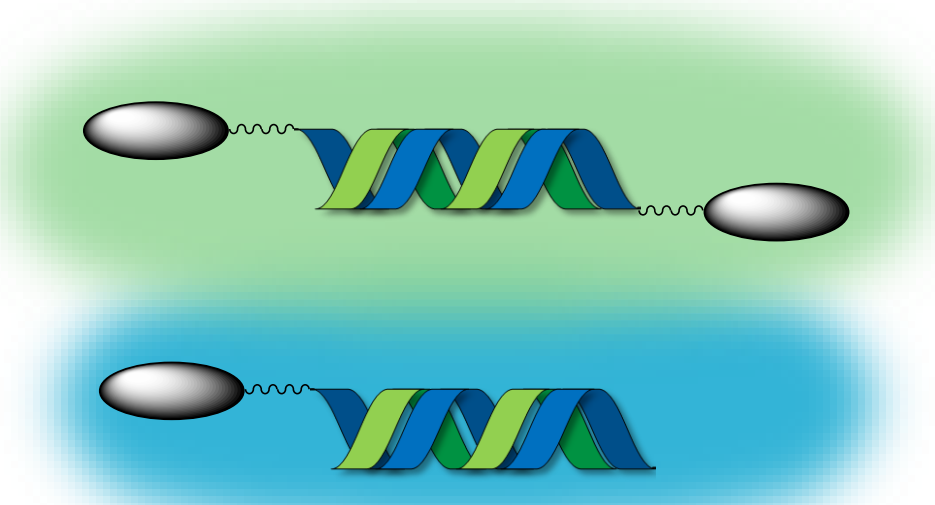
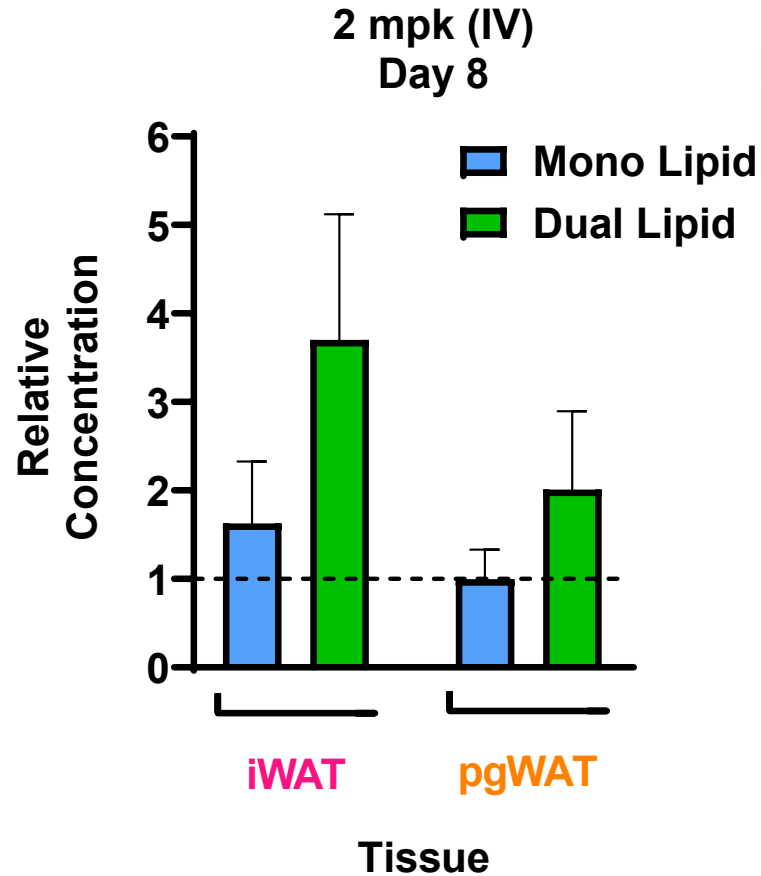
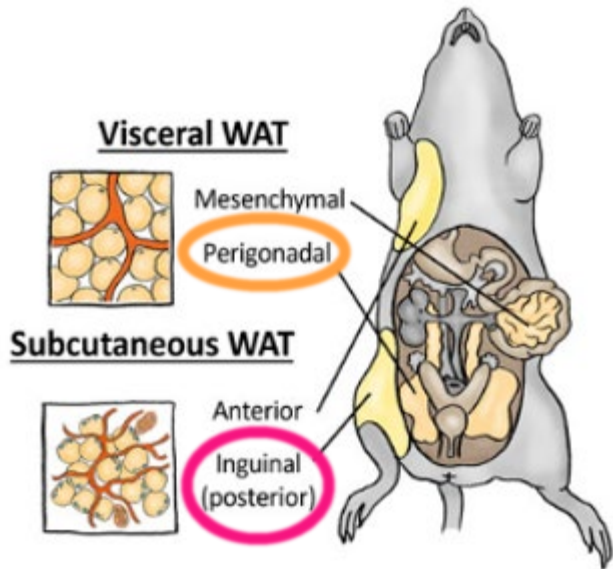
- Dual lipid conjugate found to improve KD efficacy
- Protein KD corroborated by mRNA KD

Mouse iWAT
1 mpk (SC)
Day 15



Dual Lipid Platform Achieves Improved Delivery to Mouse Adipose

Relative siRNA Concentrations in Mouse Adipose Tissues

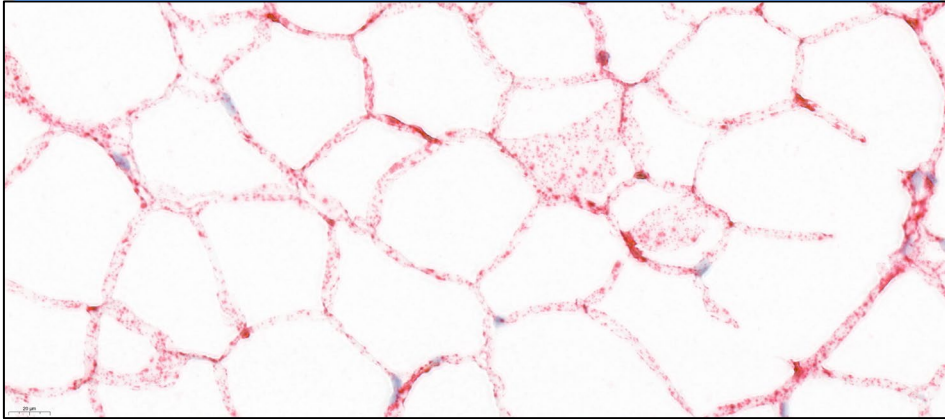


- Dual lipid platform achieves 2x relative siRNA delivery to two different adipose tissues compared to mono lipid platform

