sirnaomics
Advancing RNAi Therapeutics

GalAhead™ Platform & Programs

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Sirnaomics: Introduction

Proprietary delivery platforms

Proprietary PNP and novel GalNAc RNAi delivery platforms

First RNAi oncology success

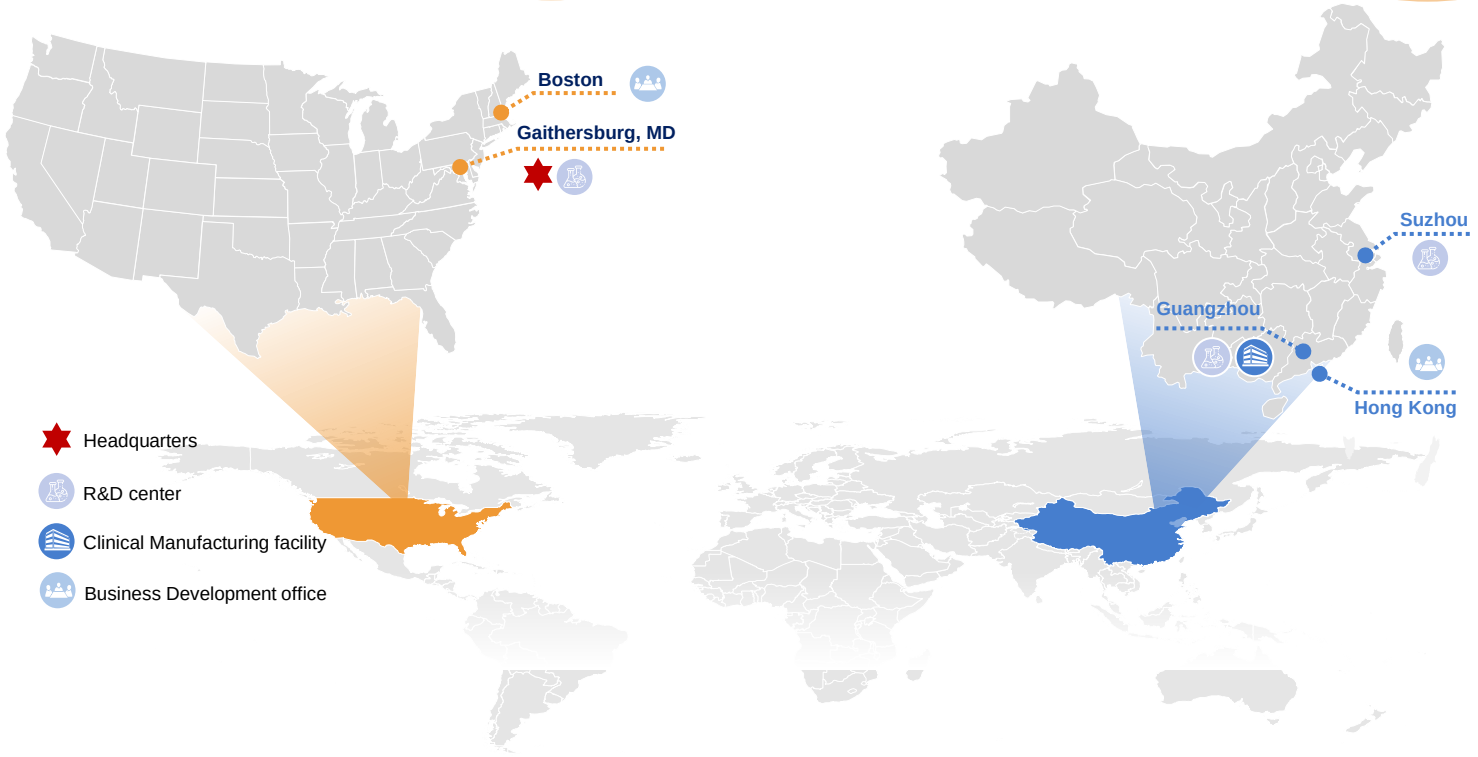
First to achieve positive Phase IIa clinical outcomes in oncology

Broad therapeutic utility

Oncology, fibrosis, medical aesthetics, anti-viral, cardiovascular and cardiometabolic diseases, etc.

Technology driven platforms

- Proprietary algorithm for siRNA drug design
- Microfluidic technology for commercial-scale manufacturing



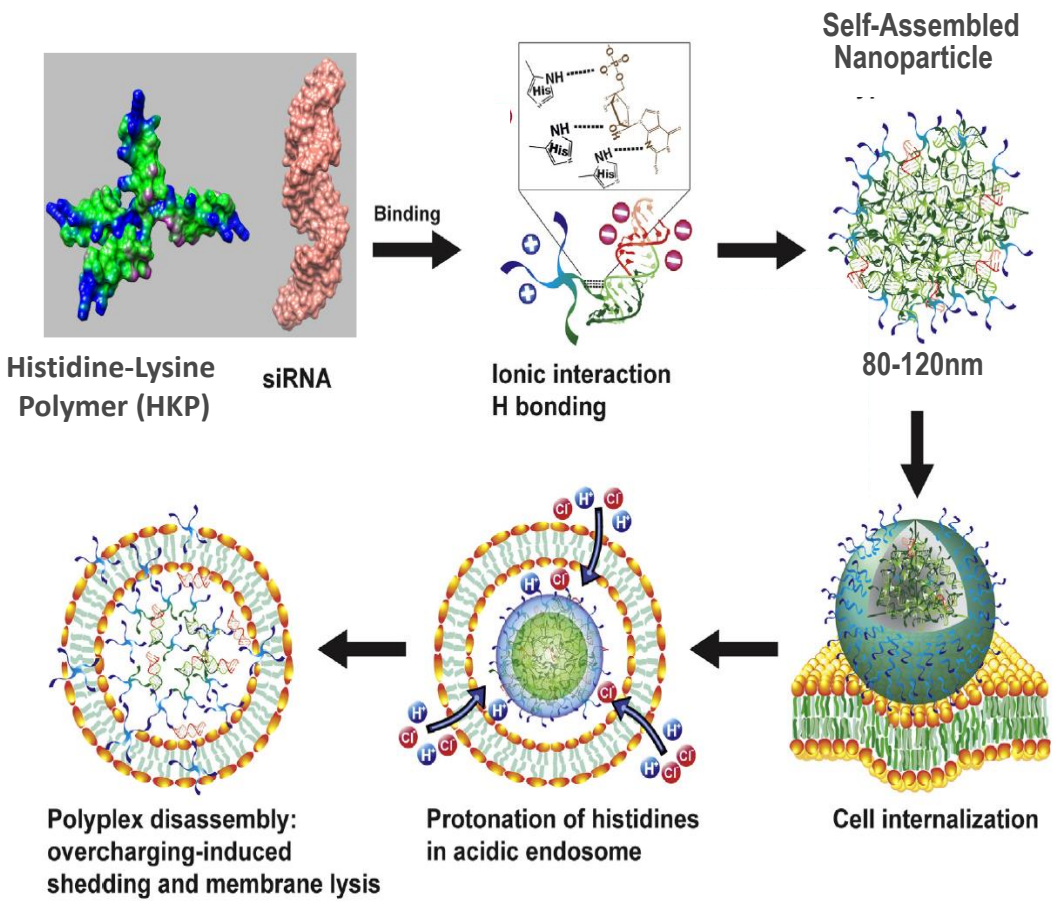
Fund raising

Raised >$250M during last 3 rounds (series C, D and E)

Successful IPO

Went public in December 2021

Peptide Nano-Particle (PNP) Technology: principles



Polypeptide Nanoparticle (PNP) delivery

- Biodegradable histidine-lysine branched polymer
- Envelops and protects siRNA to facilitate delivery into the targeted tissue and cell
- Histidine mediated protonation to facilitate siRNA payload release
- Nanoparticle size is controllable to diversify tissue distribution and enhance safety
- Addressing key cell types in liver beyond hepatocyte
- Multiple routes of administration: intra-dermal/tumoral, and systemic (systemic tox ongoing)

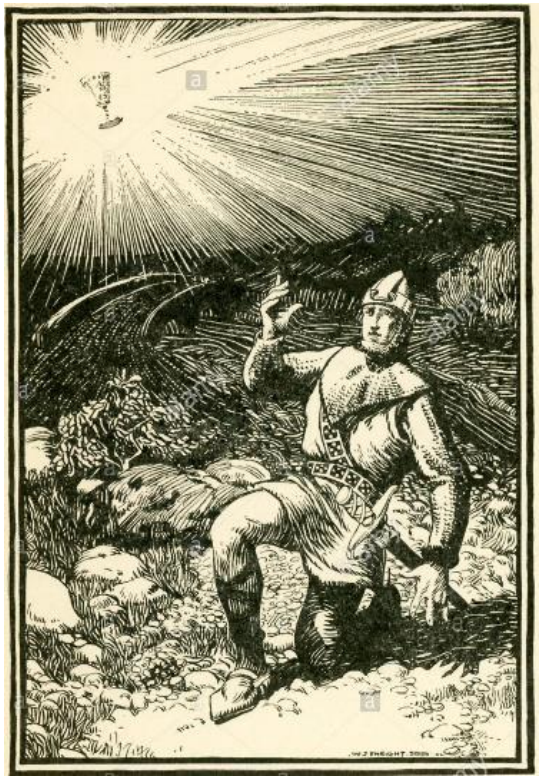
Sirnaomics: PNP-based programs

	Candidate	Gene Targets	Indications	Delivery Platform	Pre-clinical / IND Enabling / IND / Phase I / Phase II / Phase III	Rights
Oncology	STP705*	TGF-β1/COX-2	isSCC	PNP-IT	US; China (MRCT)[2]	Global
			BCC		US	Global
			Liver Cancer[1] (Basket) **		US; China (MRCT)[3]	Global
			Liver Cancer, combo with anti-PD-(L)1[5]		US	Global
	STP707	TGF-β1/COX-2	Multiple solid tumors	PNP-IV	US; China (MRCT)[4]	Global
			cSCC		US	Global
			NSCLC		US	Global
			Liver Cancer, cSCC, NSCLC, combo with anti-PD-(L)1[5]		US	Global
	STP355	TGF-β1/VEGFR2	Pan Cancer	PNP-IT / IV	US	Global
	STP369	BCL-xL/MCL-1	Head & Neck Cancer / Bladder Cancer		US	Global
Fibrosis	STP705*	TGF-β1/COX-2	Keloid Scarless Healing	PNP-ID	US	Global
			Hypertrophic Scarring		US; China (MRCT); China	Global
	STP707	TGF-β1/COX-2	Liver Fibrosis (PSC)	PNP-IV	US; China (MRCT)	Global
			Lung Fibrosis		US	Global
Medical Aesthetics	STP705*	TGF-β1/COX-2	Fat sculpting	PNP-ID	US	Global

*Notes : * denotes our core product ** denotes orphan drug*

1. *Liver cancer (basket) includes cholangiocarcinoma, hepatocellular carcinoma, liver metastases etc.*
2. *We filed our IND in China in June 2021, which is currently awaiting approval from NMPA, for study sites in China. The study sites will be part of a global multicenter clinical trials for our Phase IIb clinical trial for isSCC.*
3. *We expect to file the IND in China as part of the global multicenter clinical trials.*
4. *We expect to file the IND solely for HCC in China as part of the global multicenter clinical trials.*
5. *Studies in combination with anti-PD-(L)1 inhibitors conducted pursuant to collaborations with Innovent and Shanghai Junshi.*

GalAhead™: Sirnaomics' proprietary GalNAc-siRNA platform



GalAhead™ technology incorporates multiple components

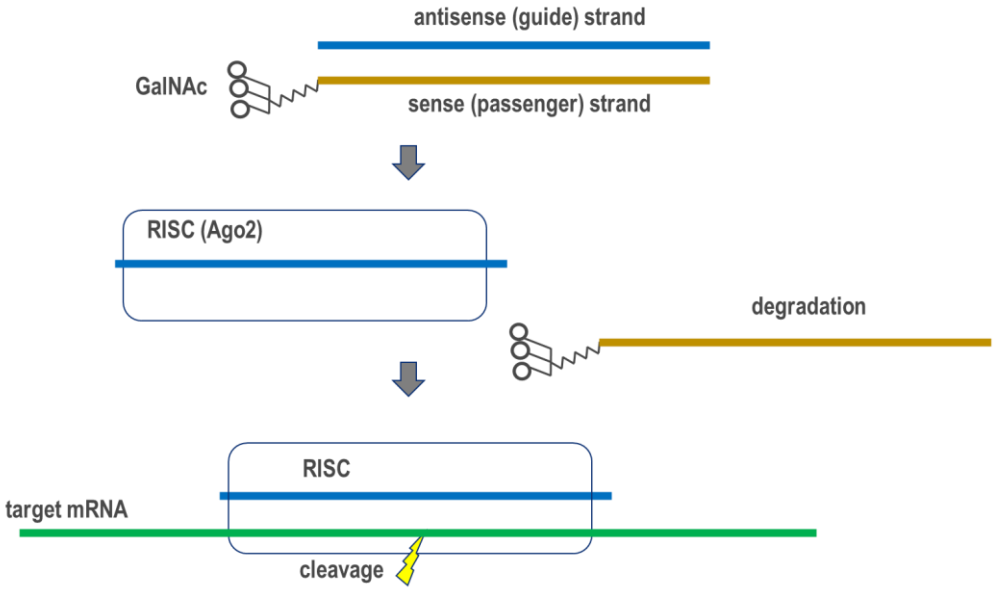
mxRNA™: miniaturized single-targeting RNAi triggers

muRNA™: multi-unit multi-targeting RNAi triggers

*Note: pronounced as in Sir **Galahad**, a knight of the King Arthur's Round Table and one of only three achievers of the Holy Grail*

mxRNAs™: Proposed mechanism of action (MOA)

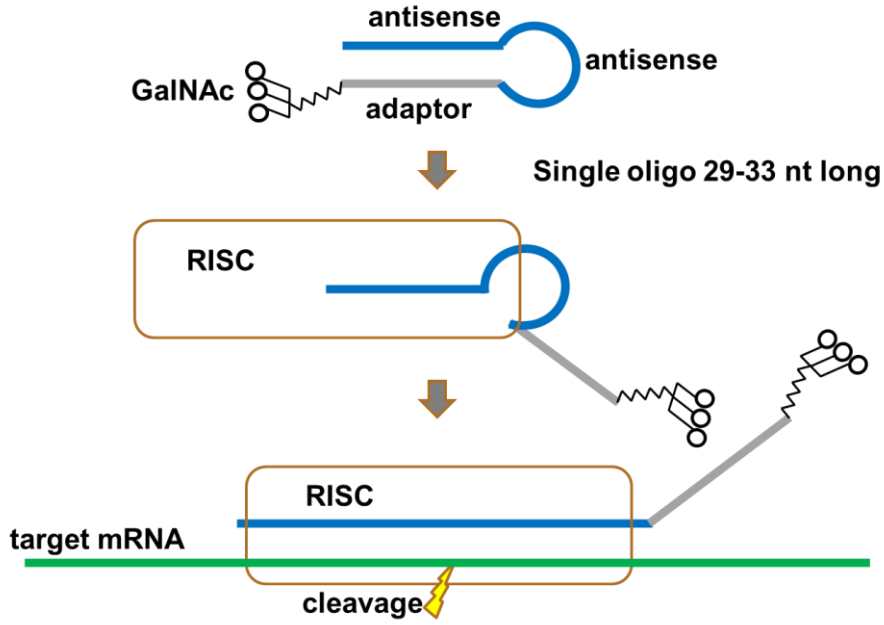
Conventional GalNAc-siRNA



Key points:

