



Sirnaomics Ltd.

GalAhead™ Platform & Programs

March 15, 2022

Boston

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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

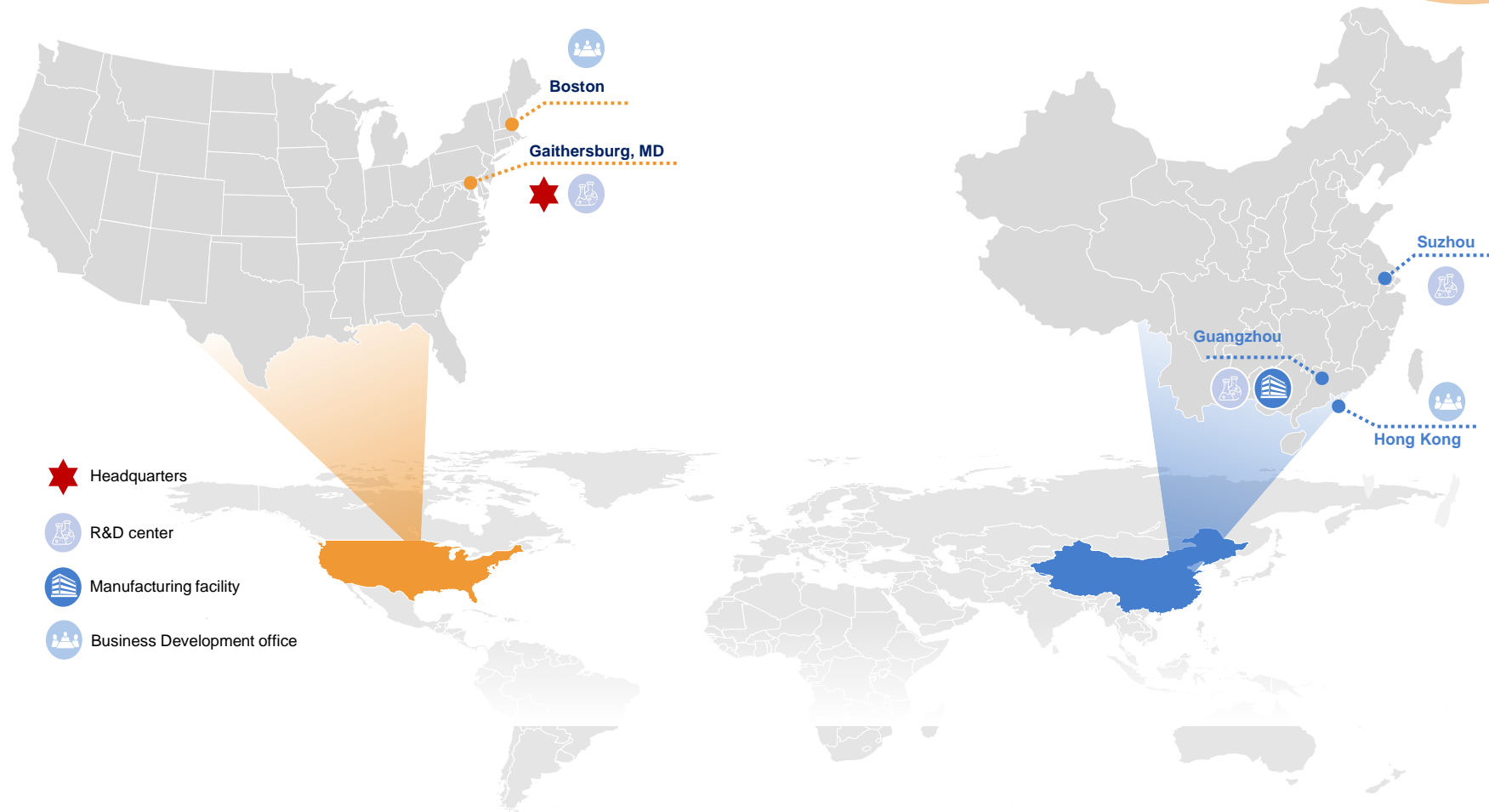
Oncology, fibrosis, medical aesthetics, anti-viral, cardiovascular and cardiometabolic diseases, etc.

Technology driven platforms

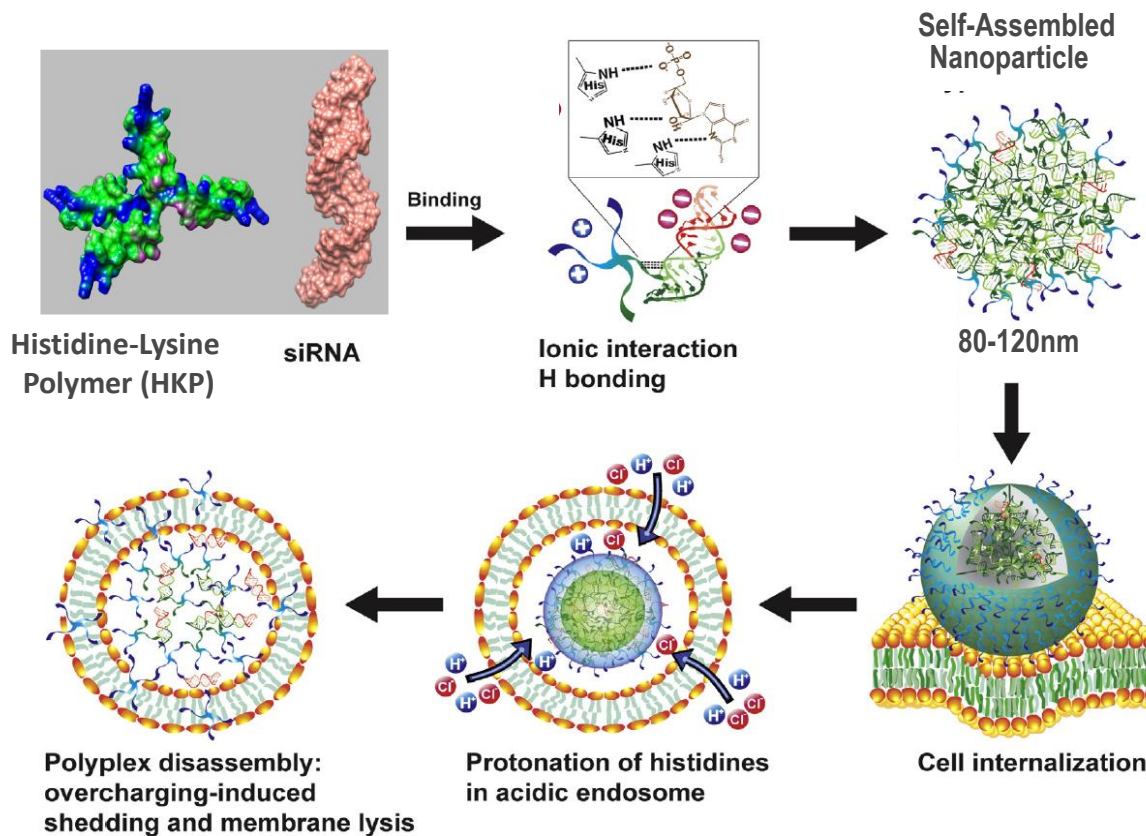
- Proprietary algorithm for siRNA drug design
- Microfluidic technology for commercial-scale manufacturing