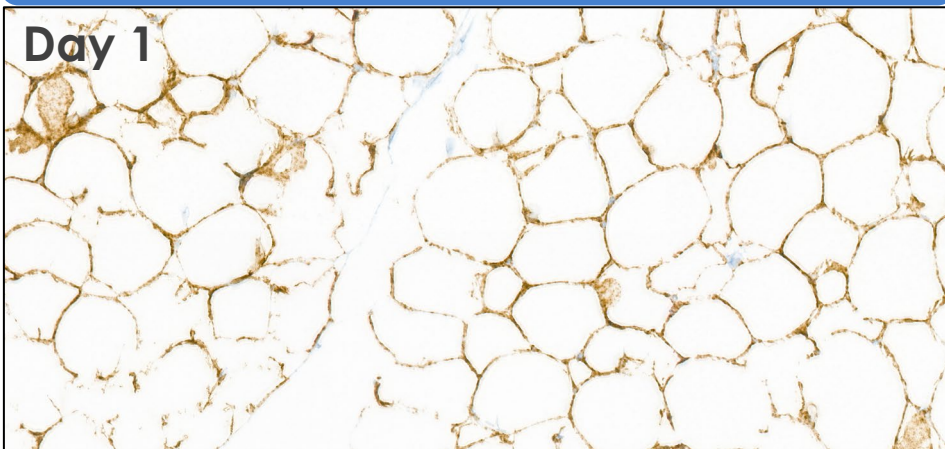
Börgeson, E., Boucher, J., & Hagberg, C. E. (2022). Of mice and men: Pinpointing species differences in adipose tissue biology. *Frontiers in cell and developmental biology*, 10, 1003118.

Platform Targets Mouse Adipocytes

miRNAscope



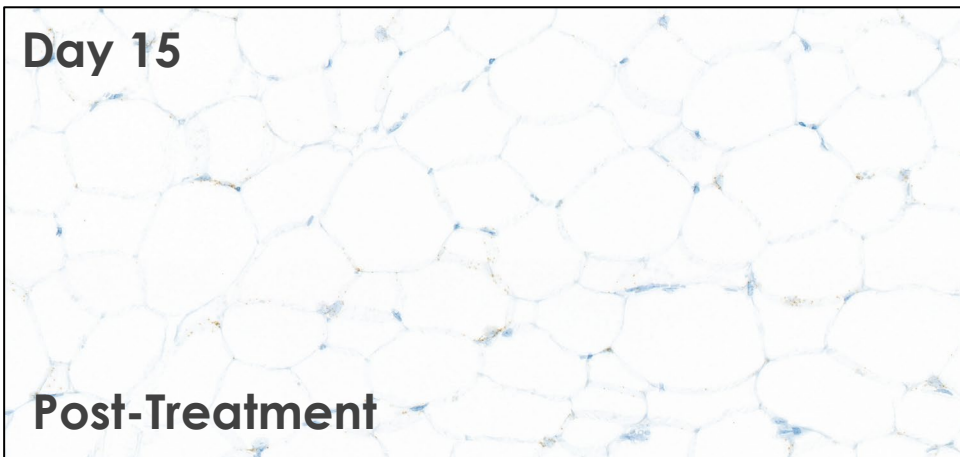
RNAscope



3 mpk
dose (SC)



Day 15



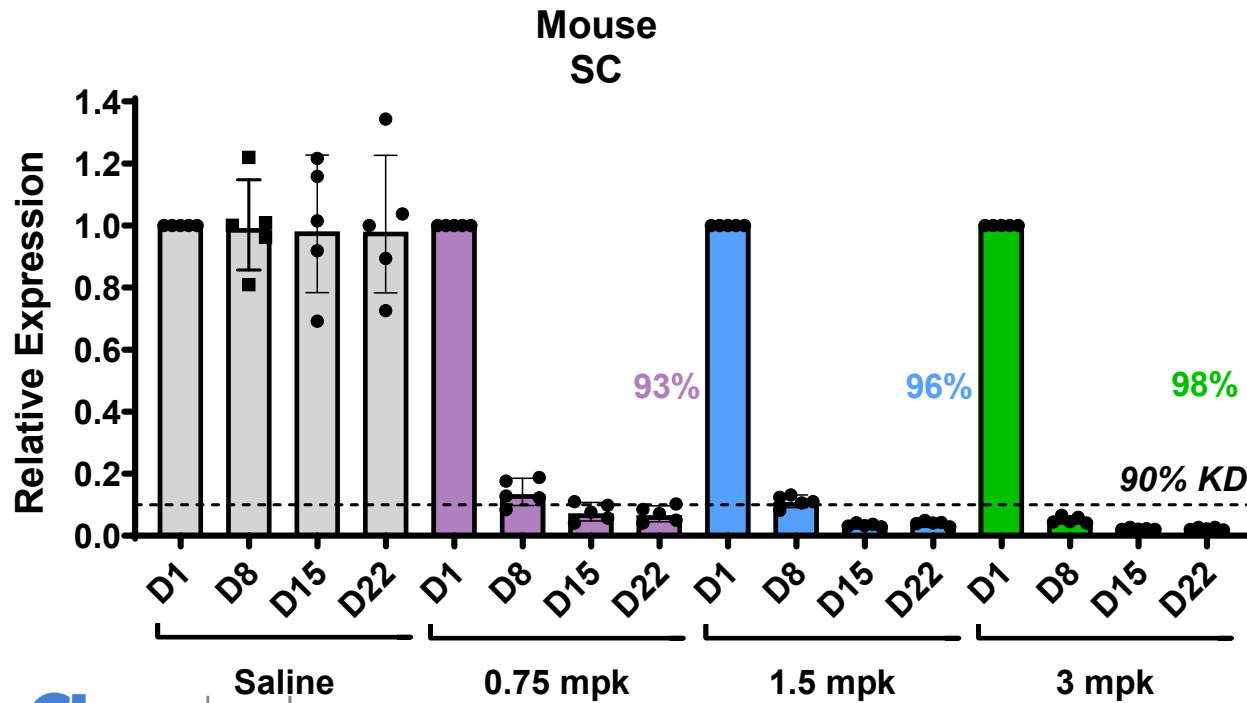
- Tissue-staining to confirm siRNA delivery and depletion of target mRNA in adipocytes
- Mice dosed with adipose platform at 3 mpk (SC), D15 harvest
- **miRNAscope visualization of trigger confirms delivery to adipocytes**
- **RNAscope confirms Adiponectin mRNA depletion**