- Two single strands
- 3 major synthesis steps; 56+ nucleotides
- High risk of off-target effects – loose degradation siRNA fragment

Sirnaomics mxRNA

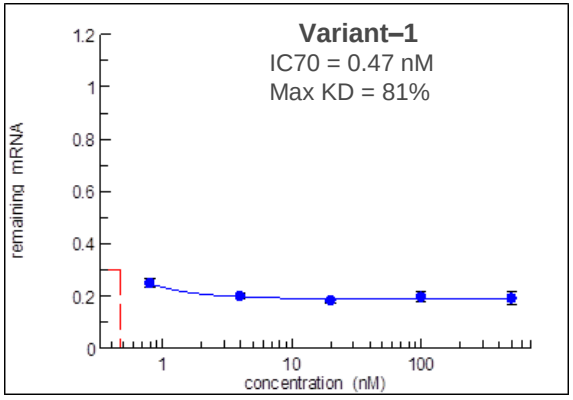


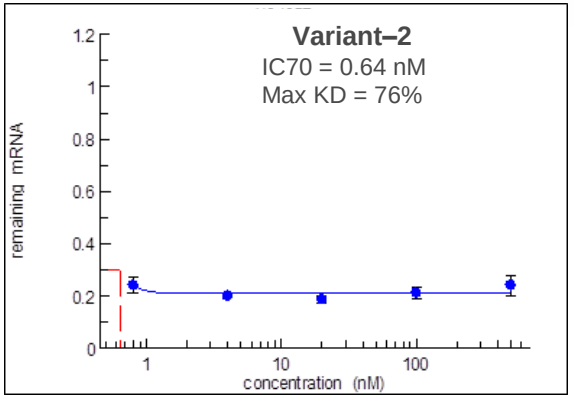
Key points:

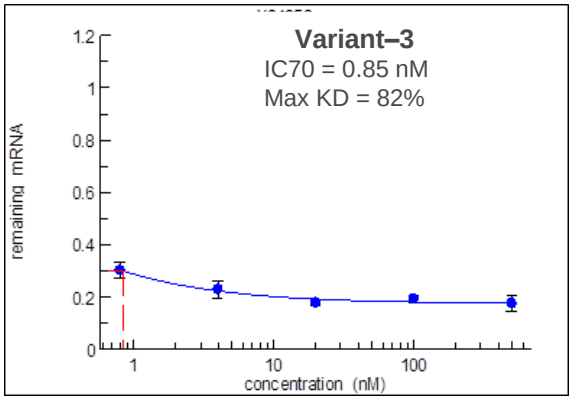
- 1 Hairpin structure
- 1 major synthesis step; 29-33 nucleotides
- Less risk of off-target effects

mxRNA™: Remarkable activity in primary hepatocytes

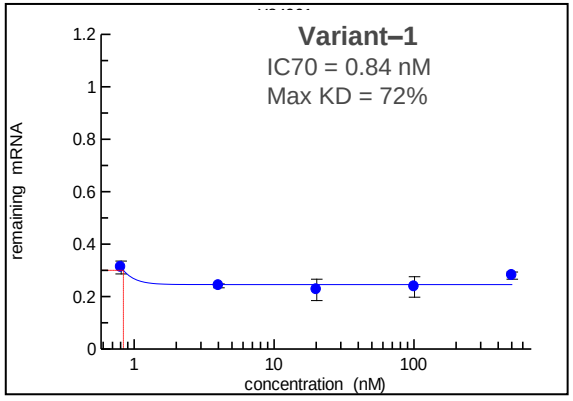
Sequence 1

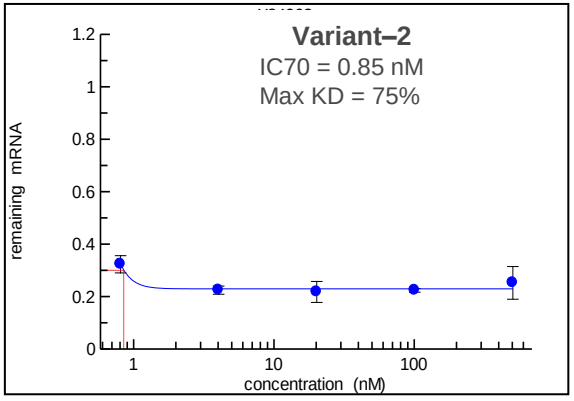


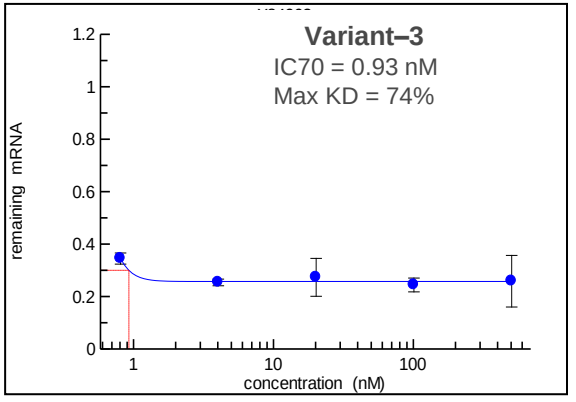




Sequence 2







Cells: primary mouse hepatocytes

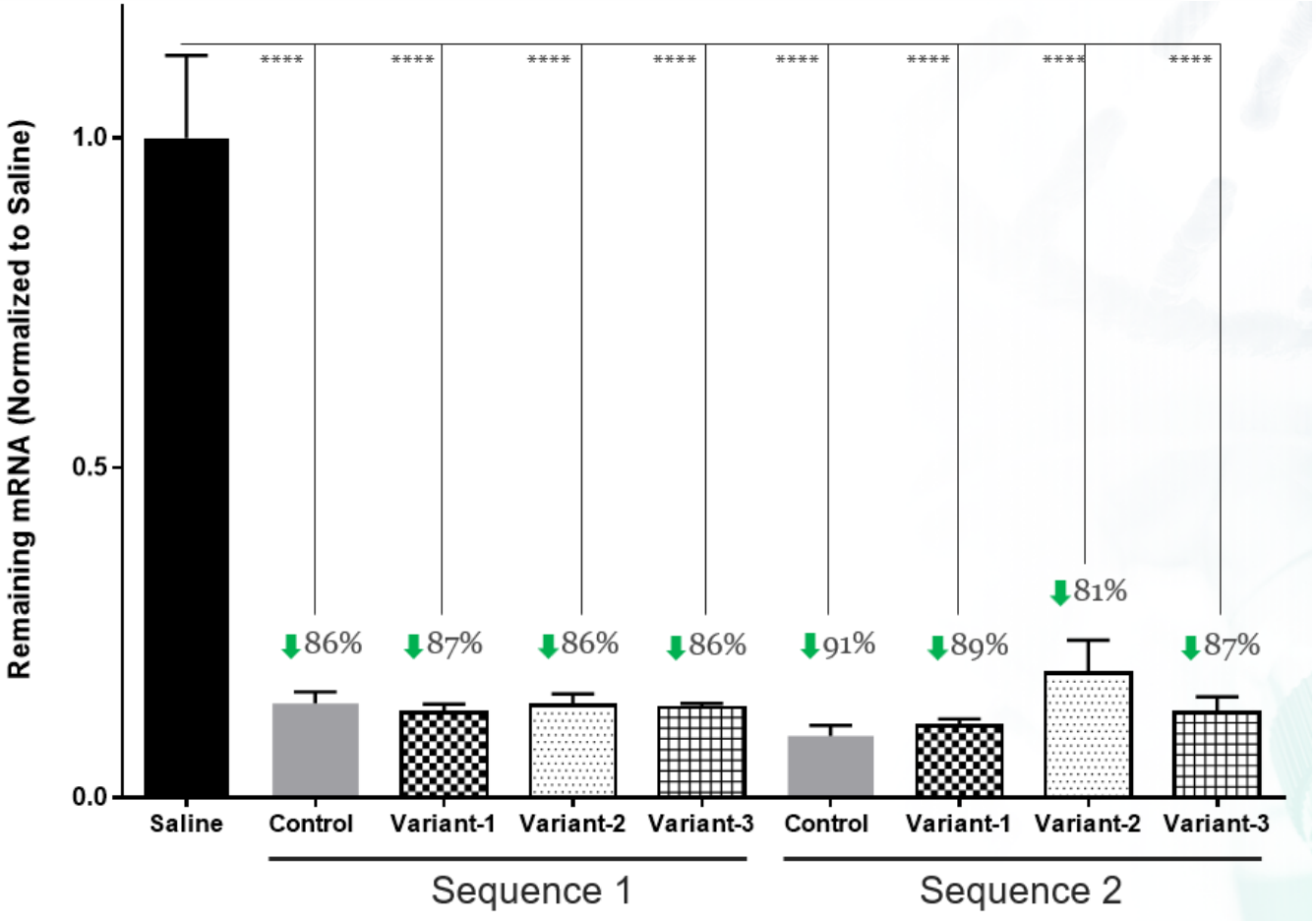
Delivery: passive uptake

Concentrations: 500, 100, 20, 4.0, 0.8 nM

Time-point: 72 hours

Readout: TMPRSS6 mRNA

mxRNA™: Outstanding in vivo activity (single dose)



Statistics:
One-Way ANOVA
Post-hoc analysis with Tukey's multiple comparisons test
**** = $p<0.0001$

Study Design

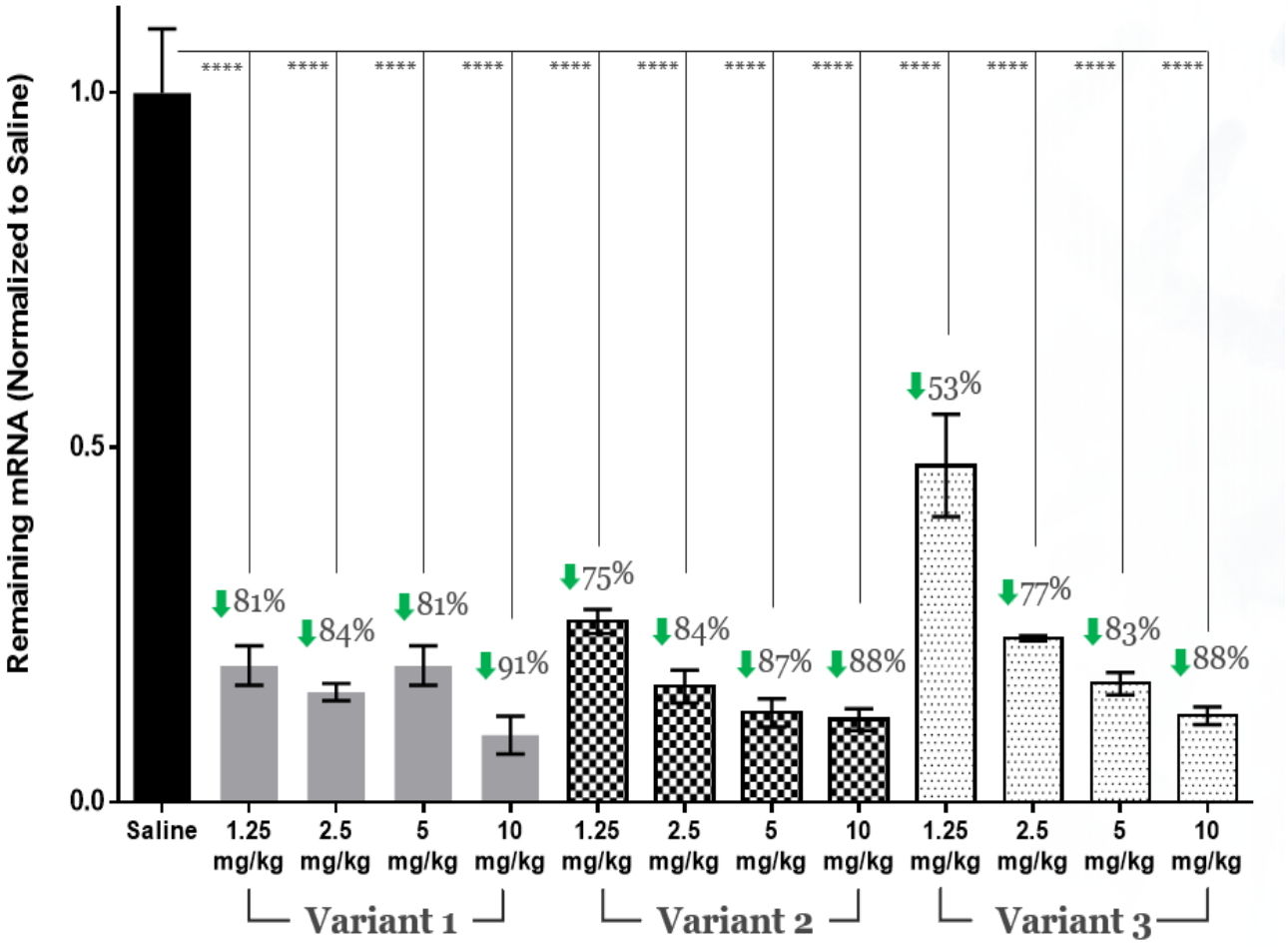
Animals:
- mice

Dose:
- 10 mg/kg

Timepoint:
- 5 days

Readout:
- TMPRSS6 mRNA

mxRNA™: Outstanding in vivo activity (dose response)



Statistics:
One-Way ANOVA
Post-hoc analysis with Tukey's multiple comparisons test
**** = $p<0.0001$

Note:
- *For 10mg/kg dose group – liver samples collected during Single Dose study were included in the bDNA assay*

Study Design

- 1, 2 & 3 configuration for sequence 1

Doses:

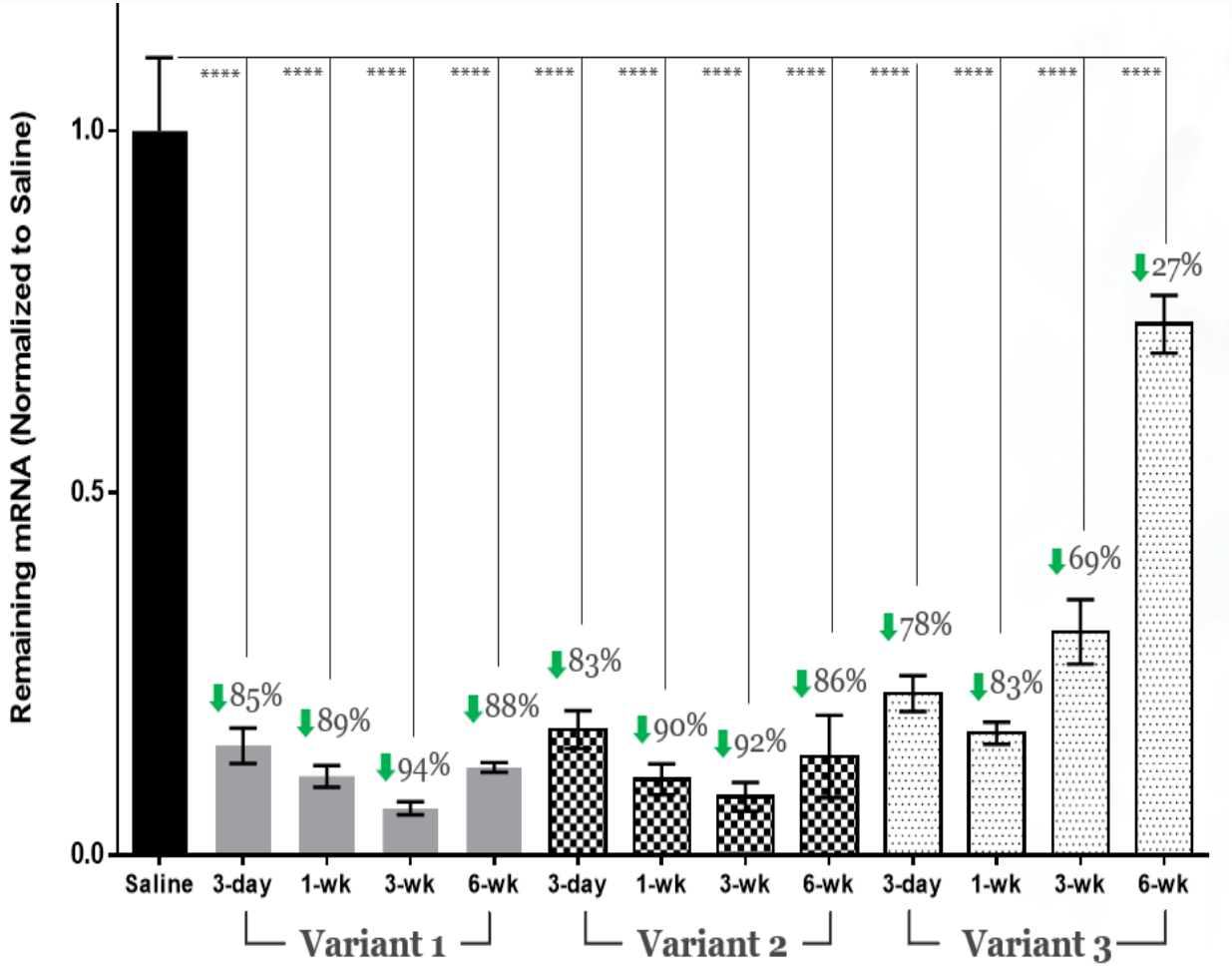
- 1.25 mg/kg
- 2.5 mg/kg
- 5 mg/kg
- 10 mg/kg

N= 4 C57/Bl6 mice/group

Timepoints:

- 5 day timepoint
- bDNA analysis: TMPRSS6 mRNA from liver tissues

mxRNA™: Outstanding in vivo activity (duration response)



Statistics:
One-Way ANOVA
Post-hoc analysis with Tukey's multiple comparisons test
**** = $p<0.0001$

Study Design

- 1, 2 & 3 configuration for sequence 1

Dose:

- 3mg/kg

N= 4 C57/Bl6 mice/group

Timepoints:

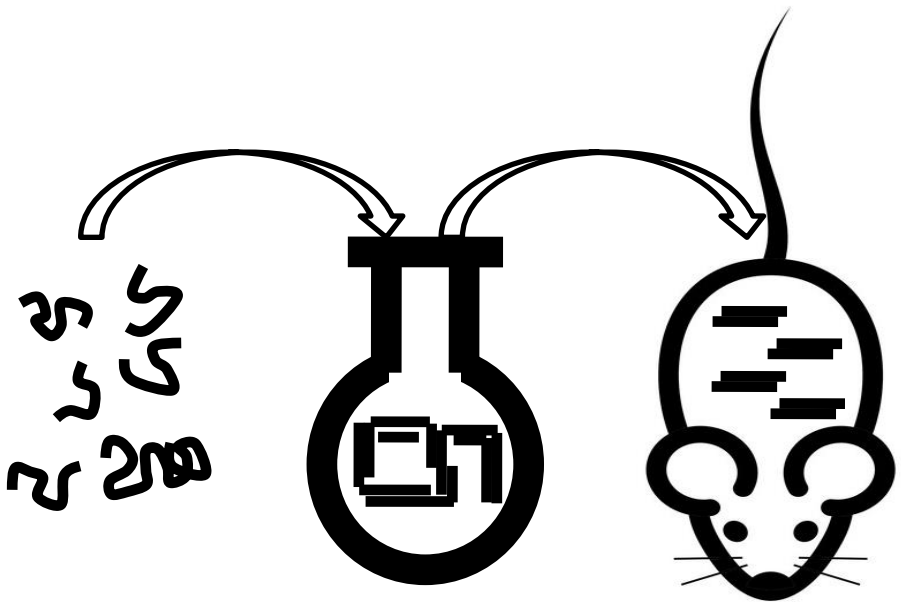
- 3-day, 1-week, 3-week, 6-week
- bDNA analysis: TMPRSS6 mRNA from liver tissues

mxRNA™: Summary

- Outstanding activity
- Relative ease of CMC
- Solid IP position (protection and FTO)

muRNA™: Concept & principles

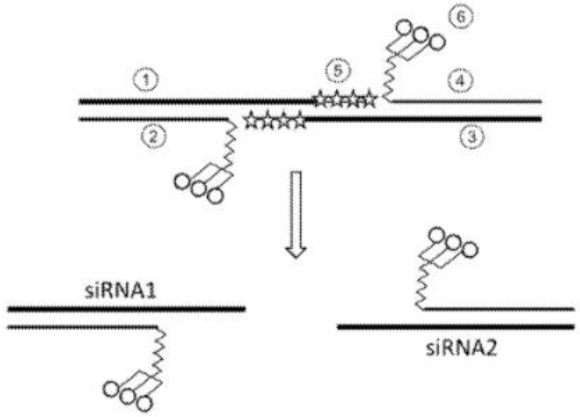
The muRNA technology uses the principle described by the German engineering term “SollBruchStelle” (SBS), meaning the “spot aimed to be broken”. The muRNAs are assembled *in vitro* using Watson-Crick interaction between comprising oligonucleotide building blocks, but fall apart *in vivo* upon exposure to the extra- and/or intra-cellular biological fluids along the pre-designed SBS moieties to produce multiple potent RNAi triggers



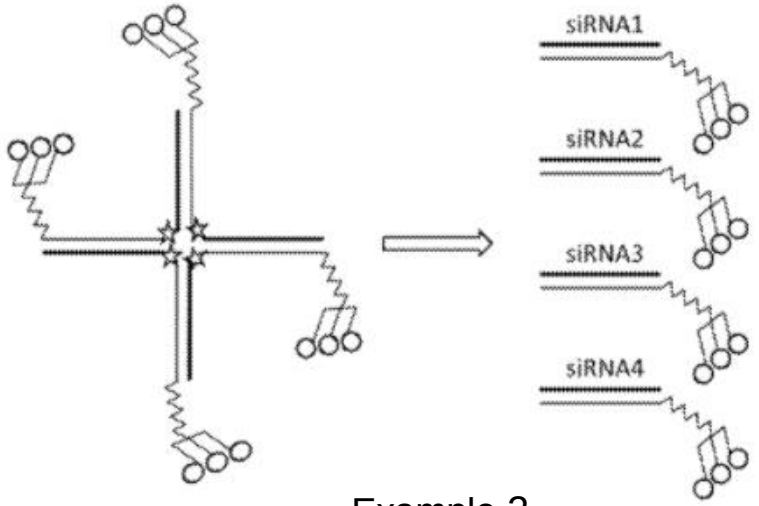
“Sollbruchstelle” (SBS) examples

muRNA™: Multi-targeting multi-unit RNAi triggers

- Unconventional concept of multi-targeting single-molecule drug, enhanced with “sollbruchstelle” (SBS; the German engineering term meaning “spot-aimed-to-be-broken”) component
- Single oligo of ~32 nt per target; *e.g.,* four ~32-mers assembled in one molecule to target four different targets
- Solid IP position: PCT/IB2019/058221 (Sep 2019; priority Sep 2018)

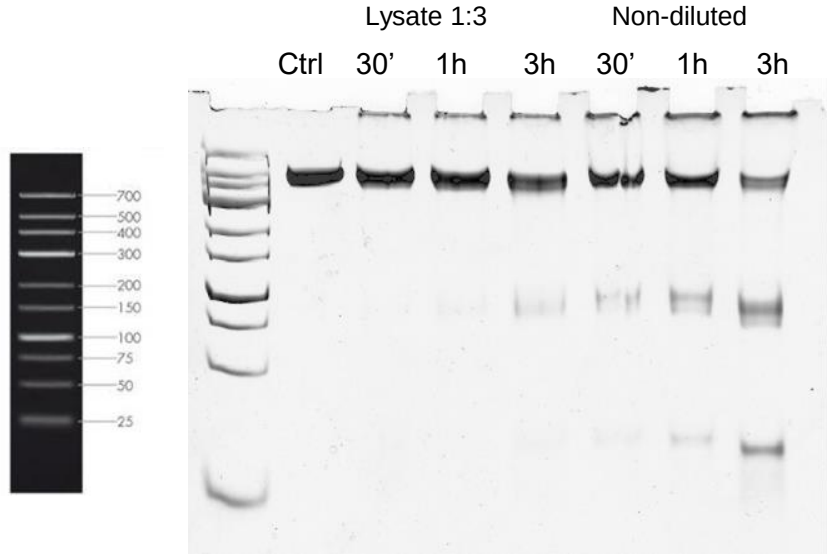


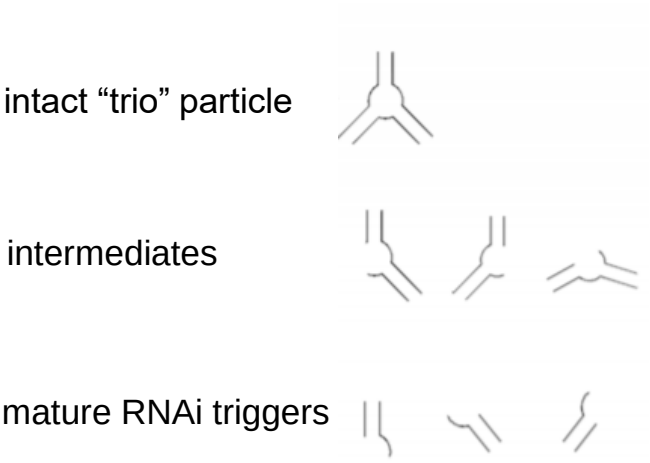
Example 1



Example 2

muRNA™: Tripartite muRNA disassembly in biological fluids

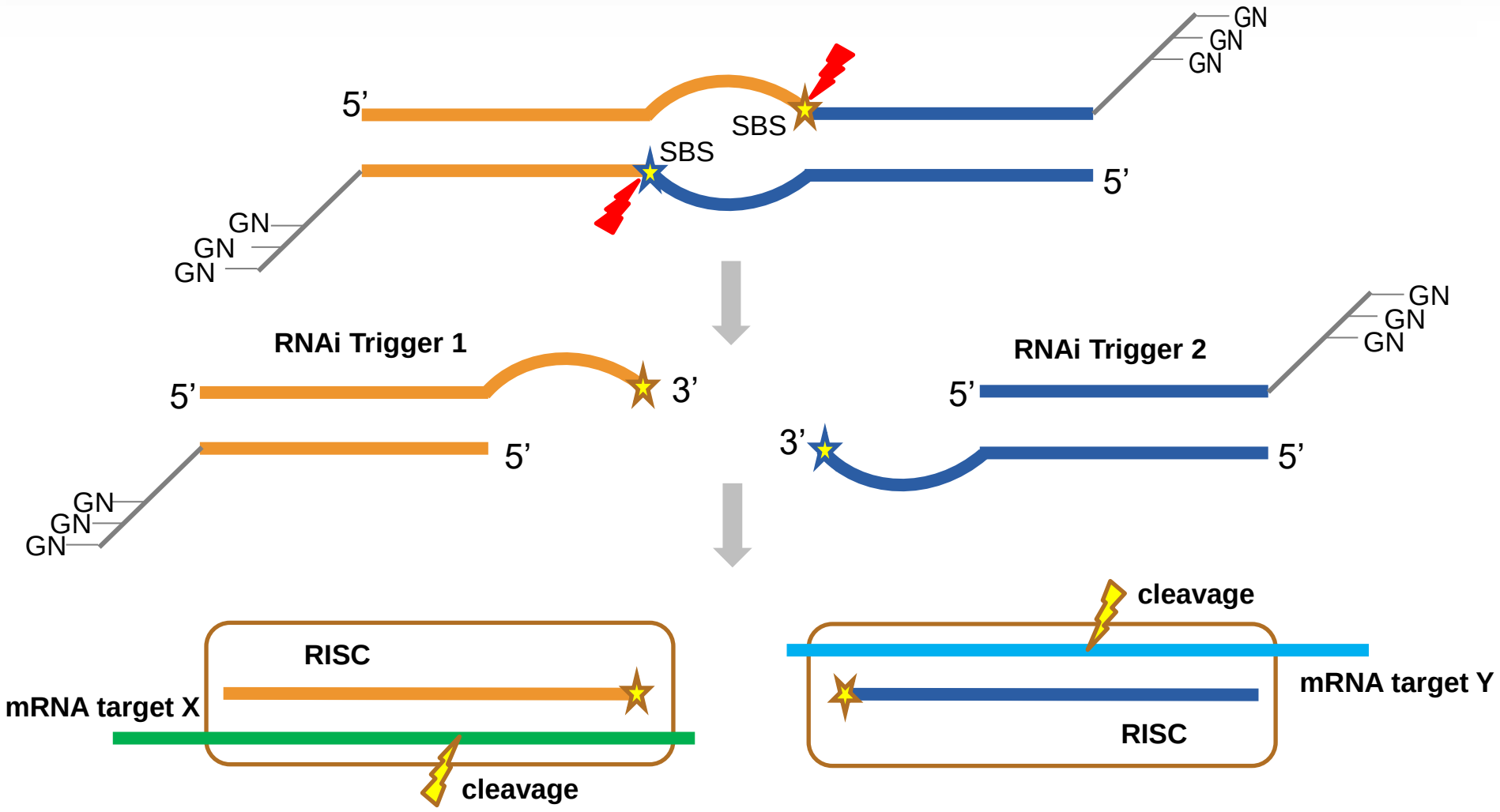




muRNAs: composed of 3 building blocks ("Trio")
Incubation: in diluted (1:3) or non-diluted liver lysosomal extract for 0.5, 1.0 or 3.0 hours
Gel: 20% non-denaturing PAAG, 1xTBE
Size marker: DNA ladder VWR #732-3300
Stain: GelRed®, Biotium