Successful fund raising

Raised >\$300M since inception; IPO in Dec 2021



Peptide Nanoparticle (PNP) Technology: Principles



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)

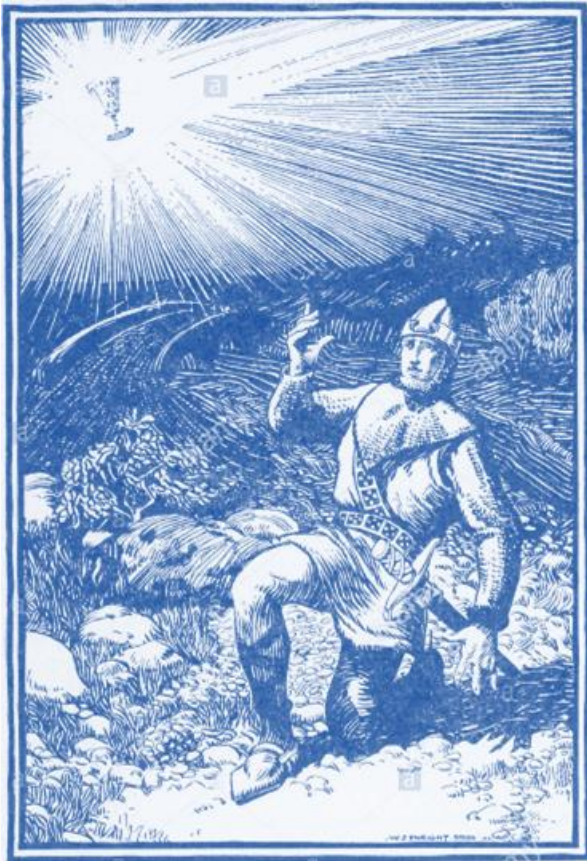
Sirnaomics: Programs

	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	China (MRCT) ²					US		Global	2 in clinical stage
			BCC		US							Global	
			Liver Cancer ¹ (Basket) **		China (MRCT) ³					US		Global	
			Liver Cancer, combo with anti-PD-(L)1		US							Global	
	STP707	TGF-β1/COX-2	Multiple solid tumors	PNP-IV	China (MRCT) ⁴					US		Global	6 in pre-clinical
			cSCC		US							Global	
			NSCLC		US							Global	
	STP355	TGF-β1/VEGFR2	Pan Cancer	PNP-IT	US							Global	16 pipeline candidates
			STP369		BCL-xL/MCL-1	Head & Neck cancer/BC	PNP-IT / IV	US					
	STP779	TGF-β1/SULF-2	Liver Cancer/ Lung Cancer/ Pancreatic Cancer	PNP-IV	US							Global	5 ongoing trials
STP302	mir-150	Colorectal Carcinoma	PNP-IT / IV								Global		
STP902	RAF-1	Breast cancer	PNP-IT / IV								Global		
STP705*	TGF-β1/COX-2	Keloid scarless healing	PNP-IT	US							Global		
		HTS		China (MRCT)					US		Global		
		China									Global		
STP707	TGF-β1/COX-2	Liver Fibrosis (PSC)	PNP-IV	US							Global	7 for oncology	
		Lung Fibrosis		China (MRCT)					US		Global		
Medical Aesthetics	STP705*	TGF-β1/COX-2	Fat sculpting	PNP-IT	US							Global	2 for fibrosis
Antiviral	STP702	M1/PA	Influenza	Airway / PNP-IV	US							OL China	1 for medical aesthetics
	STP908	ORF1Ab/N-protein	Covid-19		US							Global	
	RIM730 ⁶	SARS-CoV-2	Covid-19 vaccine	LNP Intramuscular	US							Global	
	STP909	VP16/18-E7	HPV/Cervical Cancer	PNP-IV/Topical								Global	
GalNAc-RNAi triggers	STP122G	Factor XI	Thrombotic disorders		US							Global	4 for antiviral
	STP125G	Non-disclosed	Hypertriglyceridemia									Global	
	STP144G	Complement Factor B		GalAhead™ subcutaneous								Global	
	STP145G	Non-disclosed	Complement-mediated diseases	TBU								Global	
	STP146G	Non-disclosed										Global	
	STP133G	PCSK9/ApoC3	Cardiometabolic									Global	
	STP135G	PCSK9	Hypercholesterolemia	PDov-GalNAc subcutaneous								Global	
STP155G	HBV sequences	HBV									Global	8 GalNAc-RNAi triggers	

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. 6. Research and development conducted by our subsidiary RNAimmune.