Dual Lipid Platform Achieves Deep Serum Protein and mRNA Knockdown in Mouse



- Deep protein KD achieved via dual lipid platform from 0.75 mpk

Serum Adipoq Protein Expression

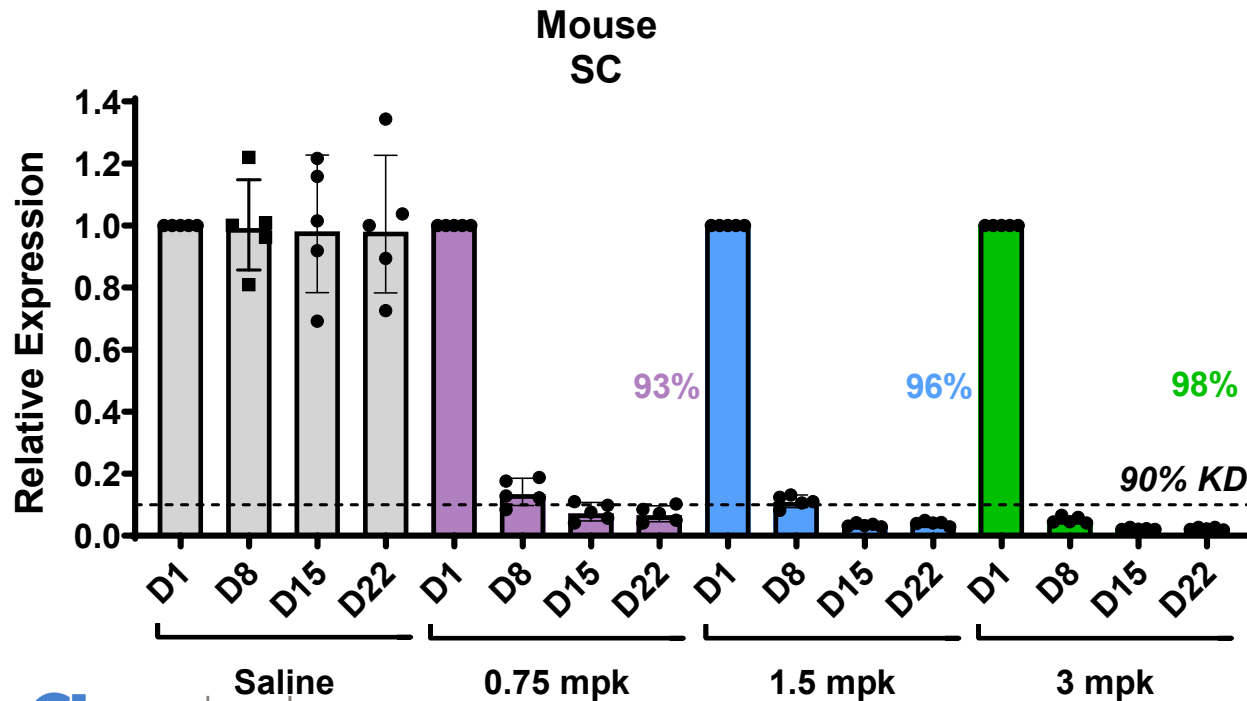


Dual Lipid Platform Achieves Deep Serum Protein and mRNA Knockdown in Mouse

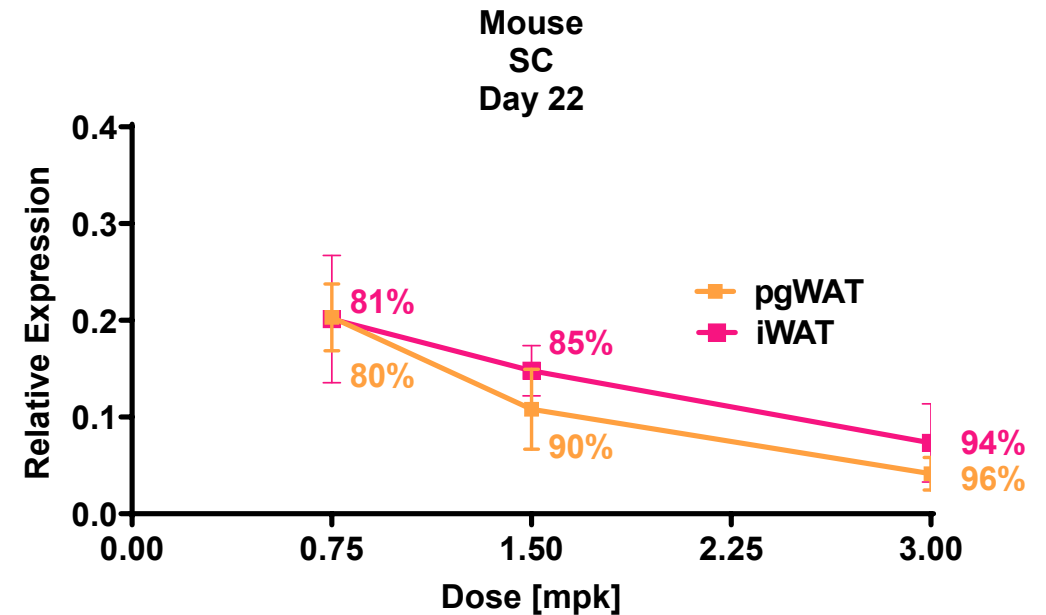


- Deep protein KD achieved via dual lipid platform from 0.75 mpk
- mRNA KD consistent in target tissues