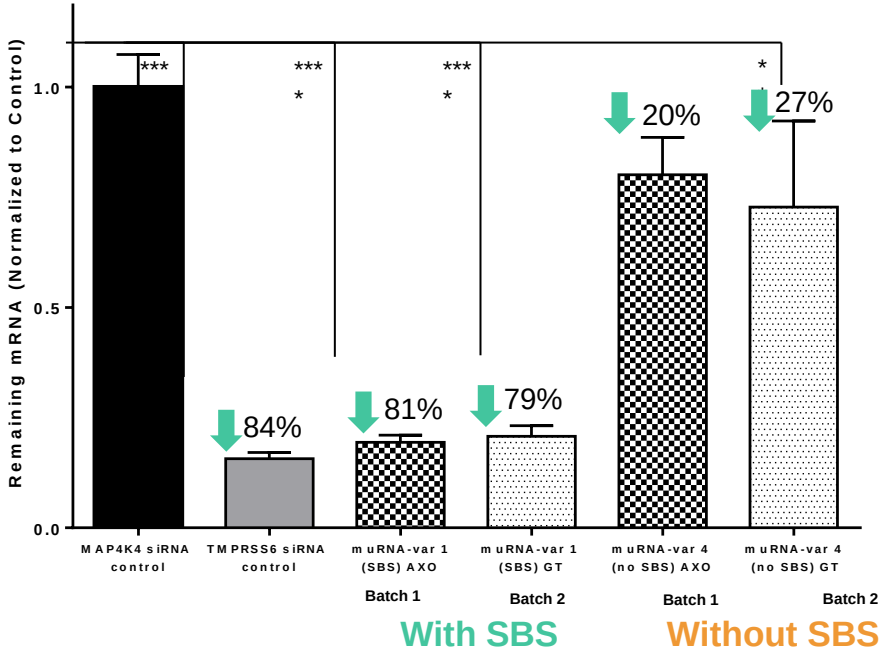
Note: disassembly of the Trio occurs not into the original building blocks, but into the new structures

muRNA™: Double targeting

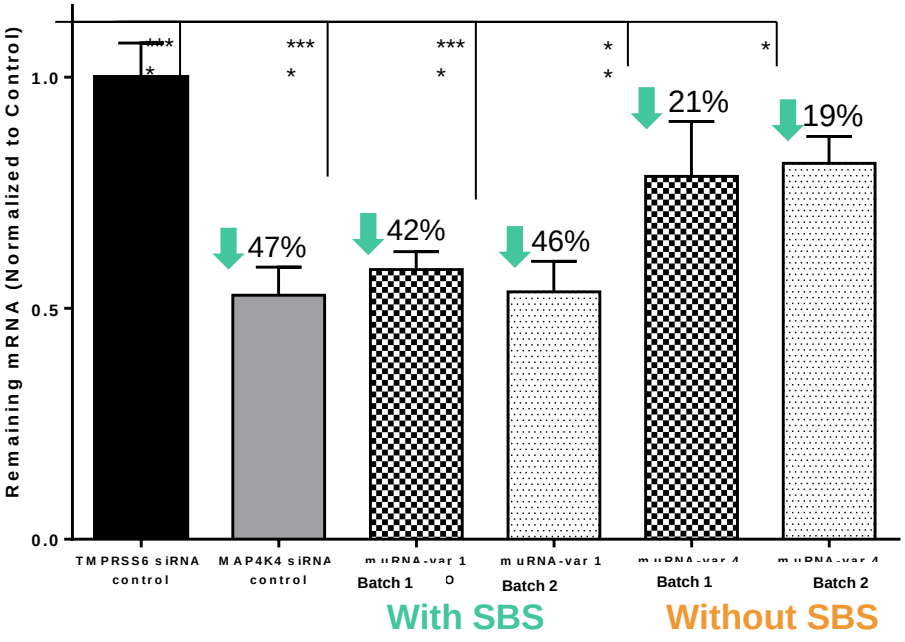


muRNA™: In vivo activity

TMPRSS6
expressed **only** in liver hepatocytes



MAP4K4
ubiquitously expressed in **all** liver cells



Dose:
- 10 mg/kg

Timepoint:
- 5 days

Statistics:
One-Way ANOVA
Post-hoc analysis with Tukey's multiple comparisons test
**** = p<0.0001

muRNA™: Summary

- High activity
- Ability to knockdown 2+ targets with one molecule
- Relative ease of CMC
- Solid IP position (protection and FTO)

GalAhead™ therapeutic pipeline: June 2022

Drug	Target	Indication	Bioinformatics	Discovery	Candidate Nomination	IND Enabling	IND
STP122G	Factor XI	Anticoagulation/Thrombosis					
STP125G	ApoC3	Hypertriglyceridemia					
STP144G	Complement Factor B	Complement-mediated diseases					
STP145G	Complement Factor C5	Complement-mediated diseases					
STP151G	TMPRSS6/ApoC3	Hemochromatosis with hypertriglyceridemia					
STP146G	Non-disclosed	Complement-mediated diseases					
STP133G	Non-disclosed	Cardiometabolic diseases					
STP138G	Non-disclosed	Hypercholesterolemia					

We are planning to file our first GalAhead IND later this year, followed by several more in 2023

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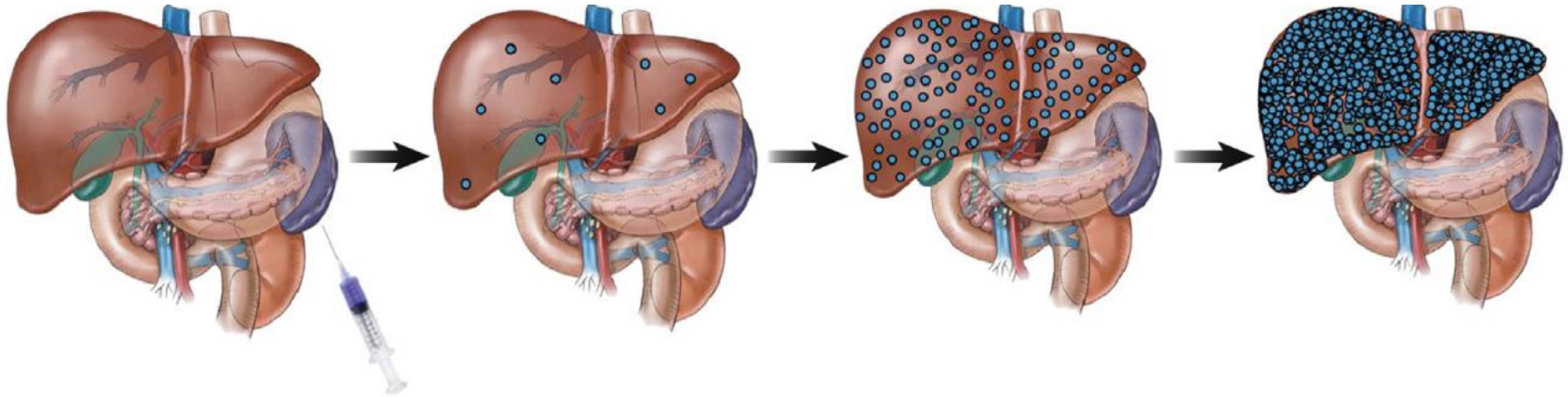
Advancing RNAi Therapeutics

STP125G (ApoC3)

STP125G: Humanized liver mouse model

20% mouse
80% human

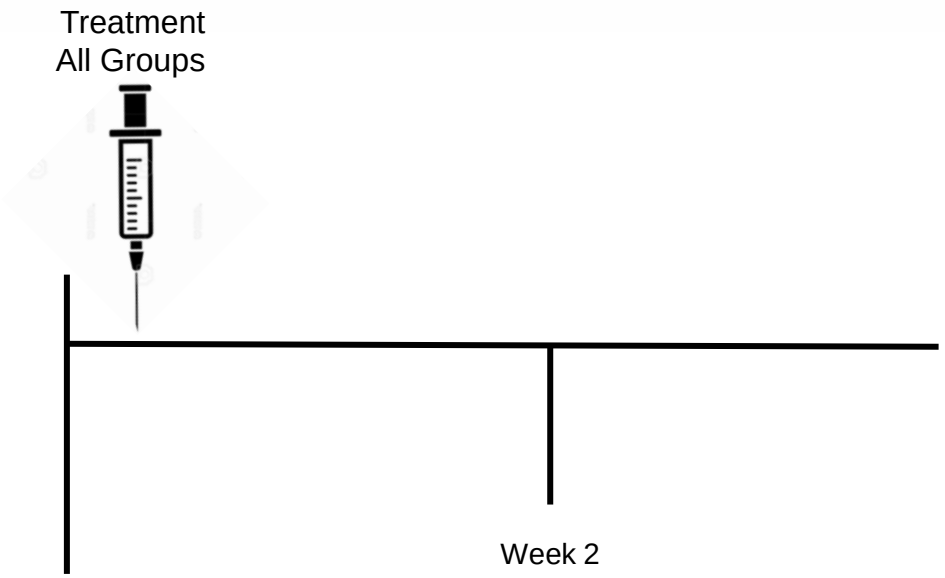
mouse liver



human hepatocytes

From M. Grompe and S. Strom (2013) Gastroenterology, 145:1209–1214

STP125G: Humanized liver mice Dose study design



Study Design

Animal Model:
- Humanized liver mouse model

Test compounds:
- STP125G - A28(14-4)mF mxRNA

Dosing:
- 10 mg/kg
- 30 mg/kg

ROA:
- Subcutaneous

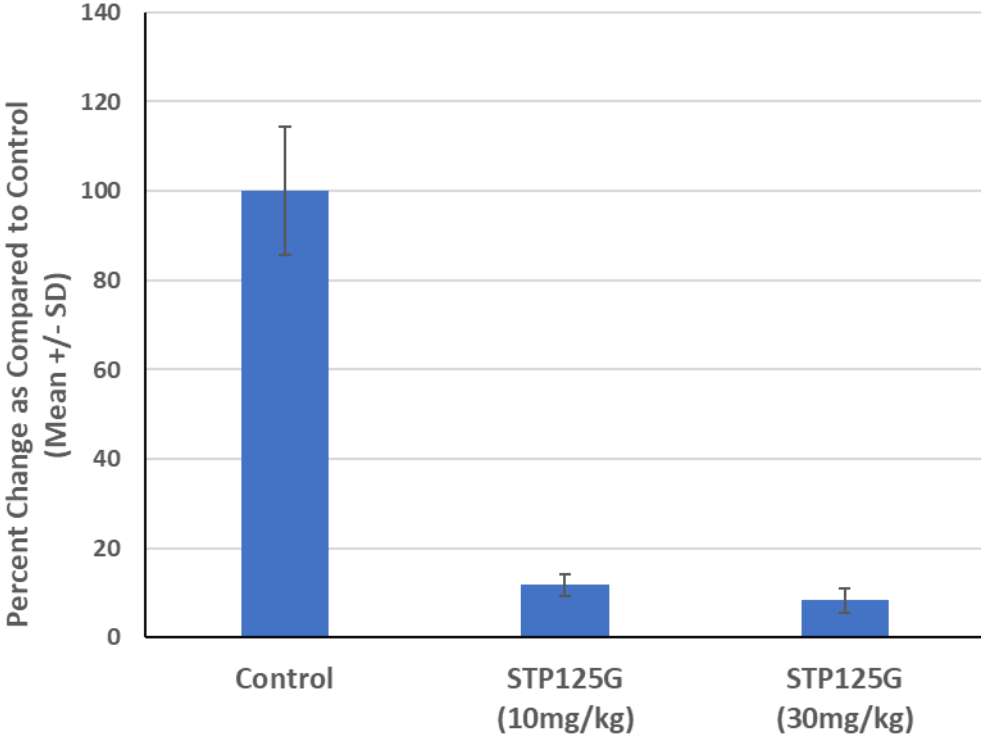
N:
- 4 mice/group

Terminal Endpoints:
- 2 weeks

Readouts:
- qPCR (mRNA)
- ELISA (protein)
- Triglycerides

STP125G: Target knock-down (2 weeks)

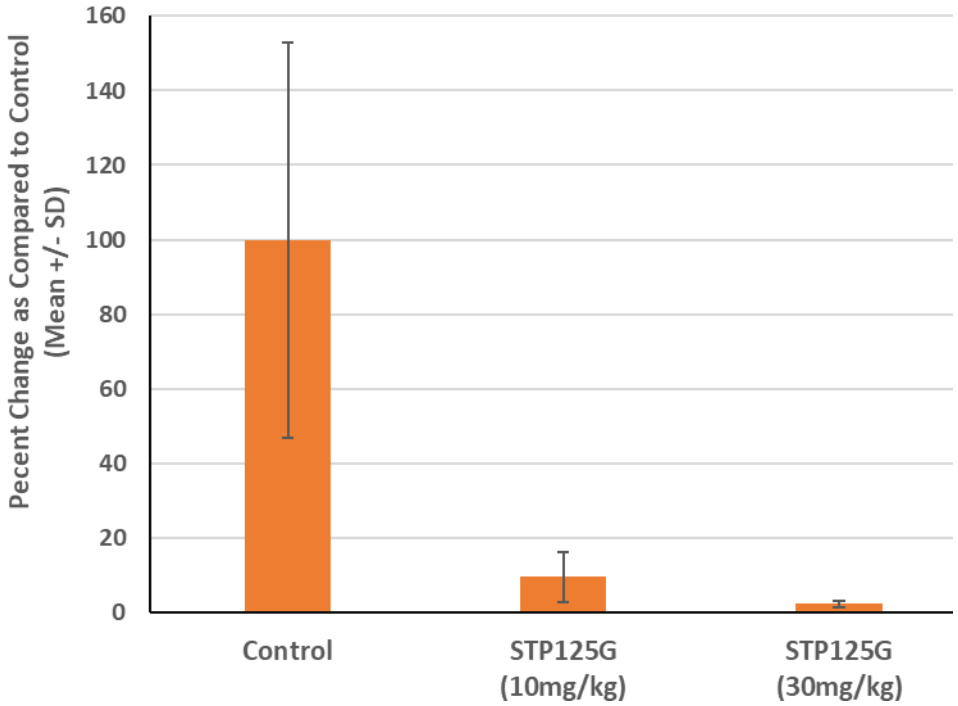
mRNA levels in liver tissues



Dose Response:

- 10mg/kg: 88% suppression
- 30mg/kg: 92% suppression

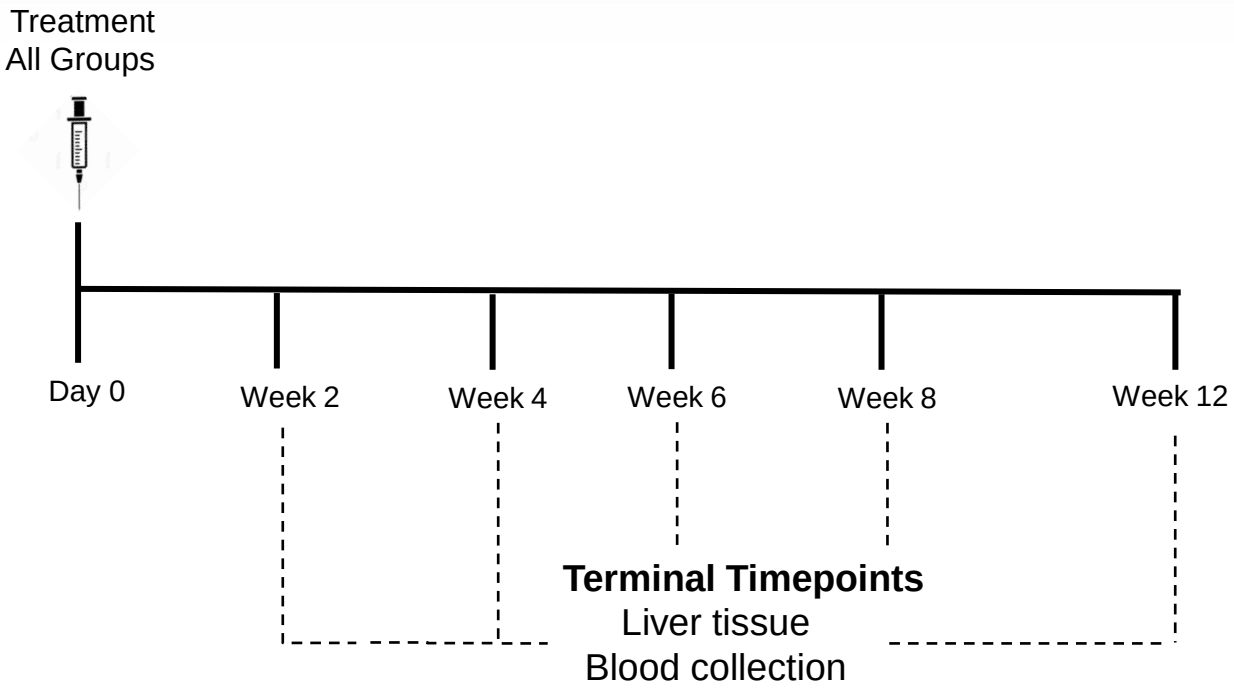
protein levels in plasma (ELISA)



Dose Response:

- 10mg/kg: 91% reduction
- 30mg/kg: 98% reduction

STP125G: Humanized liver mice Duration study design



Study Design

Animal Model:
- Humanized liver mouse model

Test compounds:
- STP125G - A28(14-4)mF mxRNA

Dosing:
- 10 mg/kg

ROA:
- Subcutaneous

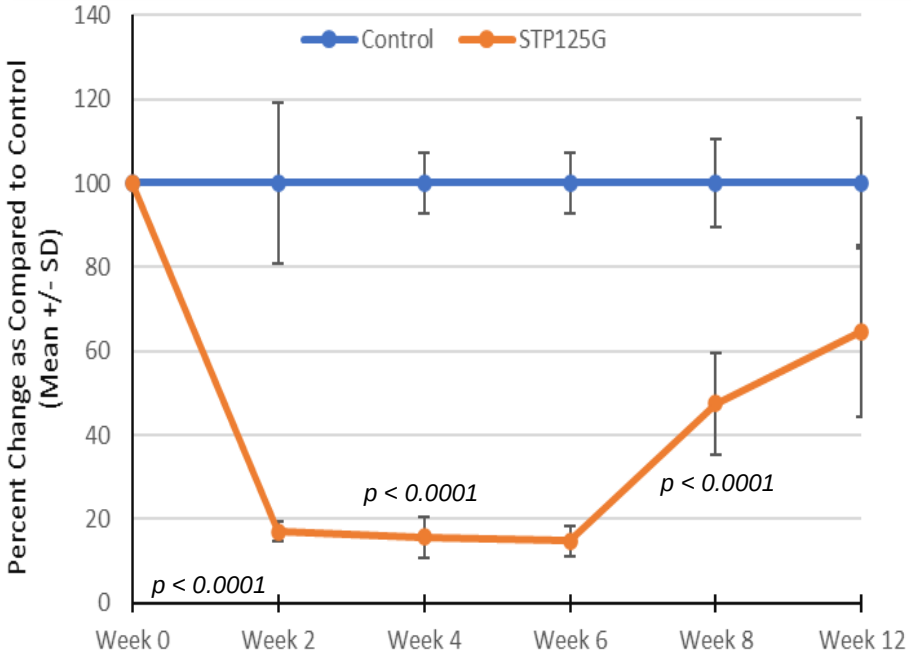
N:
- 4 mice/group

Terminal Endpoints:
- 2, 4, 6, 8 and 10-weeks

Readouts:
- qPCR (mRNA)
- ELISA (protein)
- Triglycerides

STP125G: APOC3 knockdown (Duration Response)

mRNA levels in liver tissues

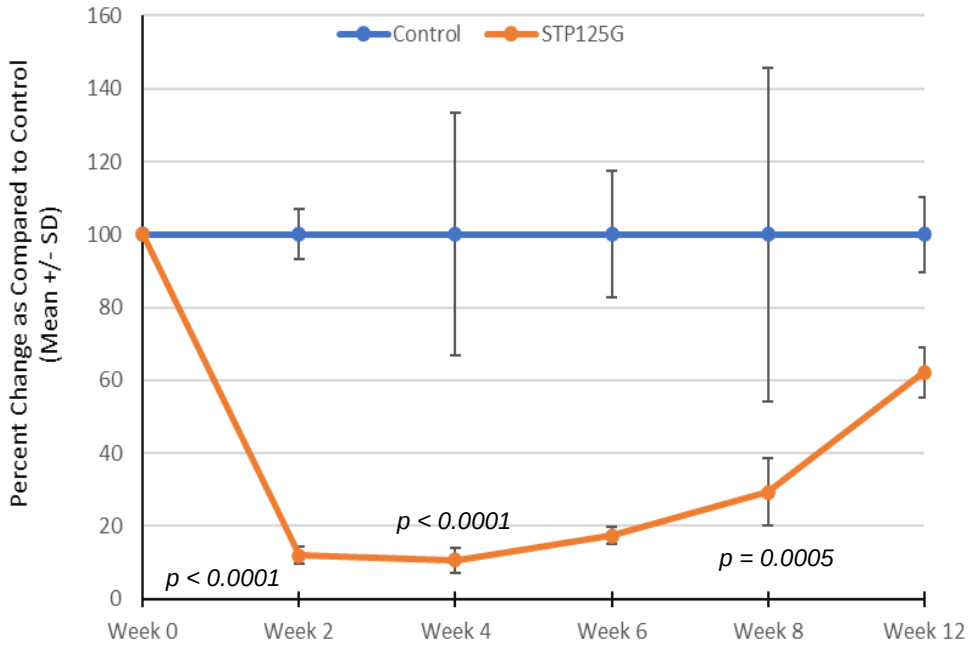


Duration Response:

- 83-85% KD between weeks 2-6
- 48% return on baseline at week 8
- 35% KD at week 12

Note:
1. *Outliers were removed from the mean (mice 17, 14 (4W) + 39 (8W) + 18 (12W))*
2. *Note: N=2 mice for week 6 (control & STP12G) and week 12 (control) timepoints*

protein levels in plasma (ELISA)



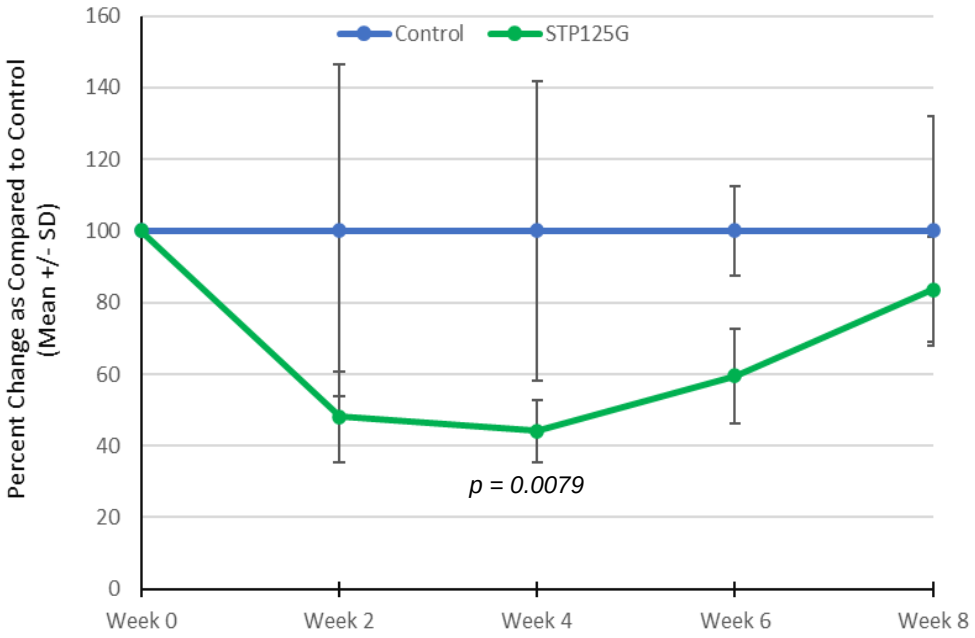
Duration Response:

- 82-89% reduction between weeks 2-6
- 30% return on baseline at week 8
- 37% reduction at week 12

Note:
1. *Outlier was removed from the mean (mouse 39 (8W))*
2. *Note: N=2 mice for week 6 (control & STP12G) and week 12 (control) timepoints*

STP125G: Reduction in TGs and TC (Duration Response)

Triglycerides (TGs) levels in serum

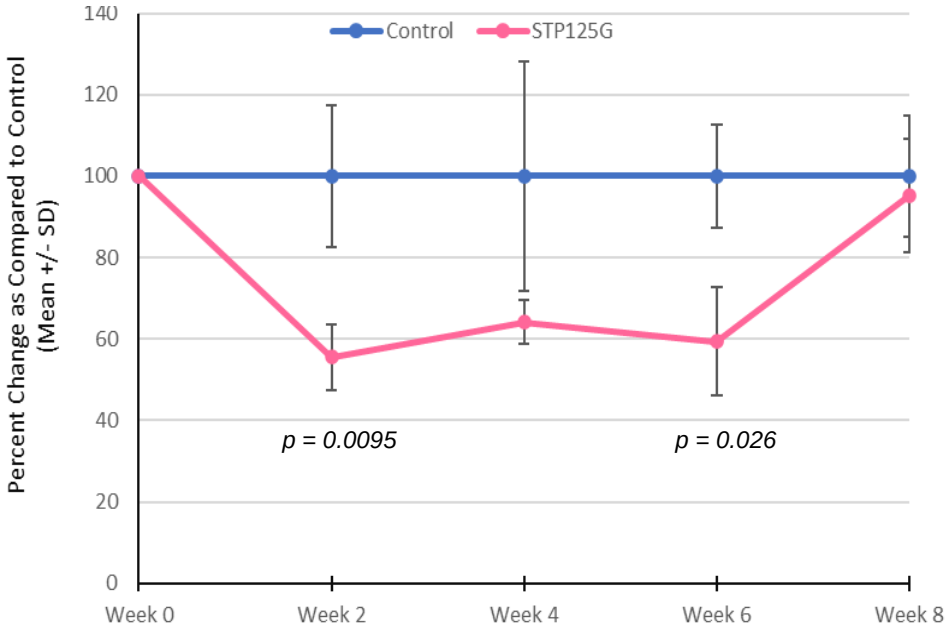


Duration Response:

- 50% reductions observed at weeks 2-4
- Return to control levels by week 8

Note: N=2 mice for week 6 timepoint

Total Cholesterol (TC) levels in serum



Duration Response:

- 40% reductions observed at weeks 2-6
- Return to control levels by week 8

Note: N=2 mice for week 6 timepoint

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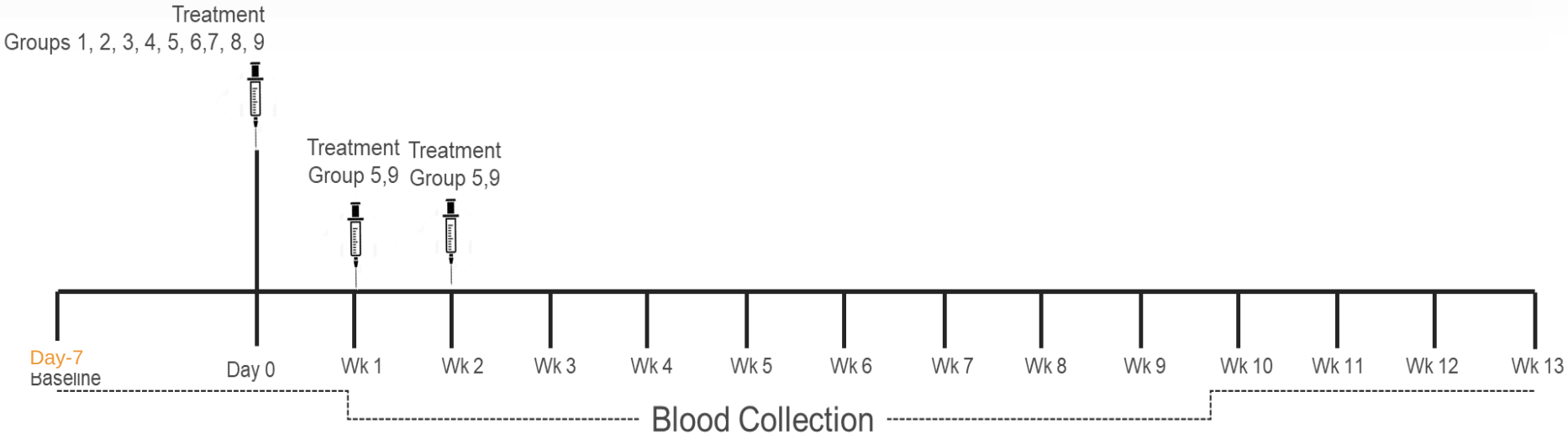
STP144G (Complement Factor B)