GalAhead™: Sirnaomics' proprietary GalNAc-siRNA platform



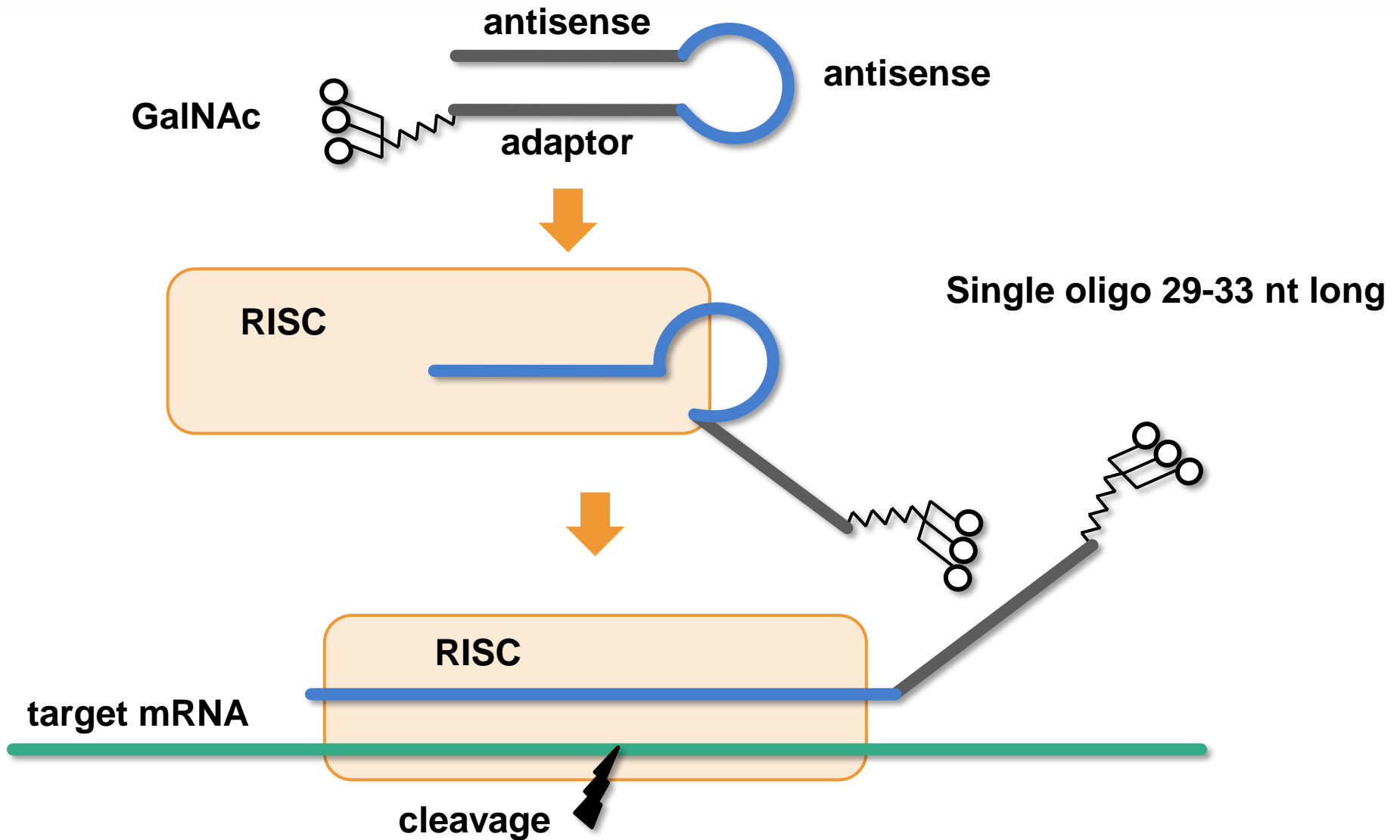
GalAhead™ technology incorporates multiple components

mxRNA™: miniaturized single-targeting RNAi triggers

muRNA™: multi-unit multi-targeting RNAi triggers

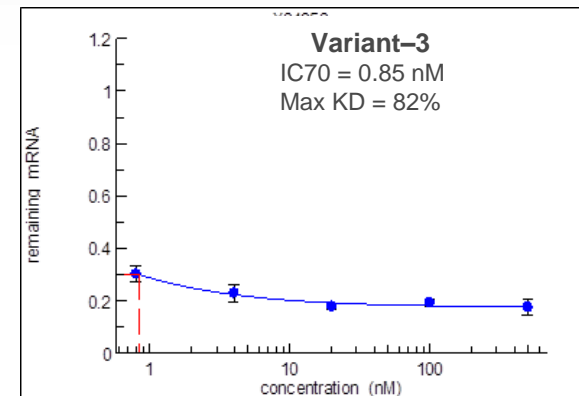
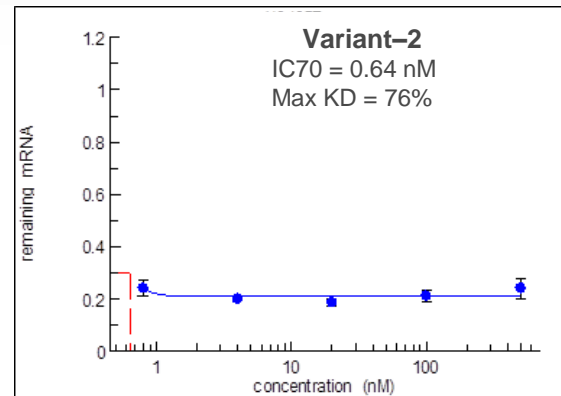
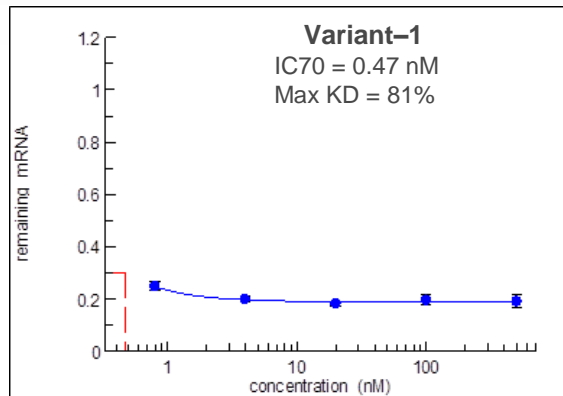
*NB: pronounced as in Sir **Galahad**, a knight of the King Arthur's Round Table and one of only three achievers of the Holy Grail*

mxRNAs™: Proposed mechanism of action (MOA)