Serum Adipoq Protein Expression



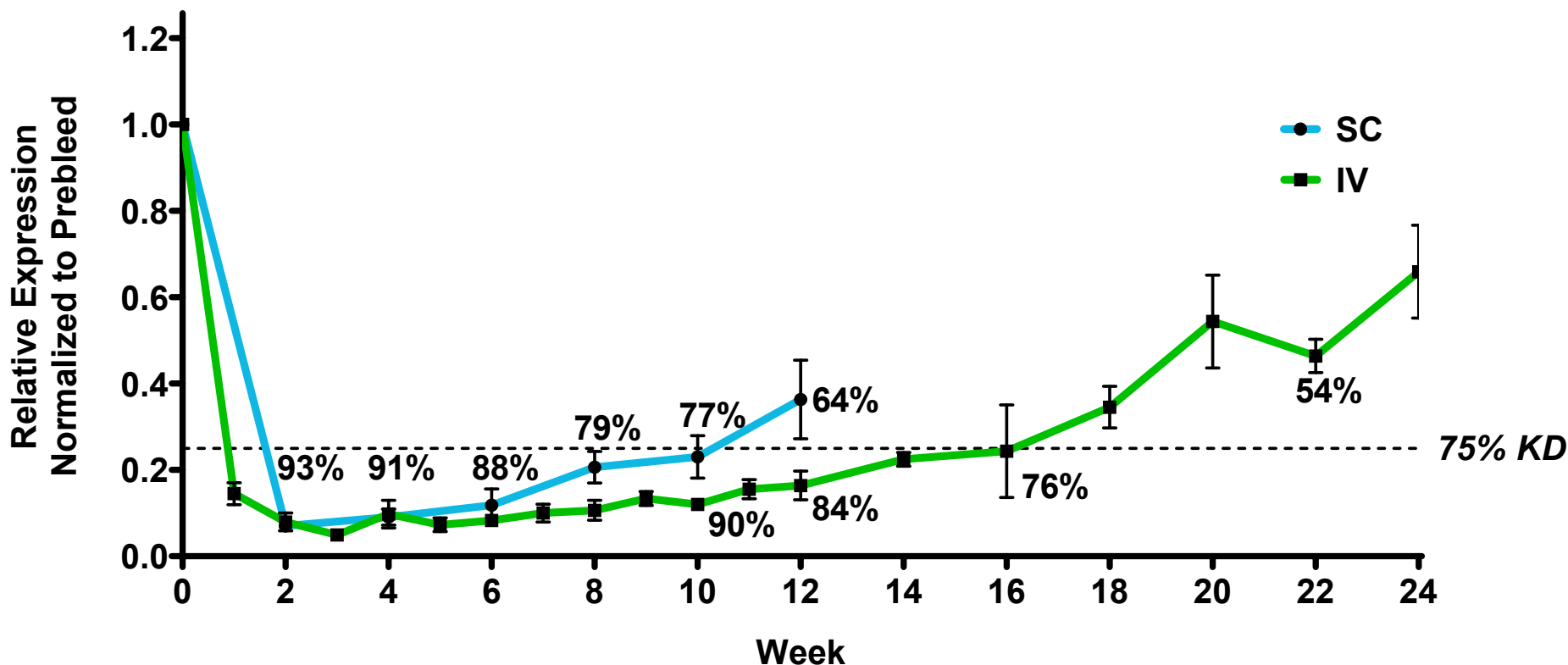
Tissue Adipoq mRNA Expression



Platform Achieves Deep and Durable Knockdown via Single 2 mpk Dose in Mouse

Serum Adipoq Protein Expression

Mouse
SC vs IV, 2 mpk
Weeks 1-24



SC Dosing

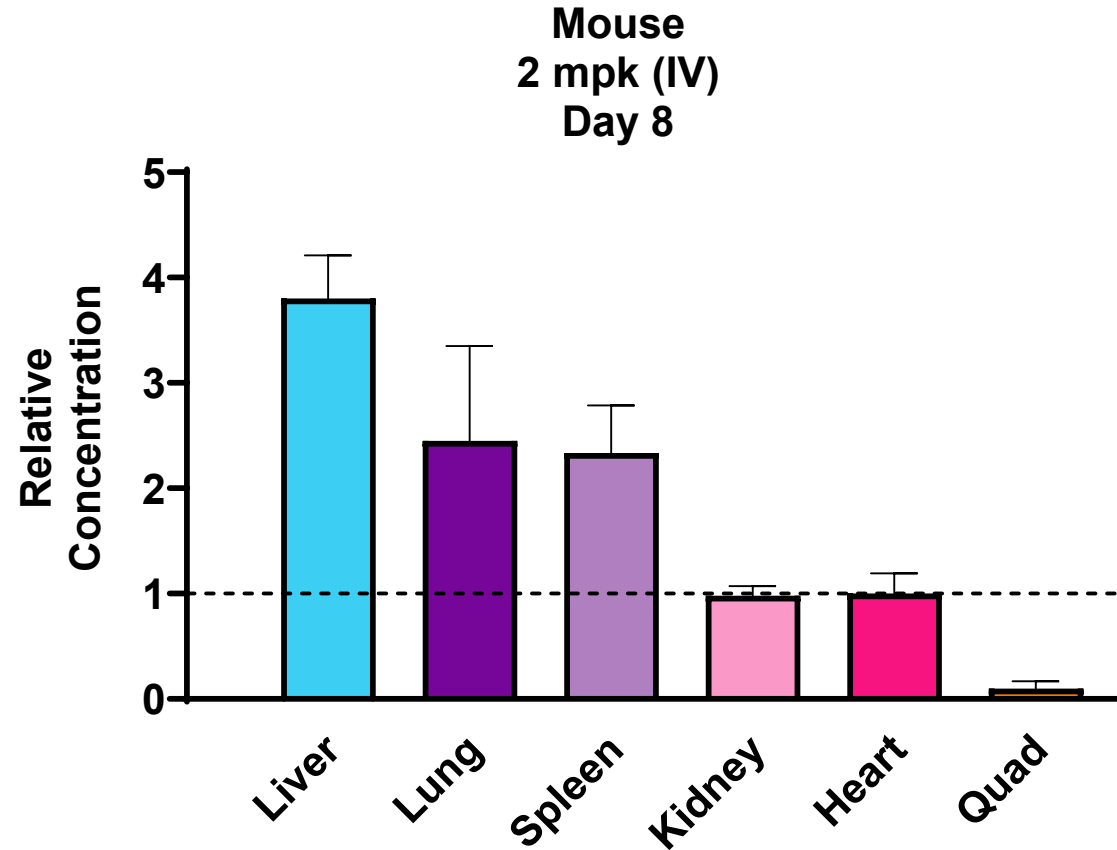
- ~90% serum Adipoq protein KD maintained through week 6
- $\geq 75\%$ KD maintained through week 10