STP144G: Non-human primates (NHP) study design



N=36 NHP total

- N = 4 NHP/group

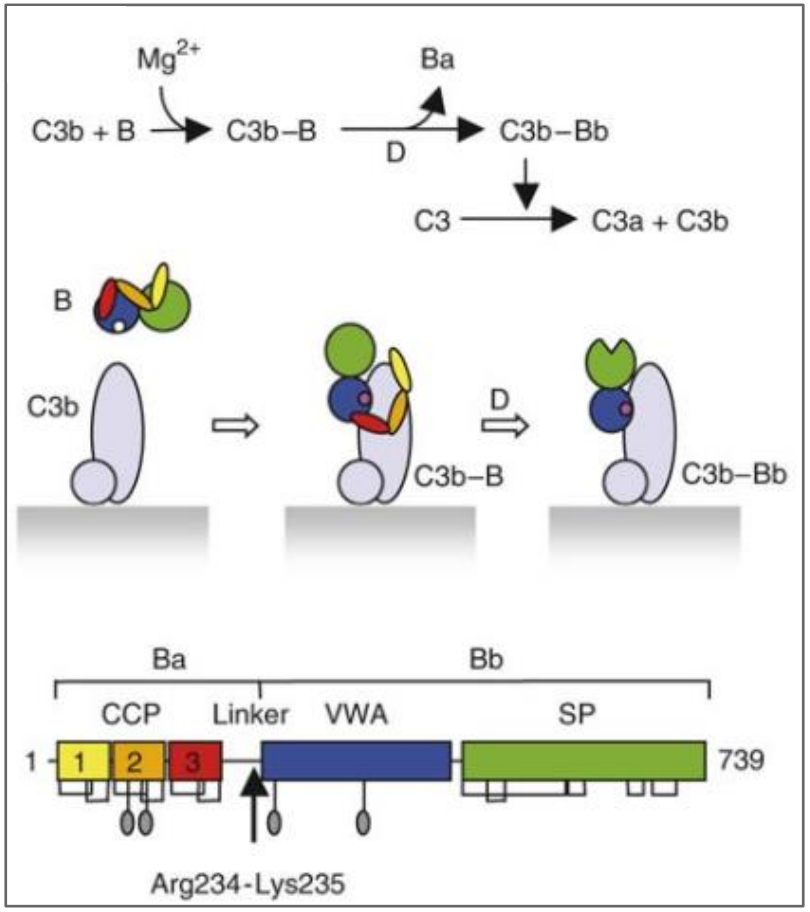
Groups:

- Group 1 (Saline) – Control (n=4)
- Group 2 (106-13(4)) - – 1 mg/kg one time injection (n=4)
- Group 3 (106-13(4))- – 3 mg/kg one time injection (n=4)
- Group 4 (106-13(4))- – 10 mg/kg one time injection (n=4)
- Group 5 (106-13(4))- – 3 mg/kg three injections once weekly (n=4) 3 Tx cycle
- Group 6 (13-5) - – 1 mg/kg one time injection (n=4)
- Group 7 (13-5) - – 3 mg/kg one time injection (n=4)
- Group 8 (13-5) - – 10 mg/kg one time injection (n=4)
- Group 9 (13-5) - – 3 mg/kg three injections once weekly (n=4) 3 Tx cycle

Outcomes

- Bb protein measurement
- Hematology and clinical chemistry –every two weeks (wk2, 4, 6, 8, 10, 13)

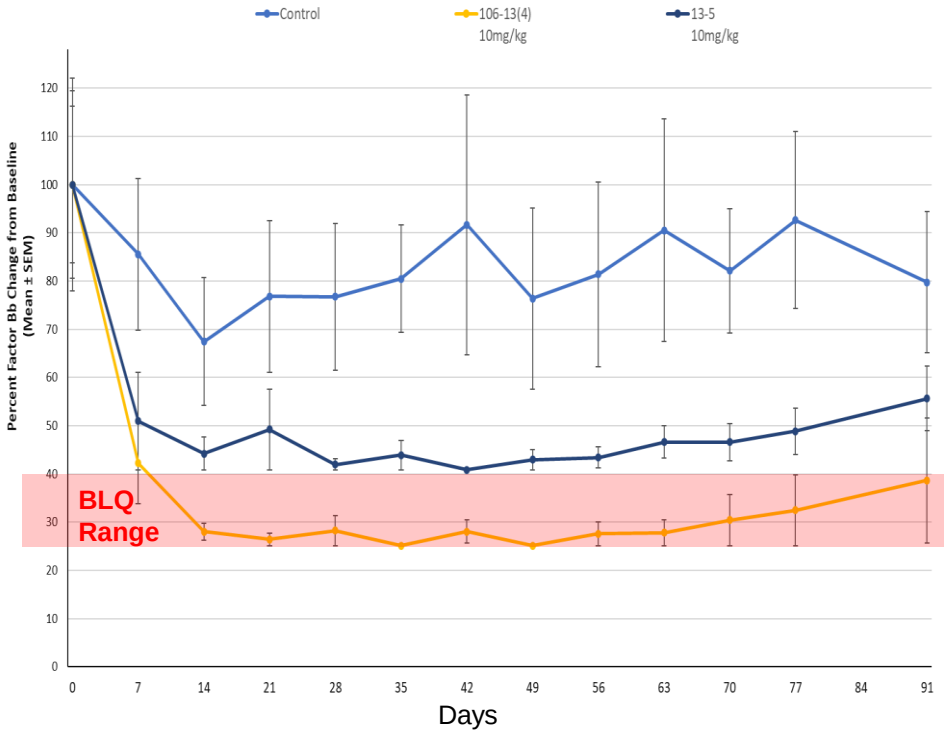
STP144G: Bb assay background



From Midler FJ et al (2007) *Nat Struct & Mol Biol* (14) 224–8

STP144G: Bb levels with lead compounds in NHP

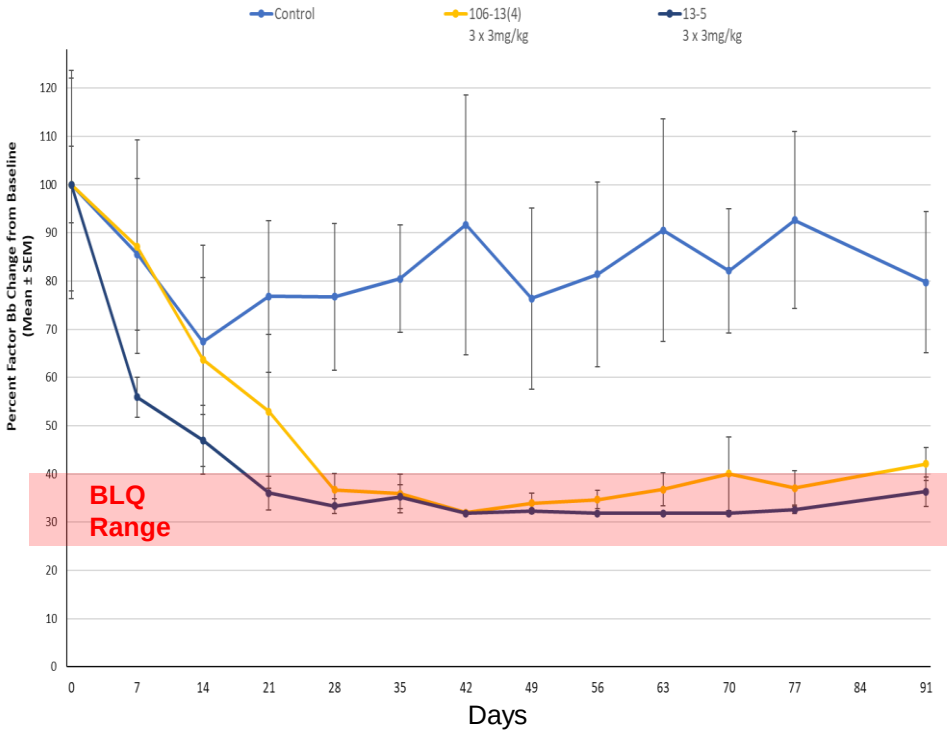
Single Treatment Comparison



Max reduction of Factor Bb and duration of response

- 106-13(4)
  - Max suppression of 74% at week 5
  - >60% reduction from week 2 to week 13
  - Mean BLQ from week 2 to week 10
- 13-5
  - Max suppression of 59% at week 6
  - >50% reduction from week 2 to week 13
  - No Mean BLQ for any of the timepoints

Multiple Treatment Comparison



Max reduction of Factor Bb and duration of response

- 106-13(4)
  - Max suppression of 68% at week 6
  - >50% reduction from week 4 to week 13
  - Mean BLQ at week 6
- 13-5
  - Max suppression of 68% at week 6
  - >50% reduction from week 2 to week 13
  - Mean BLQ from week 6 to week 11

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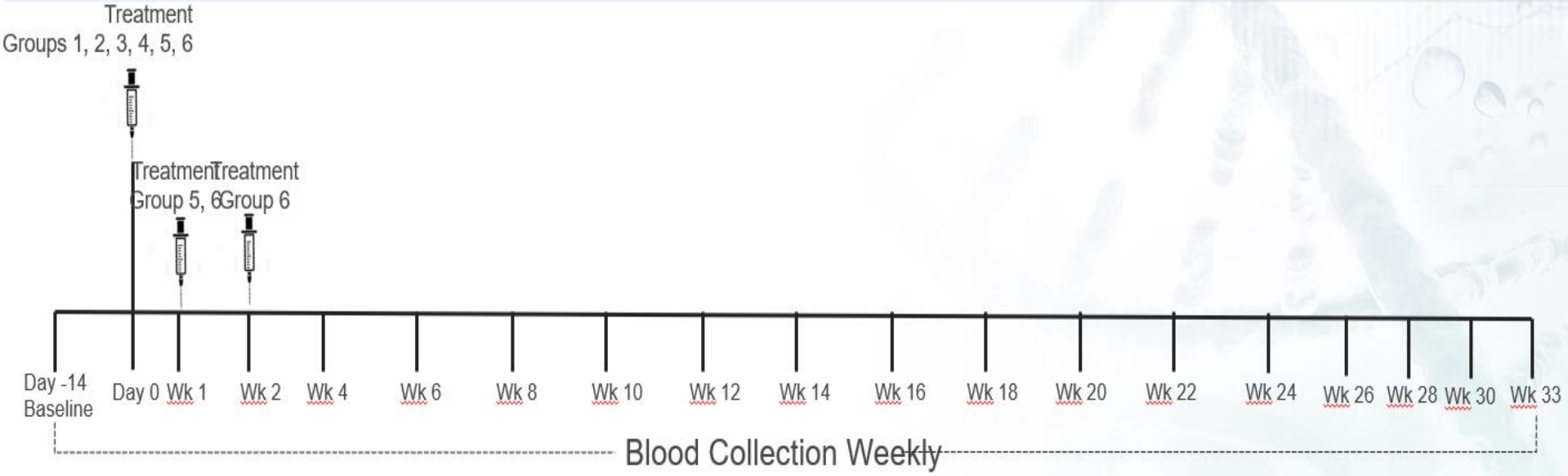
STP122G (Coagulation Factor XI)

STP122G: Non-human primates (NHP) study design



N = 24 NHP total

- N = 4 NHP/group

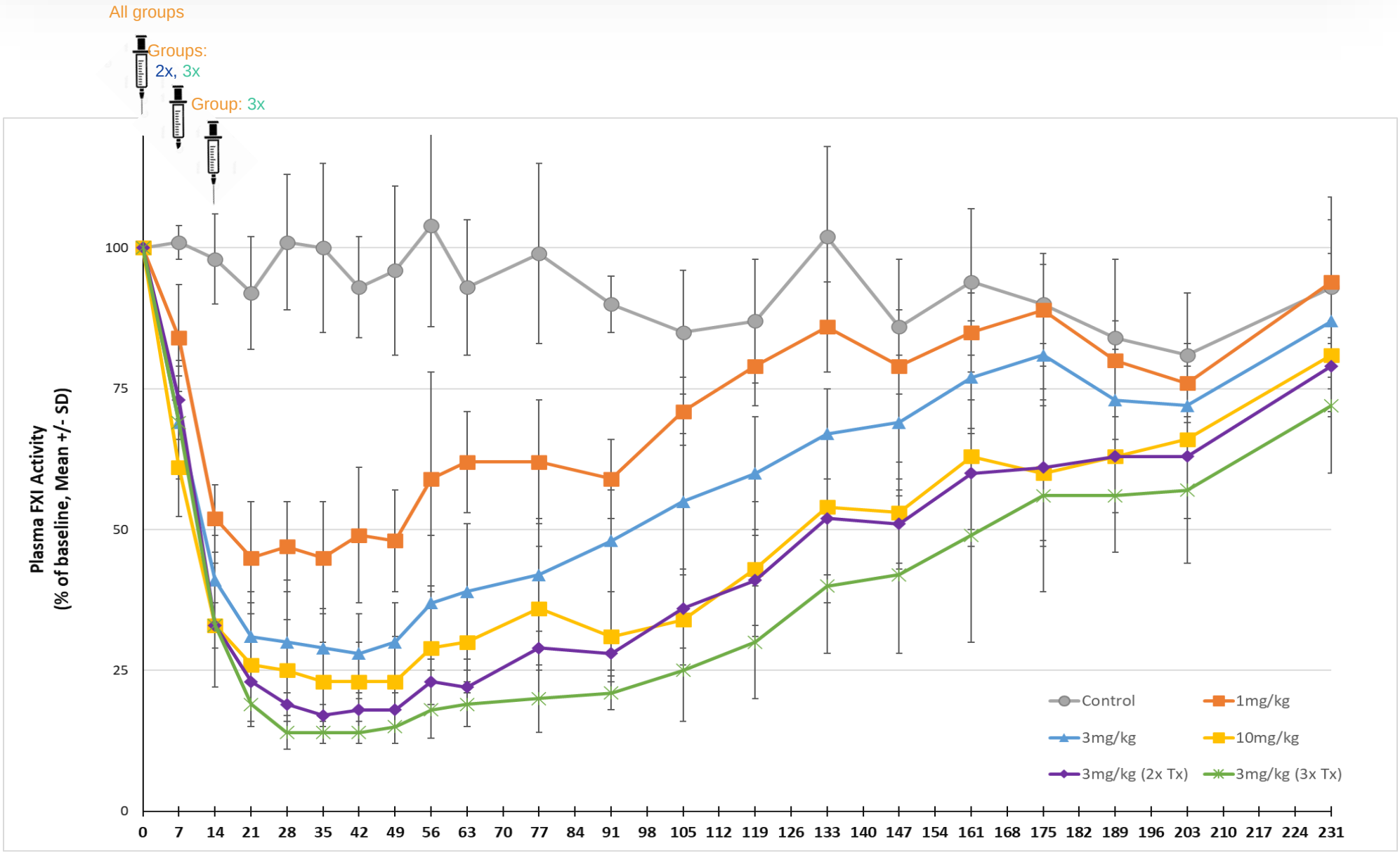
Groups:

- Group 1 (Saline) – Control (n=4)
- Group 2 (91-conv-31)- – 1mg/kg one time injection (n=4)
- Group 3 (91-conv-31)- – 3 mg/kg one time injection (n=4)
- Group 4 (91-conv-31)- – 10 mg/kg one time injection (n=4)
- Group 5 (91-conv-31)- – 3 mg/kg weekly for two weeks (n=4) 2 Tx cycle
- Group 6 (91-conv-31)- – 3 mg/kg weekly for three weeks (n=4) 3 Tx cycle

Outcomes

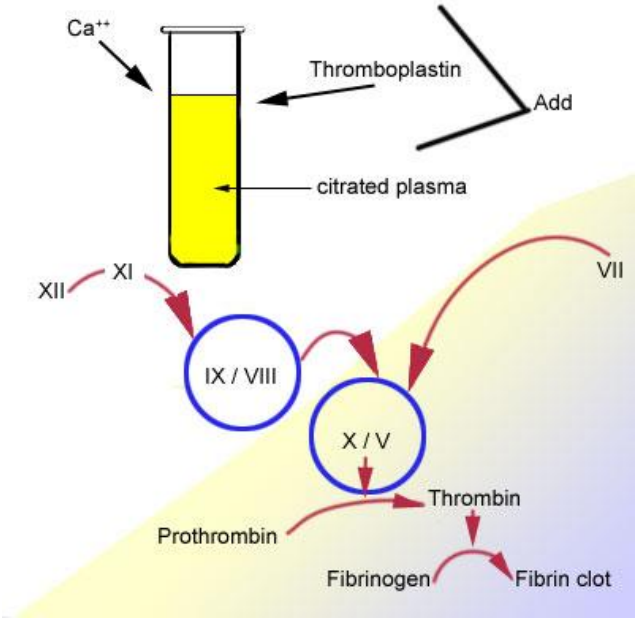
- Primary endpoint: Factor XI plasma activity
- APTT (activated partial thromboplastin time), PT (prothrombin time)
- Hematology and clinical chemistry: baseline, Wk2, Wk6, Wk18

STP122G (NHP): Primary activity readout (up to week 33)



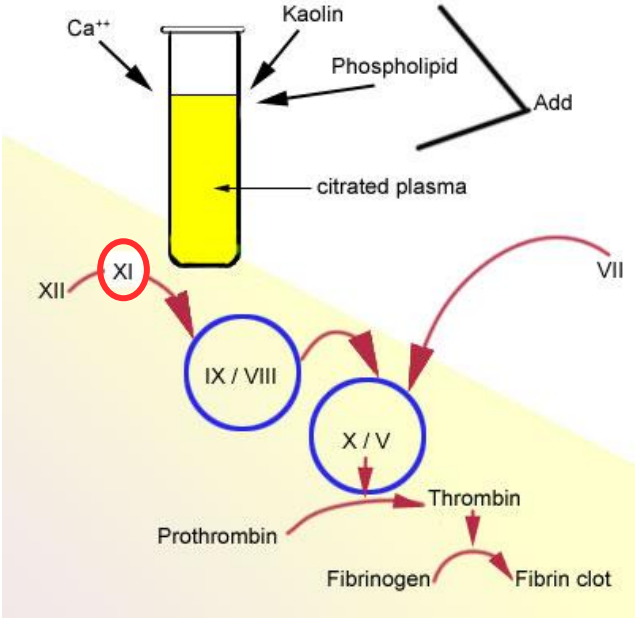
STP122G: Secondary activity readout and pathway specificity

Extrinsic Pathway:
Prothrombin time test (PT)



The prothrombin test specifically evaluates the activity of factors VII, V, and X, prothrombin, and fibrinogen

Intrinsic Pathway:
Activated Partial Thromboplastin Time test (APTT)

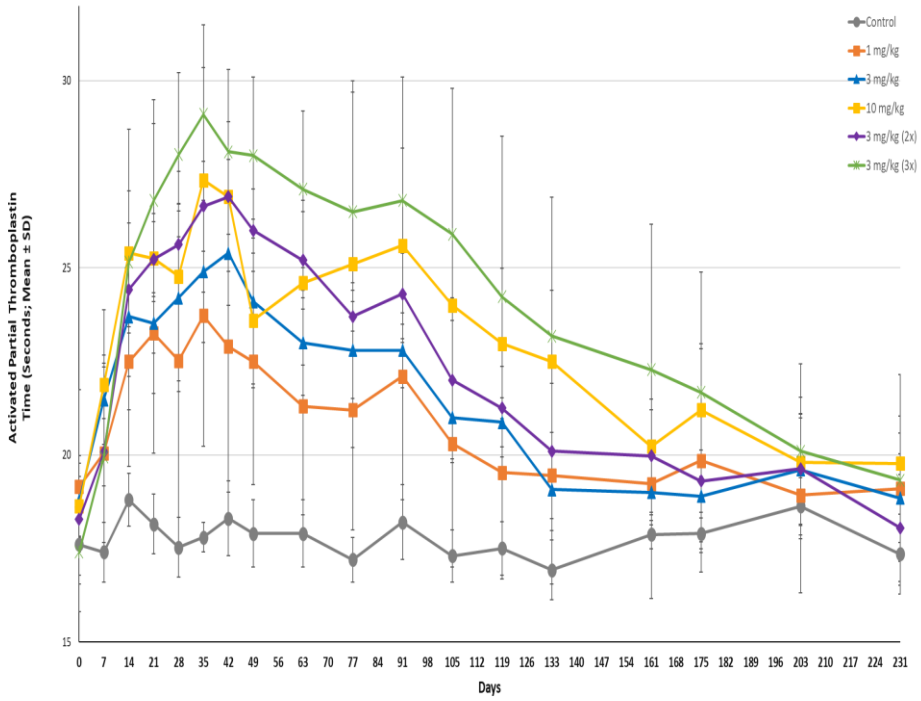


APTT measures the integrity of the intrinsic system (Factors XII, **XI**, VIII, IX) and common clotting pathways

From https://www.medicine.mcgill.ca/physio/vlab/bloodlab/pt_ptt.htm

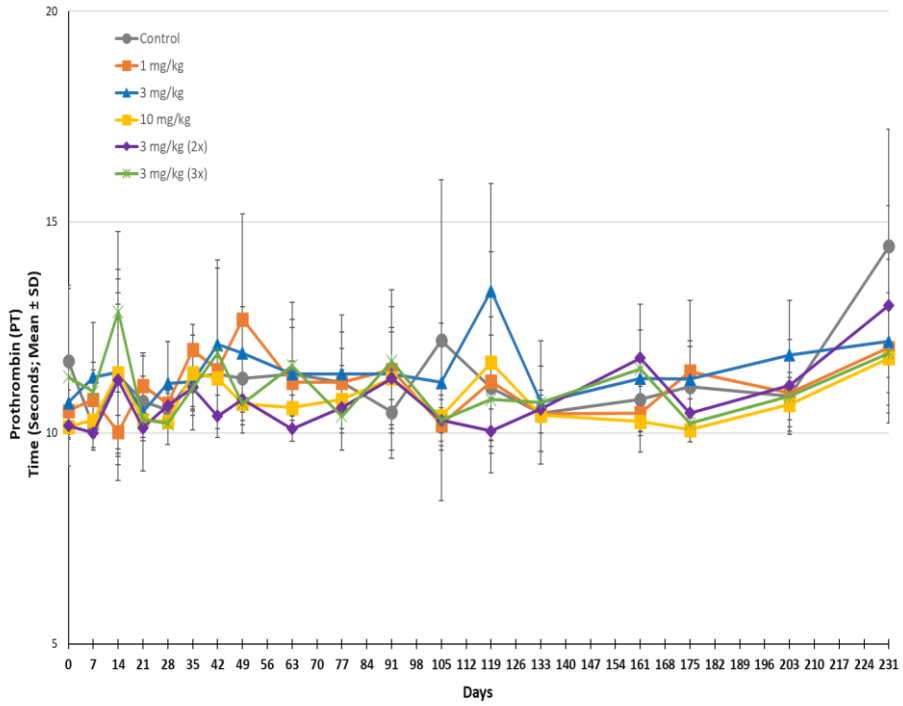
STP122G: Secondary activity readout and pathway specificity

APTT



- Reductions in plasma FXI activity correlated well with elevation of APTT
- Dose dependent elevation of APTT

PT



- No effect on PT values

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STP122G (NHP): Safety readouts

	Baseline (pre-treatment)			Week 2 (2 weeks post-treatment)			Week 6			Week 18			Week 26			Week 33		
	Control (Mean ±SD)	10mg/kg (Mean ±SD)	3mg/kg (3x) (Mean ±SD)	Control (Mean ±SD)	10mg/kg (Mean ±SD)	3mg/kg (3x) (Mean ±SD)	Control (Mean ±SD)	10mg/kg (Mean ±SD)	3mg/kg (3x) (Mean ±SD)	Control (Mean ±SD)	10mg/kg (Mean ±SD)	3mg/kg (3x) (Mean ±SD)	Control (Mean ±SD)	10mg/kg (Mean ±SD)	3mg/kg (3x) (Mean ±SD)	Control (Mean ±SD)	10mg/kg (Mean ±SD)	3mg/kg (3x) (Mean ±SD)
ALT (U/L)	47 ± 11	50 ± 19	66 ± 17	34 ± 6	44 ± 16	60 ± 8	37 ± 13	42 ± 16	53 ± 15	43 ± 19	43 ± 16	50 ± 20	46 ± 18	54 ± 22	65 ± 12	48 ± 28	44 ± 14	58 ± 10
AST (U/L)	47 ± 9	46 ± 6	66 ± 9	51 ± 12	48 ± 19	54 ± 10	49 ± 5	44 ± 3	54 ± 14	51 ± 5	59 ± 30	63 ± 9	50 ± 8	59 ± 25	67 ± 24	39 ± 6	39 ± 9	64 ± 14
ALP (U/L)	496 ± 150	603 ± 119	475 ± 111	526 ± 135	588 ± 74	473 ± 166	584 ± 151	627 ± 131	487 ± 166	581 ± 131	545 ± 45	591 ± 224	616 ± 140	623 ± 84	618 ± 170	616 ± 140	623 ± 84	618 ± 170
TBIL (umol/L)	3.6 ± 2.1	3.8 ± 1.3	4.2 ± 0.9	3.3 ± 0.4	3.6 ± 1	3.2 ± 1	3.3 ± 1.2	4.0 ± 1.6	3.8 ± 1.2	3.4 ± 1.2	3.4 ± 0.6	3.5 ± 2	4.3 ± 1.8	4.0 ± 0.8	4.2 ± 1.4	3.4 ± 1.5	4.2 ± 1.2	4.0 ± 1.1
Total Protein (g/L)	74 ± 4	73 ± 4	76 ± 2	72 ± 2	72 ± 4	73 ± 3	76 ± 5	74 ± 1	75 ± 2	73 ± 4	71 ± 2	72 ± 3	75 ± 3	74 ± 2	76 ± 3	74 ± 4	74 ± 1	73 ± 2
Platelets (10x3/uL)	399 ± 146	374 ± 93	430 ± 66	393 ± 113	381 ± 97	490 ± 58	363 ± 79	380 ± 69	462 ± 100	376 ± 101	343 ± 79	450 ± 99	387 ± 126	357 ± 74	450 ± 120	373 ± 102	375 ± 90	466 ± 88
RBCs (10x6/uL)	5.6 ± 0.3	5.9 ± 0.3	5.7 ± 0.1	5.2 ± 0.4	5.5 ± 0.1	5.3 ± 0.4	5.4 ± 0.3	5.7 ± 0.3	5.3 ± 0.4	5.4 ± 0.3	5.6 ± 0.2	5.4 ± 0.1	5.5 ± 0.6	6.0 ± 0.2	5.9 ± 0.4	5.8 ± 0.3	6.0 ± 0.2	5.9 ± 0.3
WBC (10X3/uL)	14.5 ± 3.8	11.9 ± 6.3	11.1 ± 4.3	13.3 ± 2.2	11.4 ± 3.3	10 ± 4.6	12.9 ± 1.9	11.3 ± 3.6	12.8 ± 4.8	10.8 ± 2.8	9.4 ± 4.2	11.5 ± 3.5	12.1 ± 2.5	9.4 ± 4.2	12.0 ± 2.9	11.3 ± 6.5	10.7 ± 3.9	9.7 ± 3.9
LDH	702 ± 201	856 ± 436	1156 ± 462	1128 ± 466	805 ± 458	1285 ± 527	811 ± 172	817 ± 314	996 ± 242	1045 ± 436	1178 ± 545	1607 ± 479	1044 ± 419	1205 ± 567	1544 ± 480	560 ± 147	641 ± 361	911 ± 152
GLDH	21 ± 5	29 ± 18	36 ± 2	23 ± 2	25 ± 14	28 ± 11	25 ± 5	24 ± 14	28 ± 10	23 ± 1	21 ± 7	31 ± 9	24 ± 8	21 ± 10	37 ± 3	28 ± 6	25 ± 12	34 ± 5

- Selected representative readouts for high dose groups
- No elevations of liver function enzymes post-treatments
- No changes in hematology parameters post-treatments