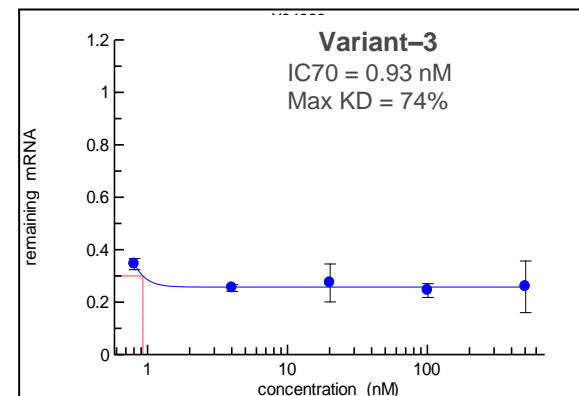
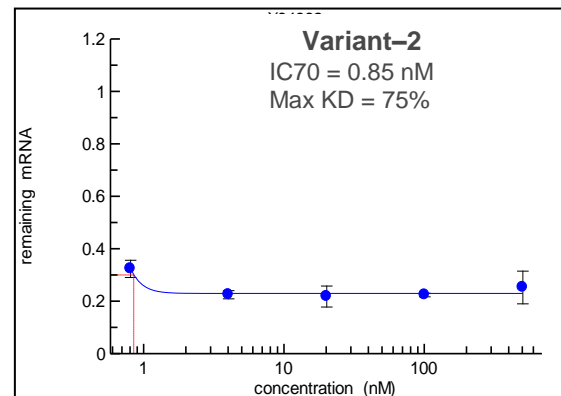
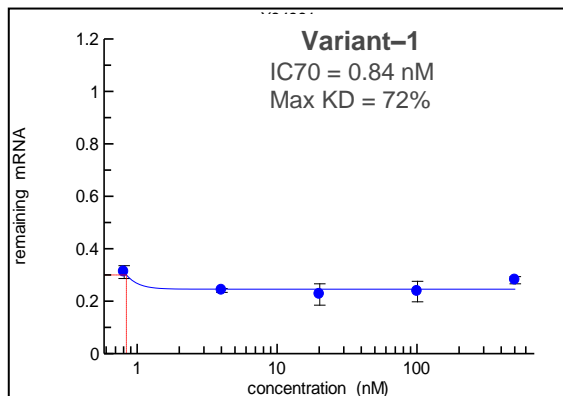


mxRNA™: Remarkable activity in primary hepatocytes

Sequence 1



Sequence 2



Cells: primary mouse hepatocytes

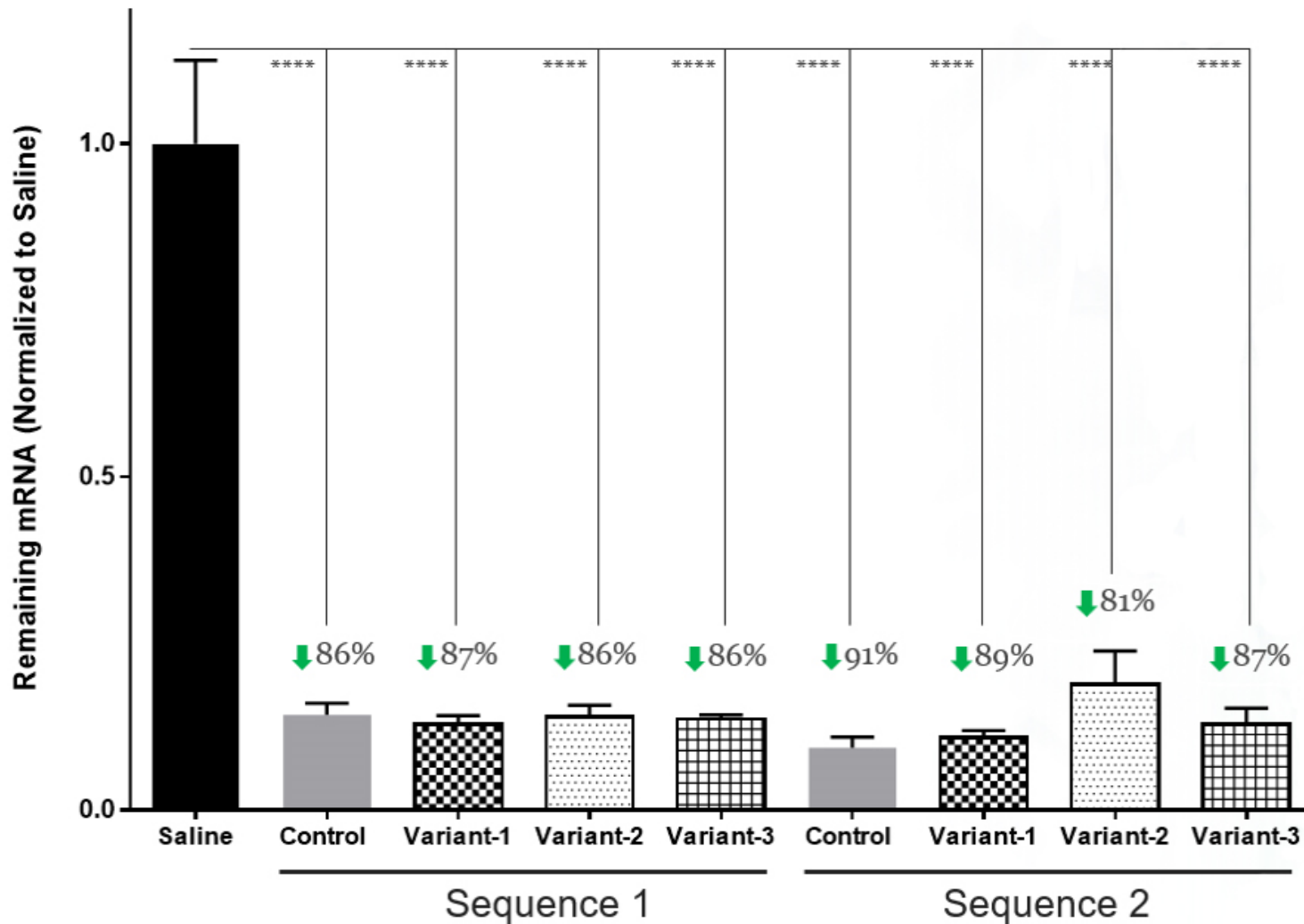
Delivery: passive uptake

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

Time-point: 72 hours

Readout: TMPRSS6 mRNA

mxRNA™: Outstanding in vivo activity (single dose)