IV Dosing

- ~90% serum Adipoq protein KD maintained through week 10
- $\geq 75\%$ KD maintained through week 16

Platform Shows Distribution to Peripheral Tissues in Mouse

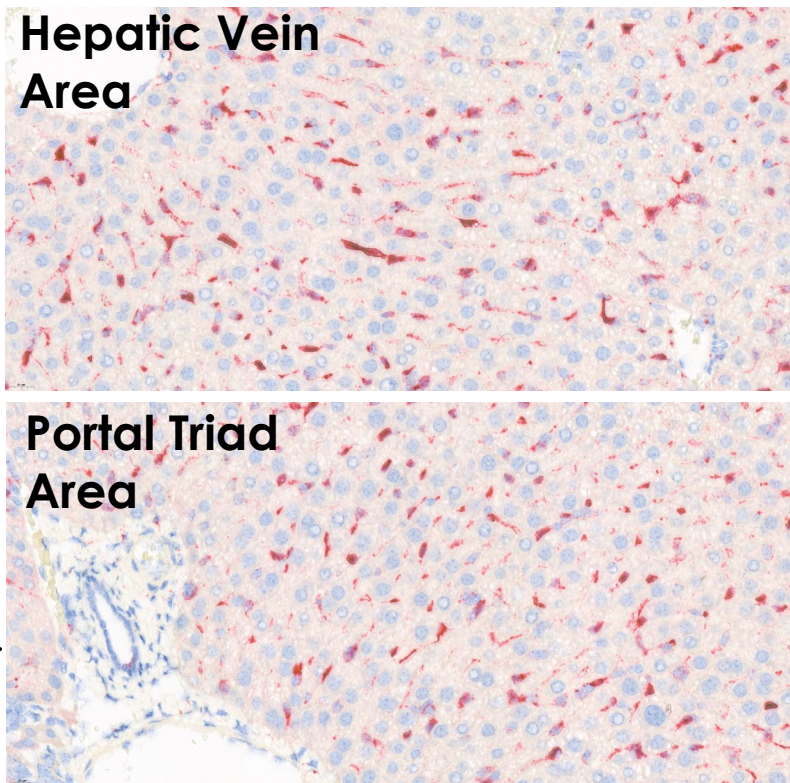
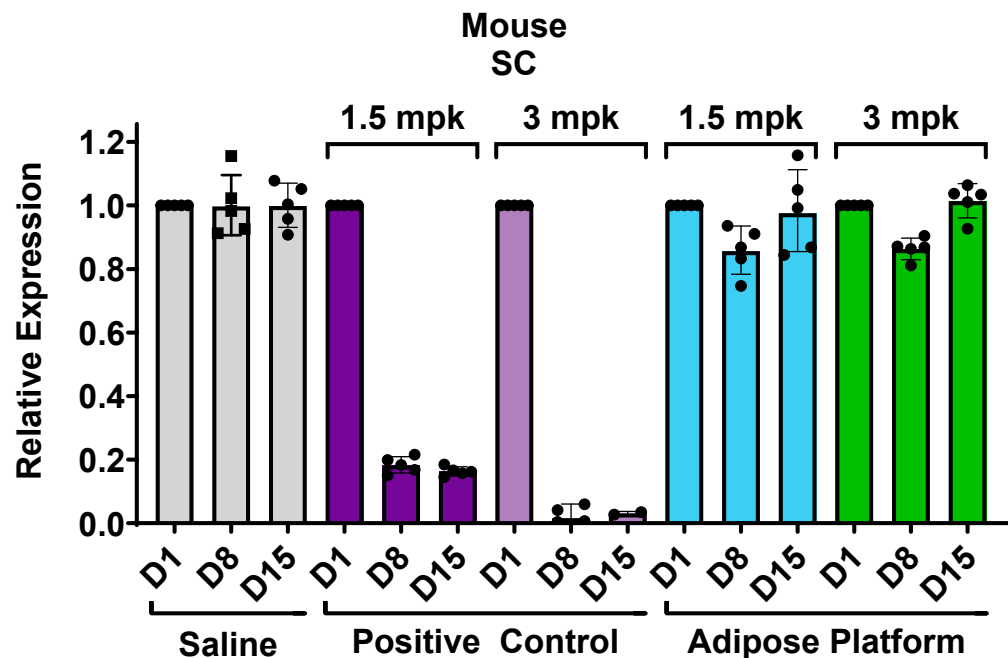
Relative Peripheral Tissue siRNA Concentrations



- Broad systemic distribution with greatest accumulation in liver
- Greater siRNA accumulation does not necessarily correspond with greater KD