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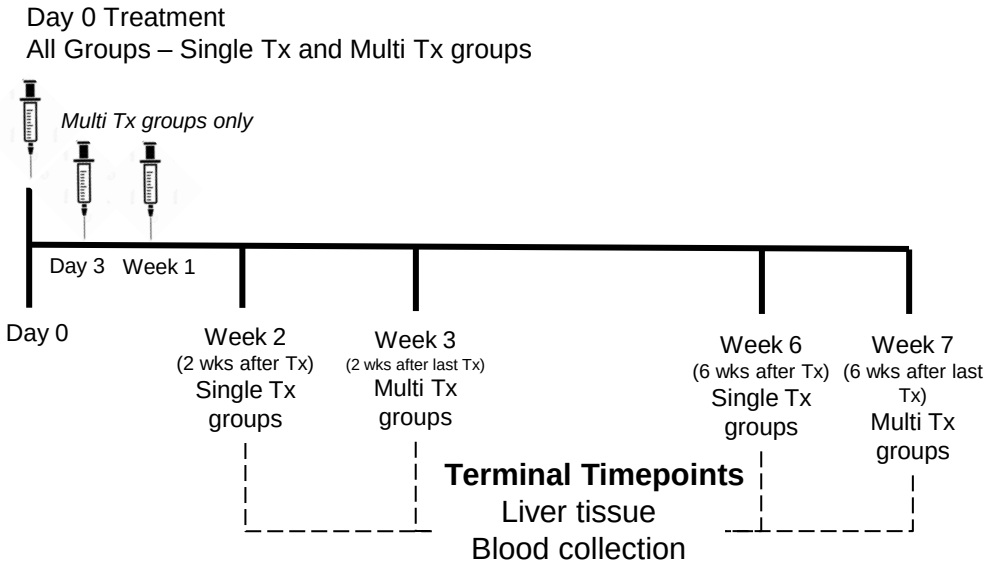
STP151G (TMPRSS6/ApoC3)

APOC3-TMPRSS6: Humanized liver mice study design



Study Design

Animal Model:
- Humanized liver mouse model
- WT Normal C57/Bl6 mice

Test compounds:
- muRNA (APOC3-TMPRSS6)

Dosing:
- Single Tx: 10mg/kg, 25mg/kg, 50mg/kg
- Multi Tx (3x): 25mg/kg

ROA:
- Subcutaneous

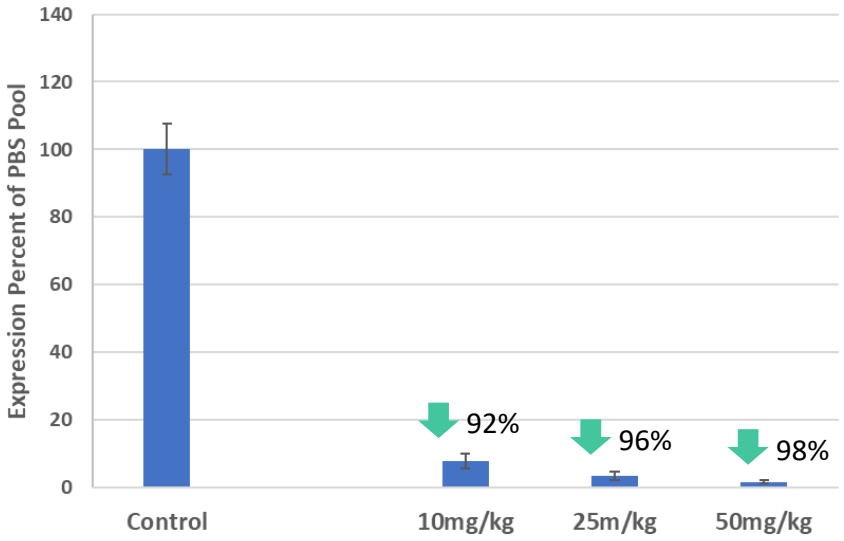
N:
- 4 mice/group

Terminal Endpoints:
- 2 weeks, 3 weeks
- 6 weeks, 7 weeks

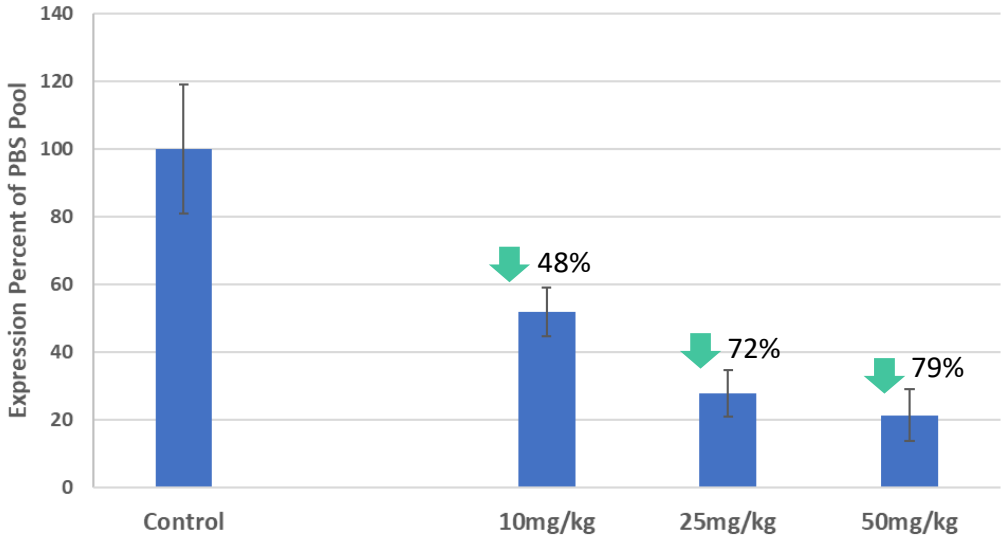
Readouts:
- qPCR (mRNA) – APOC3, TMPRSS6
- ELISA (protein) – APOC3

Single Treatment: Week 2

APOC3: mRNA in Liver Tissues



TMPRSS6: mRNA in Liver Tissues

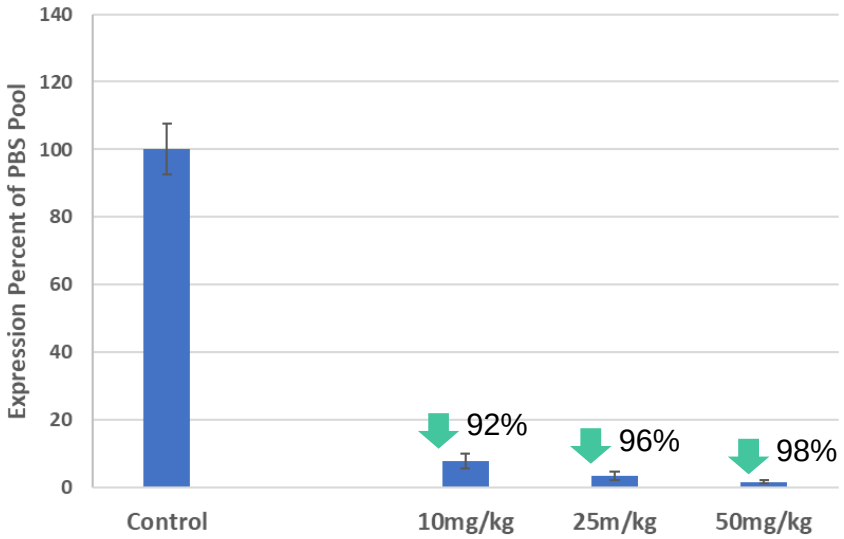


Successful knockdown of TWO hepatocyte-specific targets

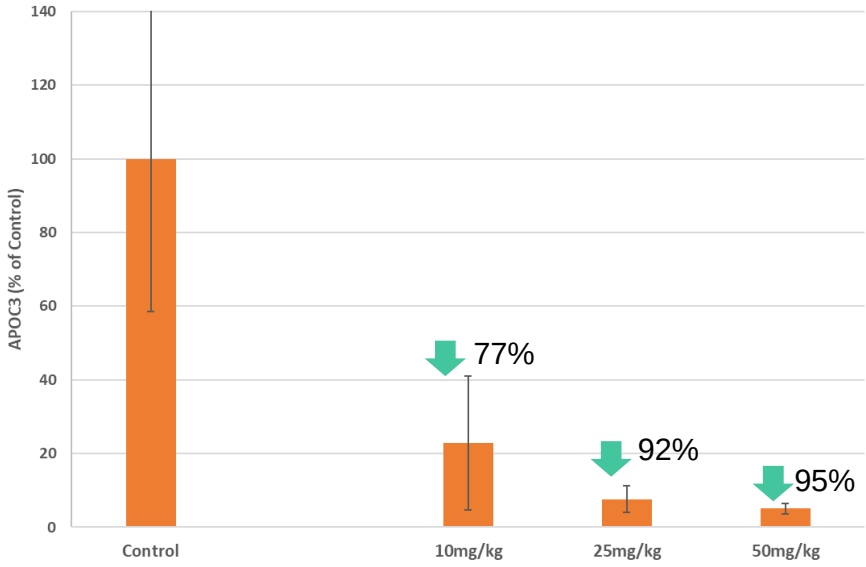
- APOC3 resulted in >90% KD at 25mg/kg
- TMPRSS6 resulted in >70% KD at 25mg/kg

Correlation: mRNA – Protein (Single treatment)

APOC3: mRNA in Liver Tissues



APOC3: Protein in Plasma

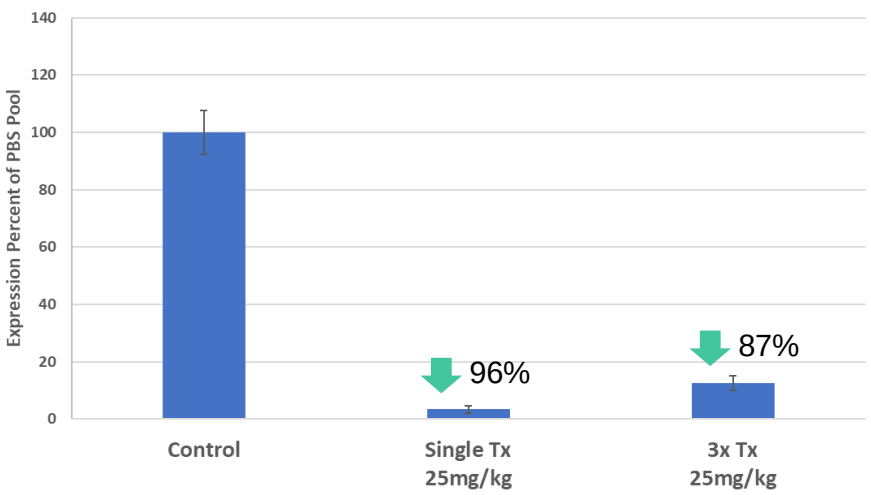


High Correlation between mRNA and Protein

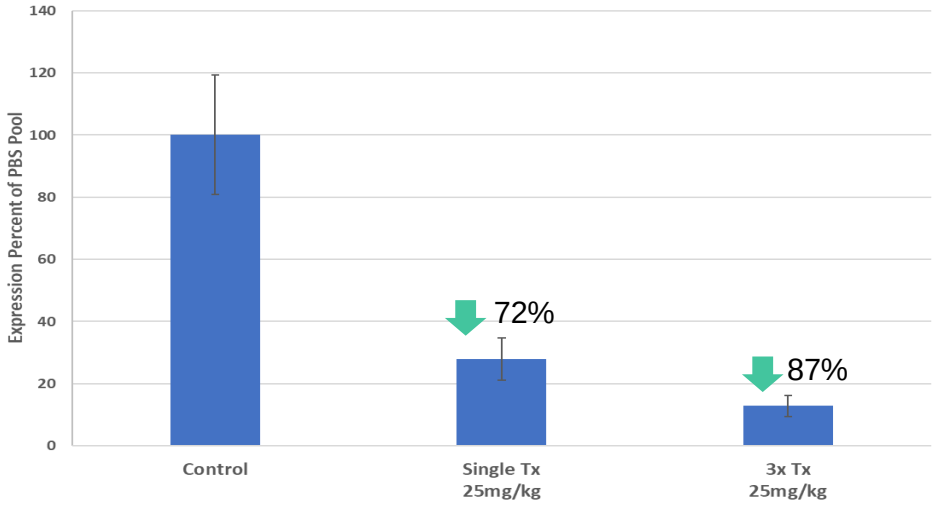
- KD of mRNA expression was correlated with lowering of protein levels in the plasma

Single vs Multi Treatments (week 2 after last dose)

APOC3: mRNA in Liver Tissues



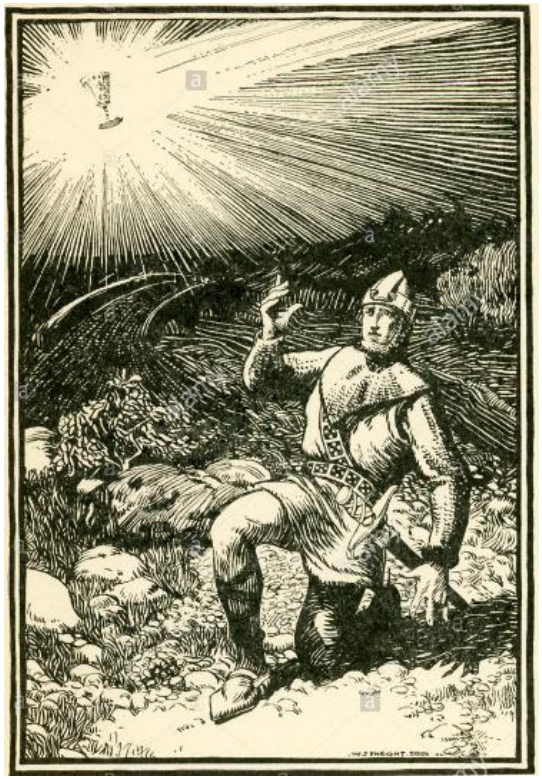
TMPRSS6: mRNA in Liver Tissues



High Potency

- Comparable KD between single and multiple treatments
- Successful KD of two hepatocyte-specific targets with both single and multiple treatments

GalAhead™: Sirnaomics' proprietary GalNAc-siRNA platform



GalAhead™ technology incorporates multiple components

mxRNA™: miniaturized single-targeting RNAi triggers

muRNA™: multi-unit multi-targeting RNAi triggers

*Note: pronounced as in Sir **Galahad**, a knight of the King Arthur's Round Table and one of only three achievers of the Holy Grail*

GalAhead™ therapeutic pipeline: June 2022

Drug	Target	Indication	Bioinformatics	Discovery	Candidate Nomination	IND Enabling	IND
STP122G	Factor XI	Anticoagulation/Thrombosis					
STP125G	ApoC3	Hypertriglyceridemia					
STP144G	Complement Factor B	Complement-mediated diseases					
STP145G	Complement Factor C5	Complement-mediated diseases					
STP151G	TMPRSS6/ApoC3	Hemochromatosis with hypertriglyceridemia					
STP146G	Non-disclosed	Complement-mediated diseases					
STP133G	Non-disclosed	Cardiometabolic diseases					
STP138G	Non-disclosed	Hypercholesterolemia					

We are planning to file our first GalAhead IND later this year, followed by several more in 2023

Questions?

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