Animals: mice

Dose: 10 mg/kg

Timepoint: 5 days

Readout: Tmprss6 mRNA

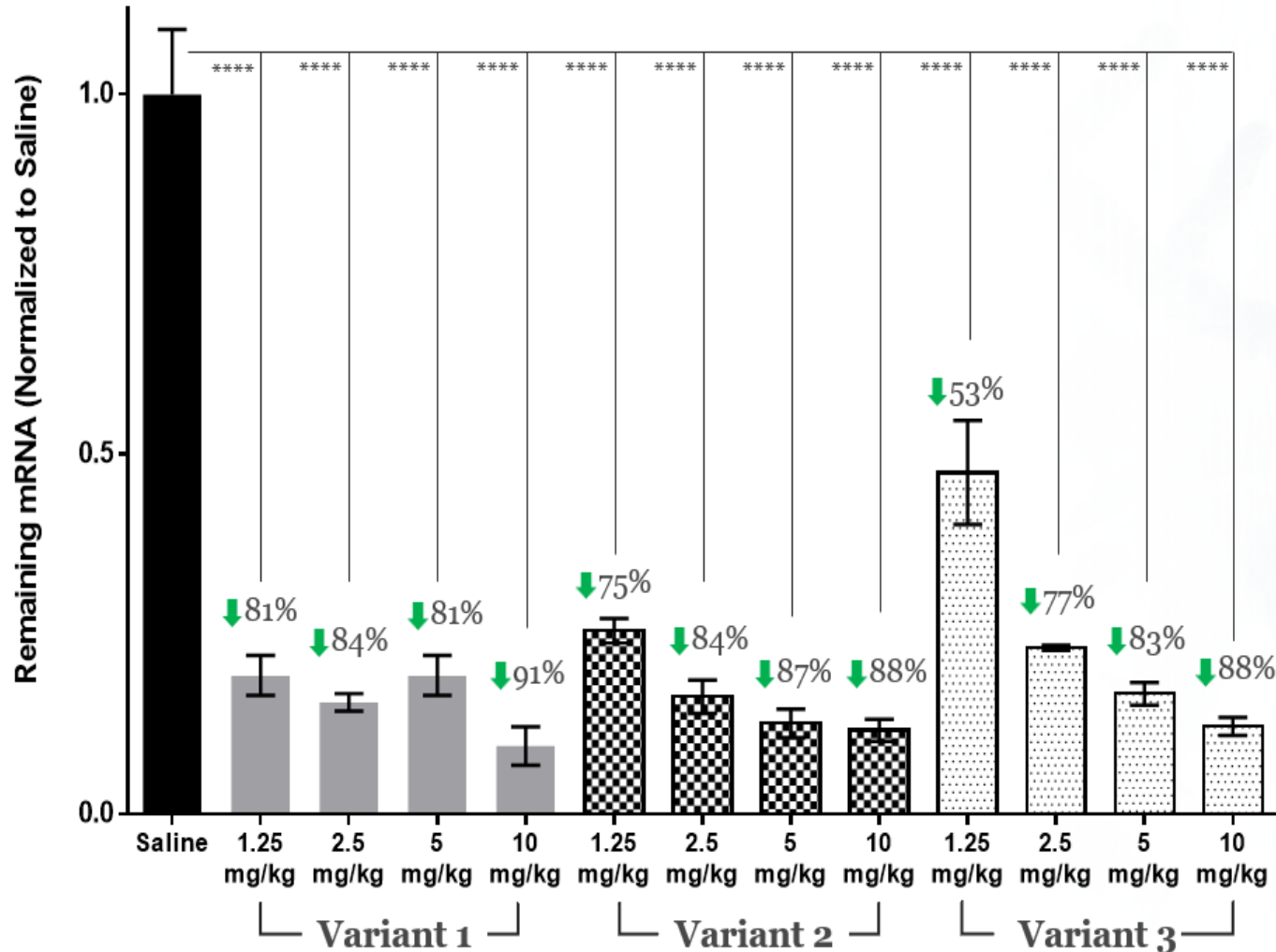
Statistics:

One-Way ANOVA

Post-hoc analysis with Tukey's multiple comparisons test

**** = $p < 0.0001$

mxRNA™: Outstanding in vivo activity (dose response)



Study Design

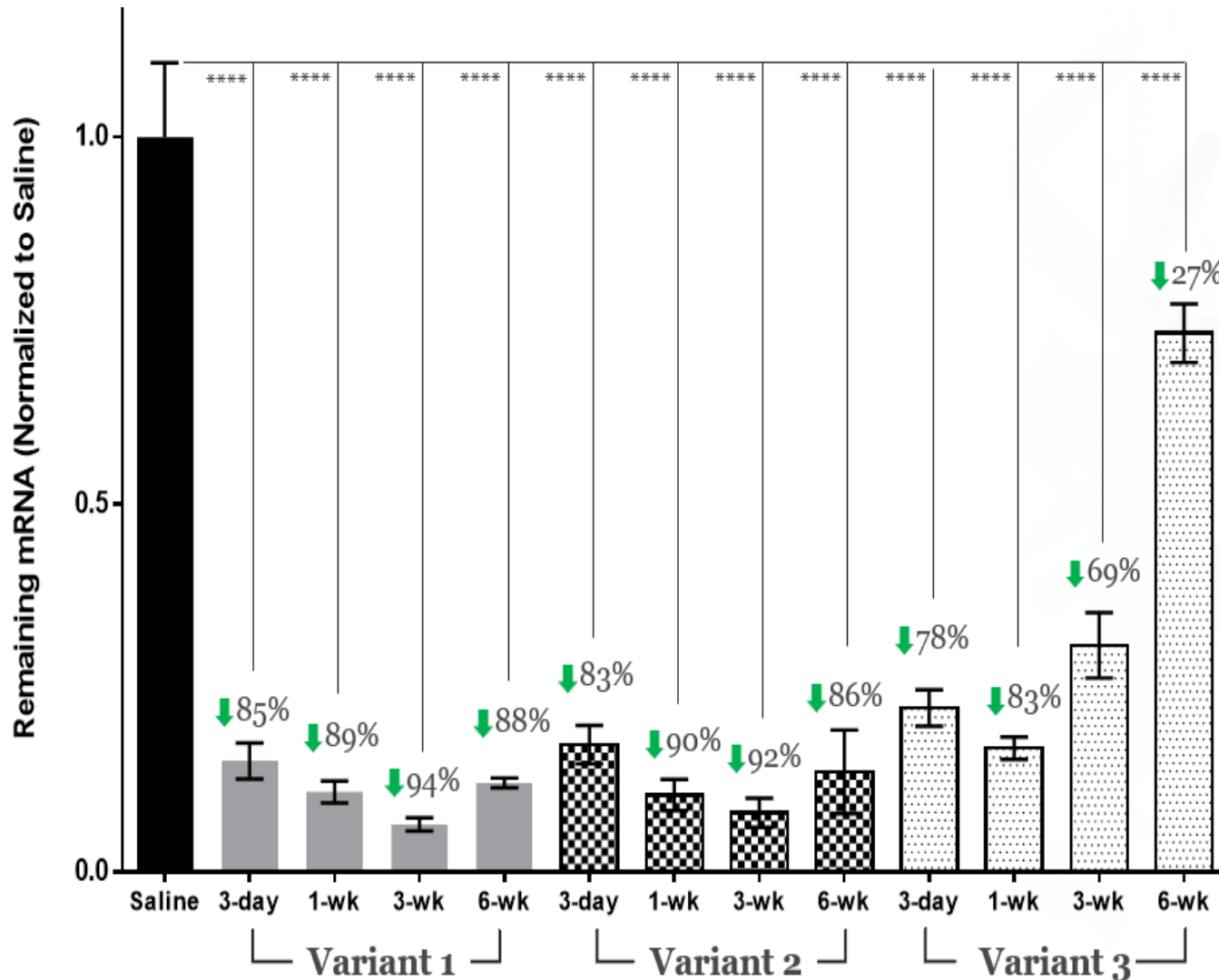
- 1, 2 & 3 configuration for sequence 1
- Doses: 1.25 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg
- N= 4 C57/Bl6 mice/group
- 5 day timepoint
- bDNA analysis: TMPRSS6 mRNA from liver tissues