Platform Does not Target Hepatocytes and Lung Alveolar Cells in Rodent

Serum FXII Protein Expression in Liver

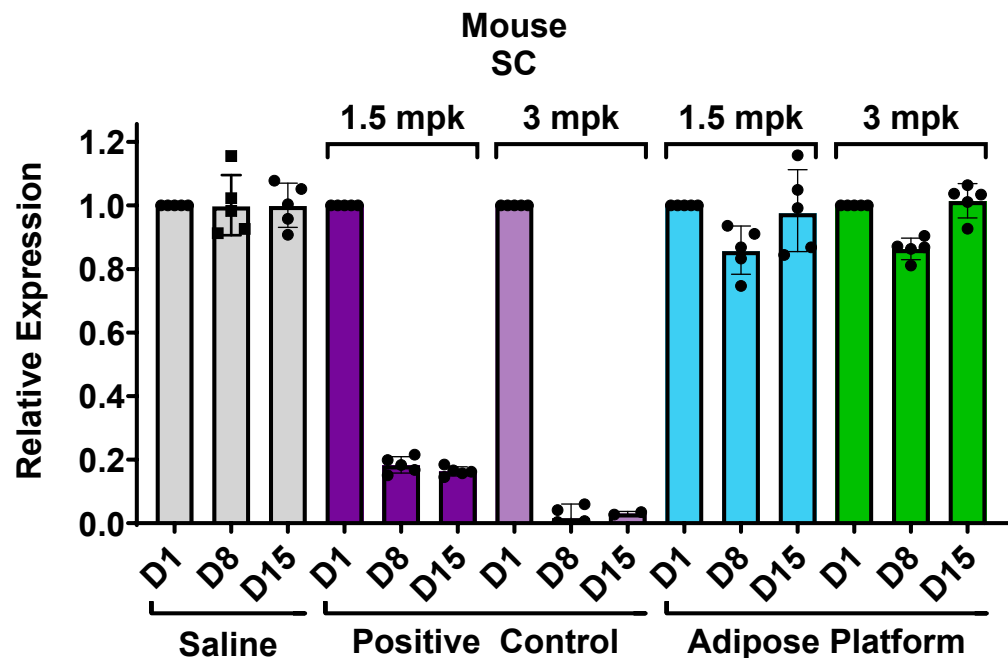


- Targeted hepatocyte-specific gene, FXII
- **Adipose platform did NOT show FXII KD in liver at 1.5 and 3 mpk**

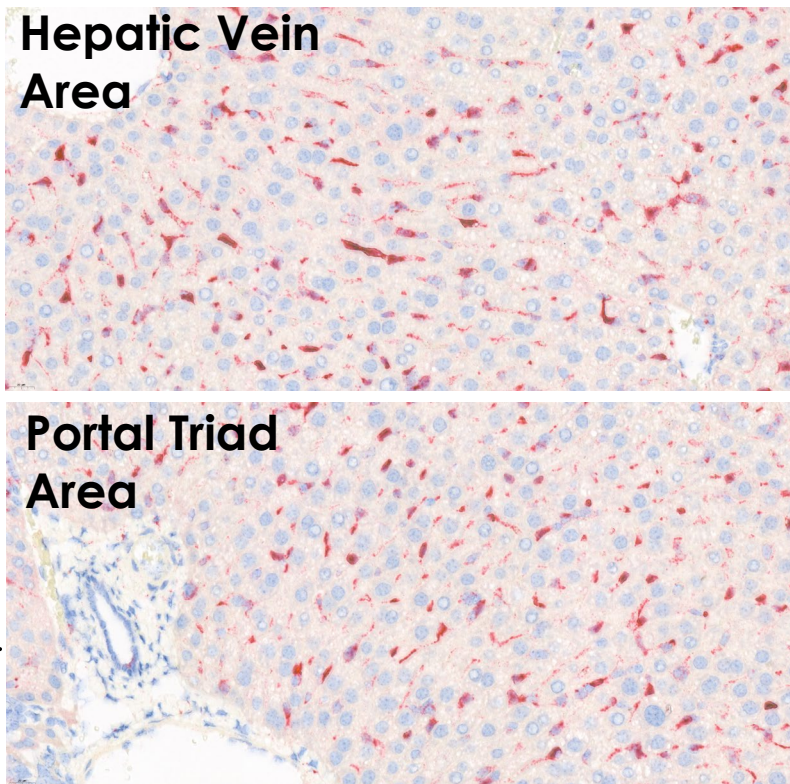
- miRNAscope showed majority of siRNA accumulation in non-hepatocyte cells