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

Note:

1. For 10mg/kg dose group – liver samples collected during Single Dose study were included in the bDNA assay

mxRNA™: Outstanding in vivo activity (duration response)



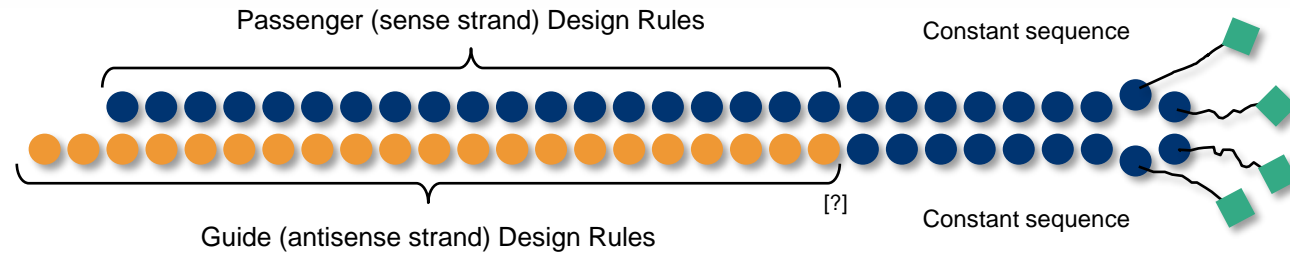
Study Design

- 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

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

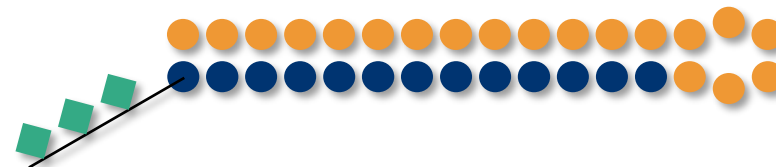
mxRNA™: Potential CMC advantage

Dicerna



- Synthesis one: 36 nucleotides
- Synthesis two: 20 nucleotides
- Annealing

sirnaomics
Advancing RNAi Therapeutics

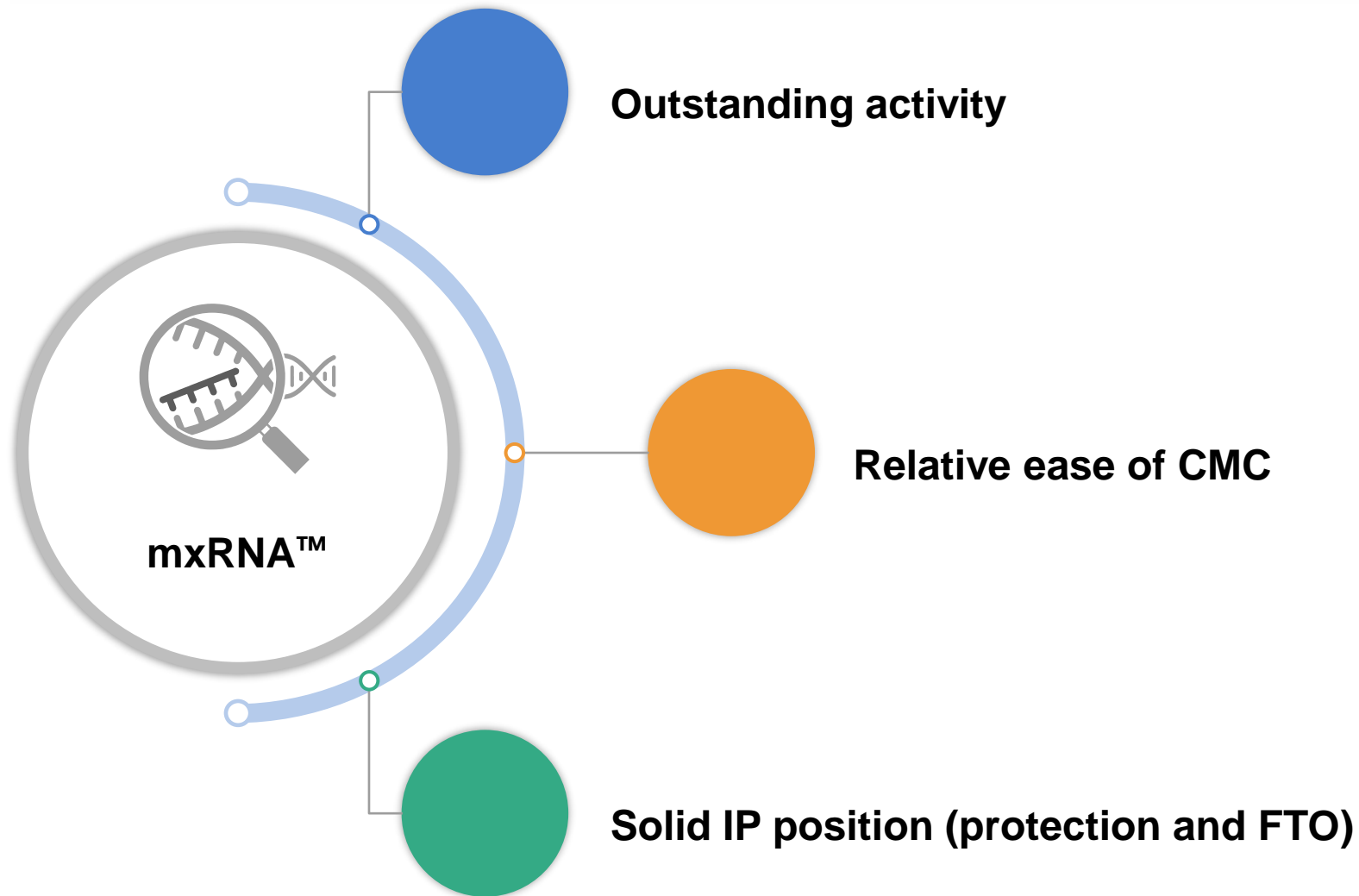


- Synthesis one: 31-33 nucleotides







Note:

1. In November 2021, Novo Nordisk announced plans to acquire Dicerna for \$3.3 Billion

mxRNA™: Potential advantage package



GalAhead™ Programs: March 2022

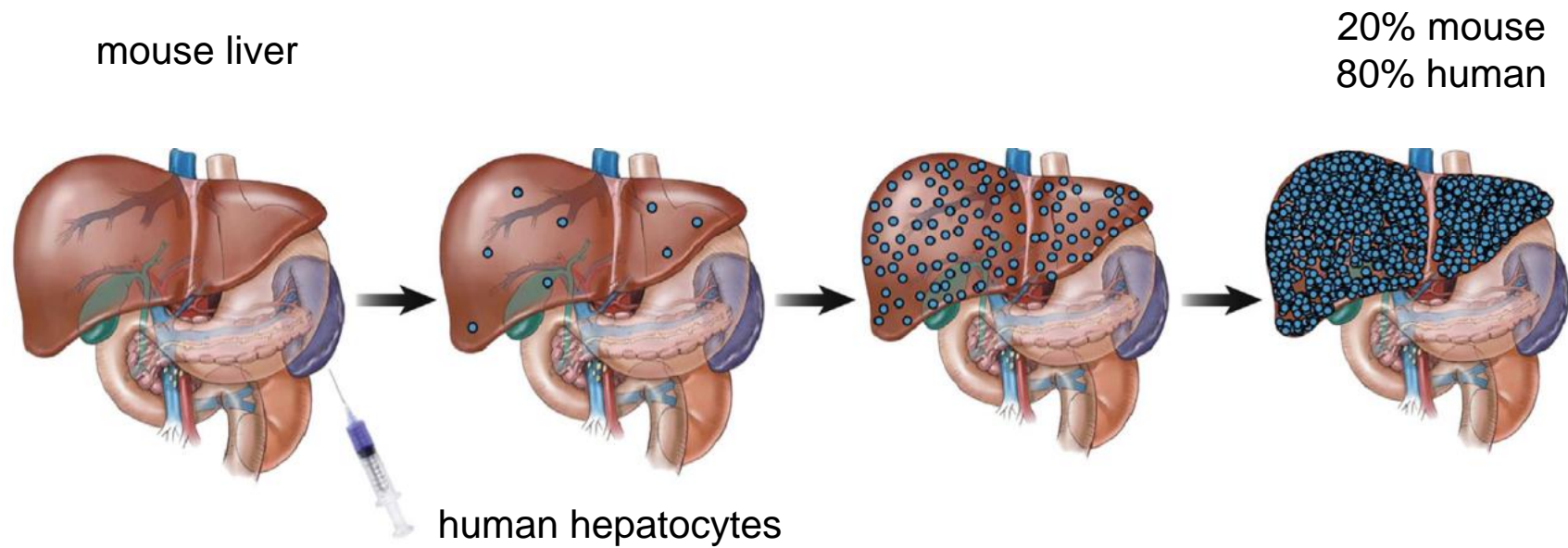
Drug	Target	Indication	Bioinformatics	Discovery	Candidate Nomination	IND Enabling	IND
STP122G	Factor XI	Anticoagulation/Thrombosis					
STP125G	Non-disclosed	Hypertriglyceridemia					
STP144G	Complement Factor B	Complement-mediated diseases					
STP135G	Non-disclosed	Hypercholesterolemia					
STP145G	Non-disclosed	Complement-mediated diseases					
STP146G	Non-disclosed	Complement-mediated diseases					