Platform Does not Target Hepatocytes and Lung Alveolar Cells in Rodent

Serum FXII Protein Expression in Liver

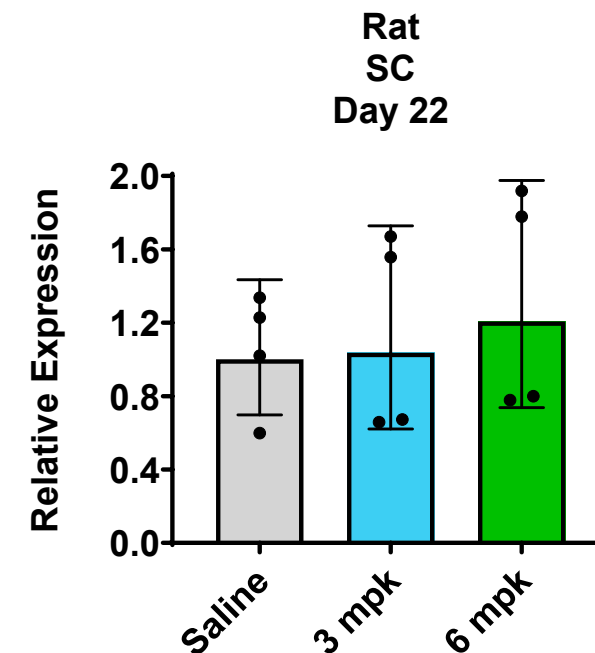


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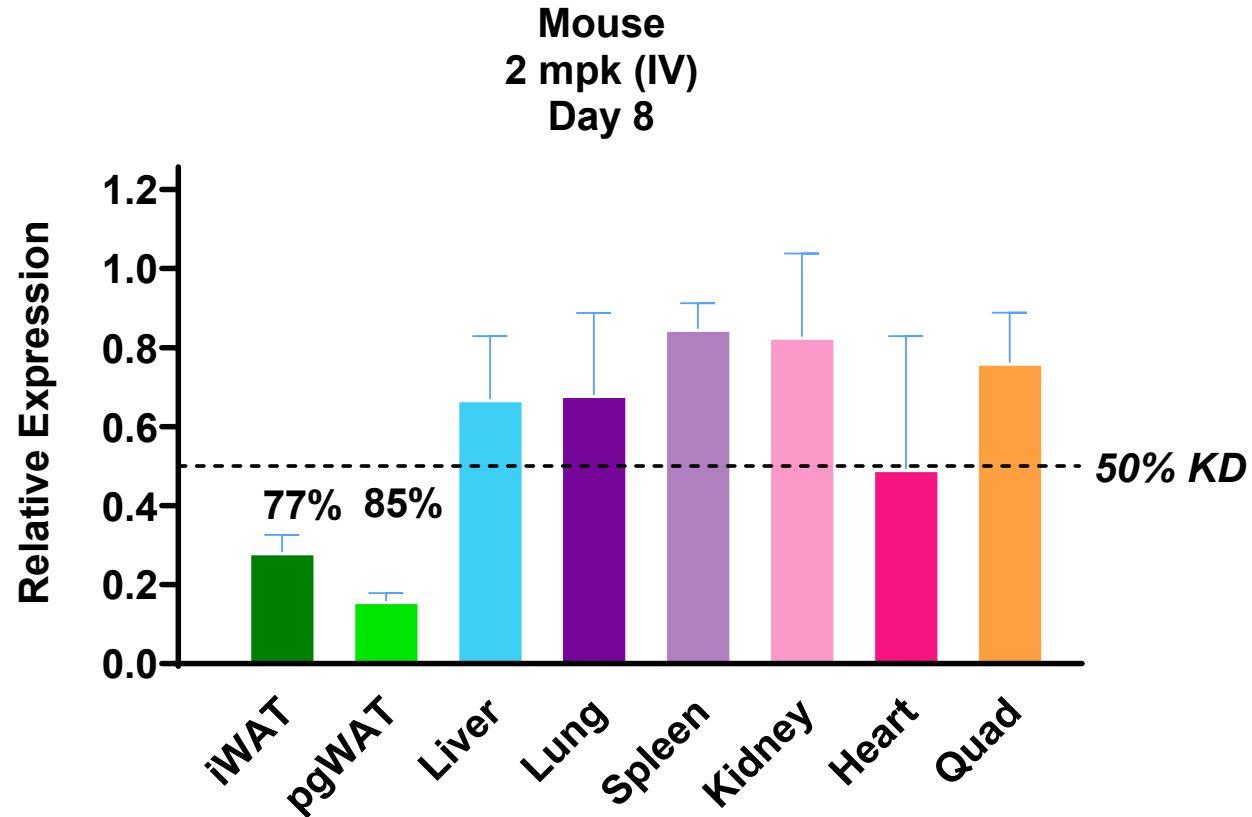
Tissue RAGE mRNA Expression in Lung



- Targeted lung-specific gene, RAGE
- Adipose platform did NOT show RAGE KD in lung at 3 and 6 mpk**

Platform Demonstrates Functional Tissue Selectivity in Mouse

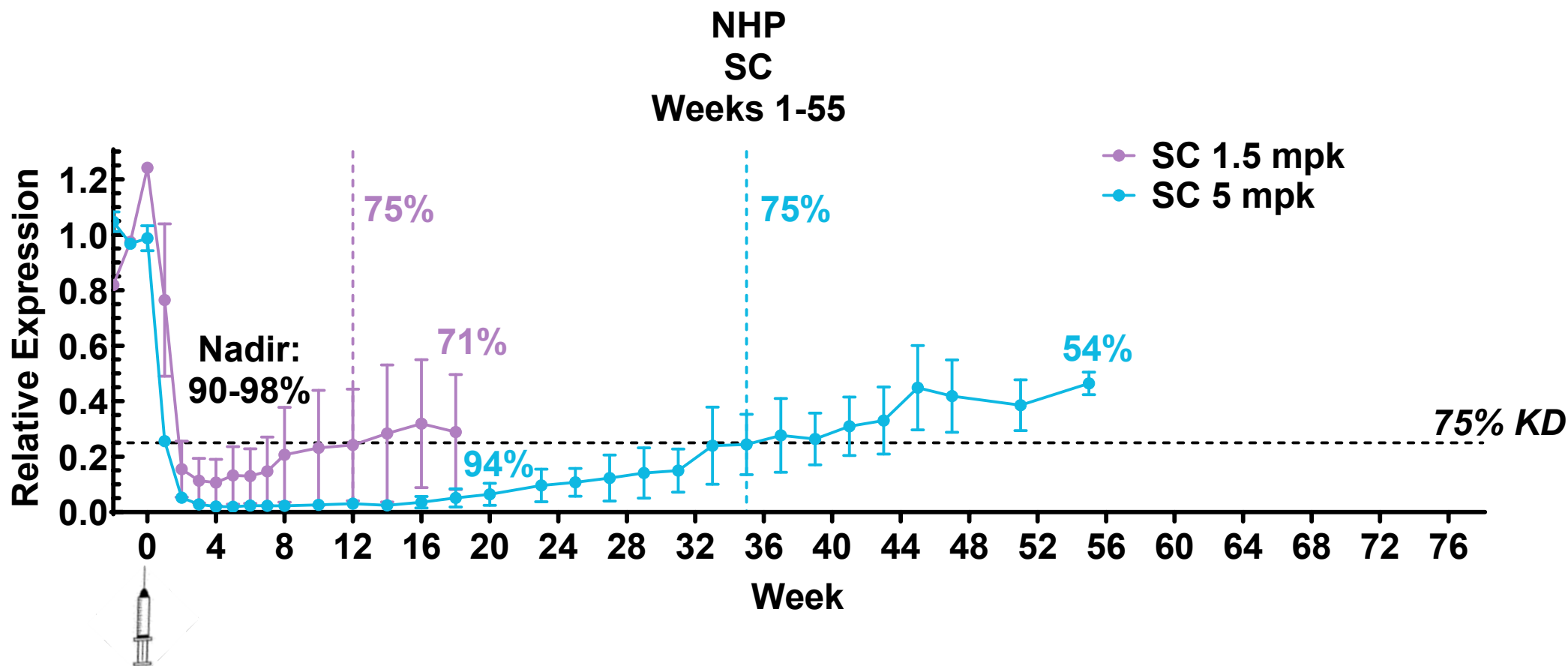
Tissue SOD1 mRNA Expression



- Despite peripheral tissue accumulation, significant KD observed selectively in adipose tissues

Platform Achieves Deep and Durable Knockdown via Single Dose in NHP

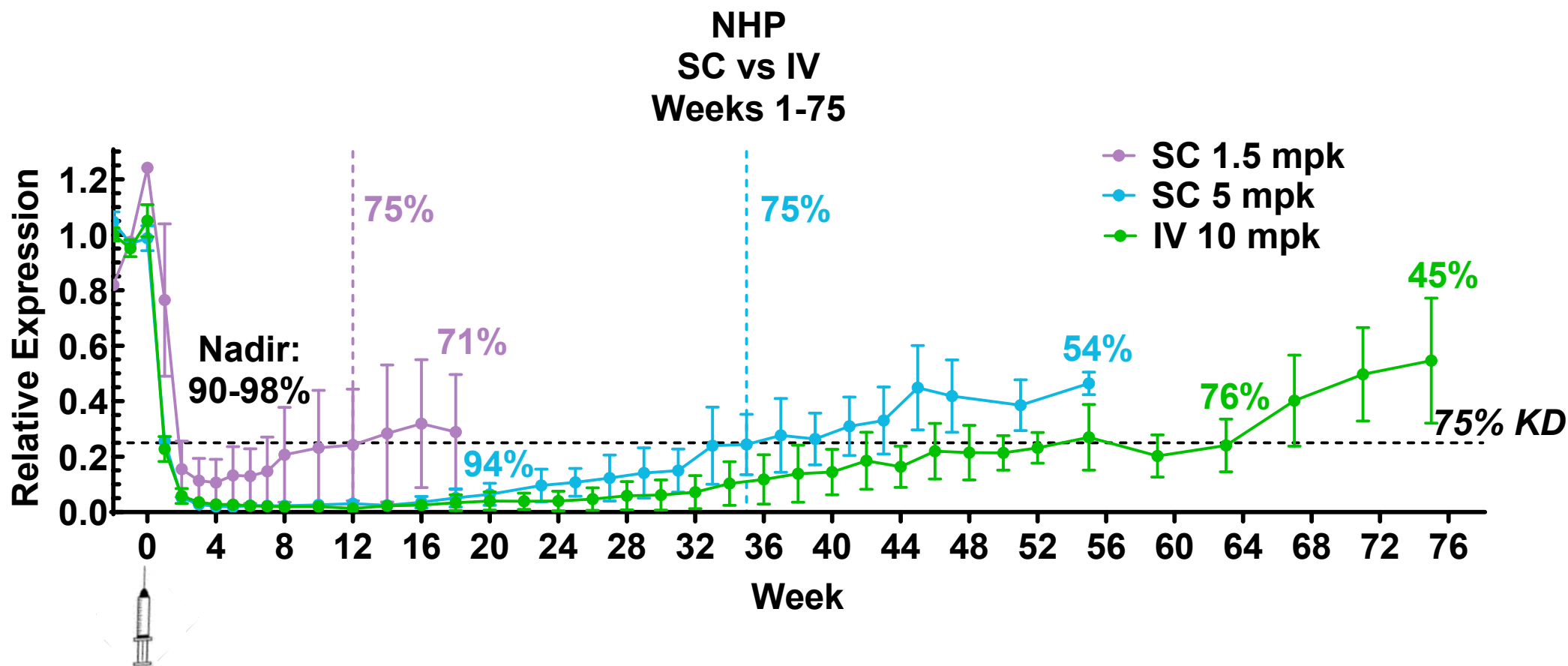
Serum Adipoq Protein Expression



- Single SC dose 1.5 mpk: $\geq 75\%$ KD maintained for ~3 months
- Single SC dose 5 mpk: $\geq 75\%$ KD maintained for ~9 months

Platform Achieves Deep and Durable Knockdown via Single Dose in NHP

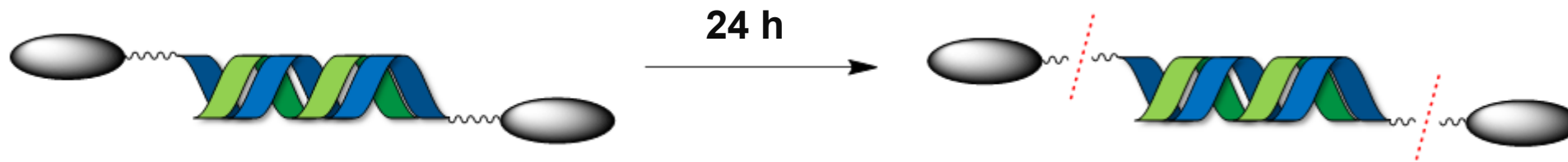
Serum Adipoq Protein Expression



- Single SC dose 1.5 mpk: $\geq 75\%$ KD maintained for ~3 months
- Single SC dose 5 mpk: $\geq 75\%$ KD maintained for ~9 months
- Single IV dose 10 mpk: $\geq 75\%$ KD maintained for ~16 months

Metabolism & Clearance Overview of TRiM™ Adipose Platform in Rat

Tissue Metabolism:



Tissue Clearance:

Rat Tissue	$T_{1/2}$ (days)	Calculated 95% Clearance by:
Liver	Phase 1: 4 Phase 2: 15	9-10 weeks (~2.5 months)
Kidney	12	8-9 weeks (~2 months)
Heart	22	15-16 weeks (4 months)

- Both lipids cleaved within 24 hours
- Interval of 3-4 months between doses is anticipated to allow 95% clearance in all tissues

Adipose Platform Demonstrates Good Safety Profile

- ❖ Non-GLP exploratory tox study in rat:
 - ❖ Day 1, Day 15 SC dose up to 120 mpk
 - ❖ Necropsy at Day 16 and Day 29
- ❖ No mortality
- ❖ No noteworthy observations or body weight changes
- ❖ Minimal findings in clinical chemistry, hematology, and coagulation
- ❖ Histopathology: no adverse drug-related findings at Day 16 and Day 29 necropsies



Summary

- ❖ A new extrahepatic TRiM™ platform for siRNA delivery to adipose tissue has been developed that achieves deep and durable target gene knockdown in mouse and NHP
- ❖ Good safety profile in rat



Thank you!

Questions?