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

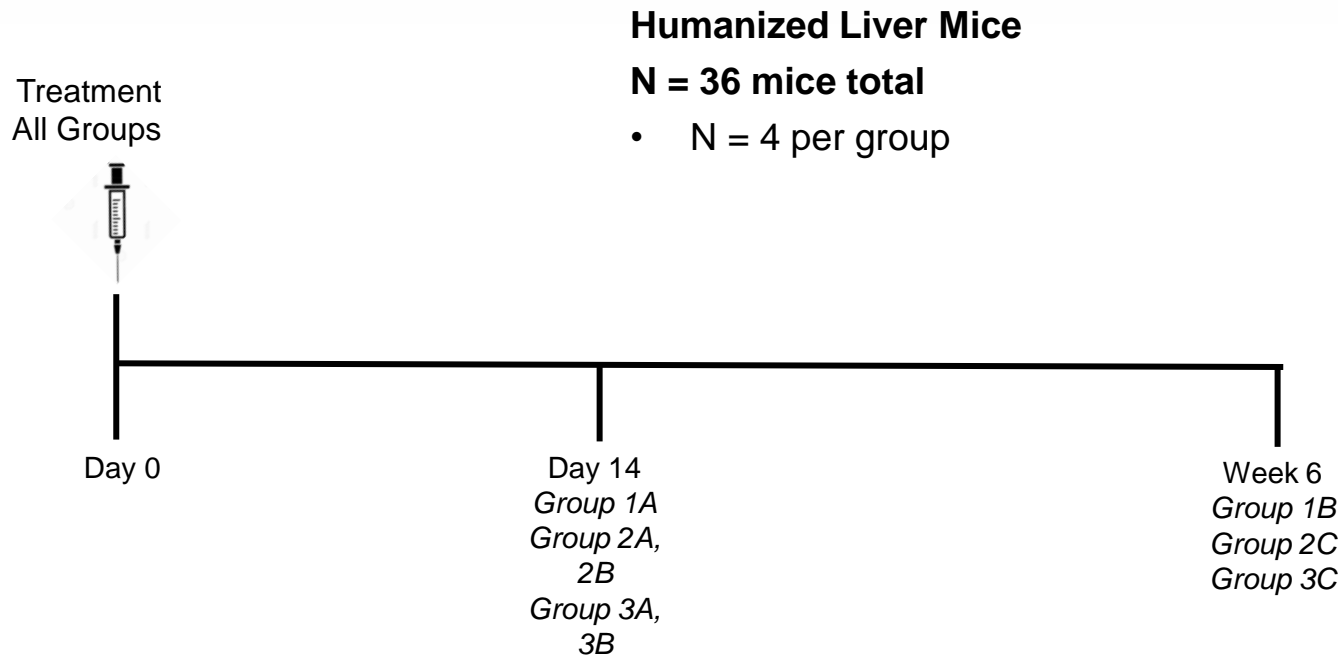


STP125G (non-disclosed target)

Humanized liver mouse model



STP125G: Humanized liver mice study design



Control (PBS) Day 14	A28 (14-4)mF mxRNA Day 14	A277 (12-5) mxRNA Day 14	Control (PBS) Week 6	A28 (14-4)mF mxRNA Week 6	A277 (12-5) mxRNA Week 6
Group 1A	Group 2A (10mg/kg)	Group 3A (10mg/kg)	Group 1B	Group 2C (10mg/kg)	Group 3C (10mg/kg)
	Group 2B (30mg/kg)	Group 3B (30mg/kg)			

Animals:

- humanized mice

Treatment & sample collection site:

- DaVinci (MA)

Test compounds:

- A28(14-4)mF mxRNA
- A277(12-5) mxRNA

Dosing:

- 10 mg/kg
- 30 mg/kg

Administration:

- subcutaneous

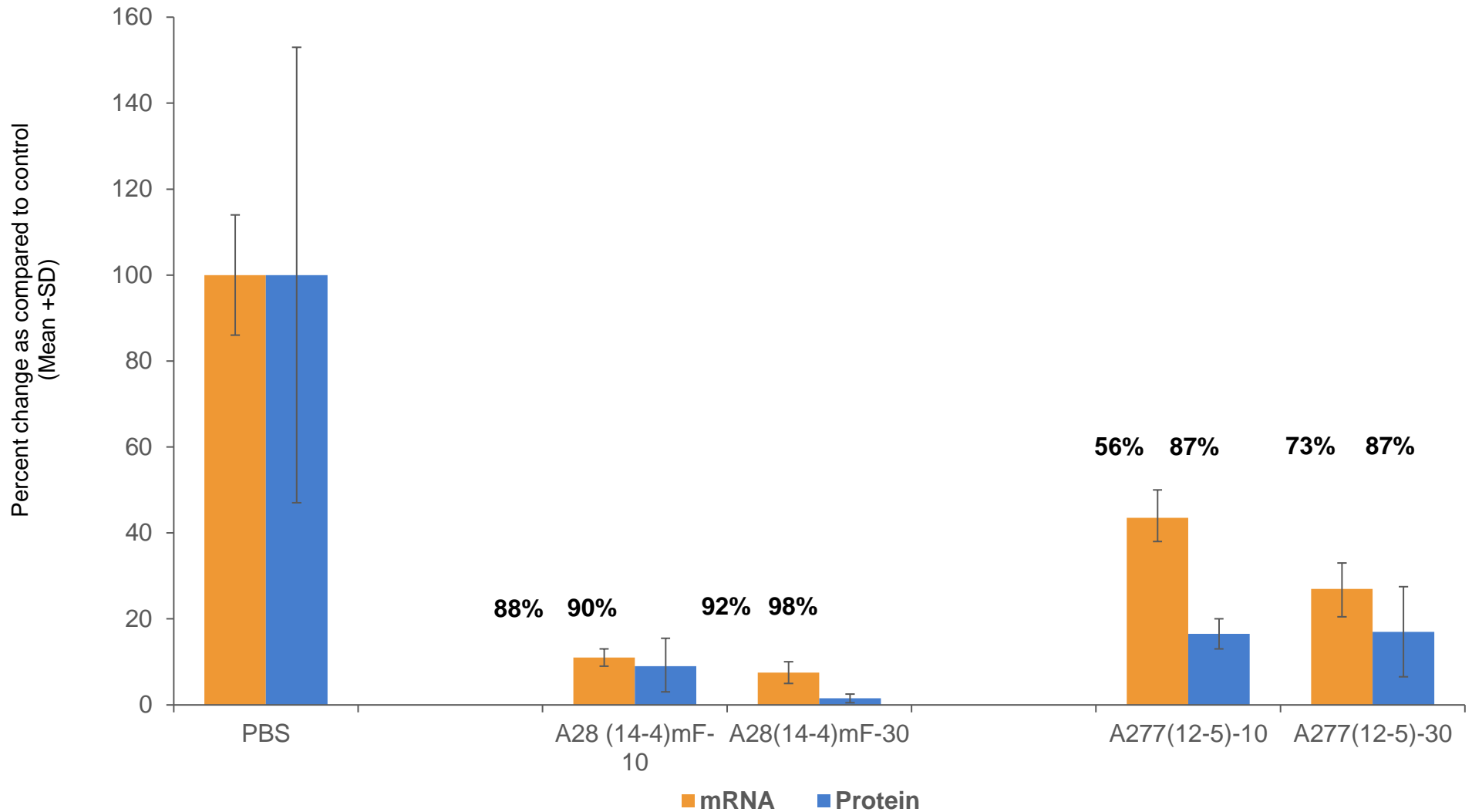
Timepoints:

- 2 weeks (dose response – 10mg/kg and 30mg/kg)
- 6 weeks (duration response – 10mg/kg)

Readouts:

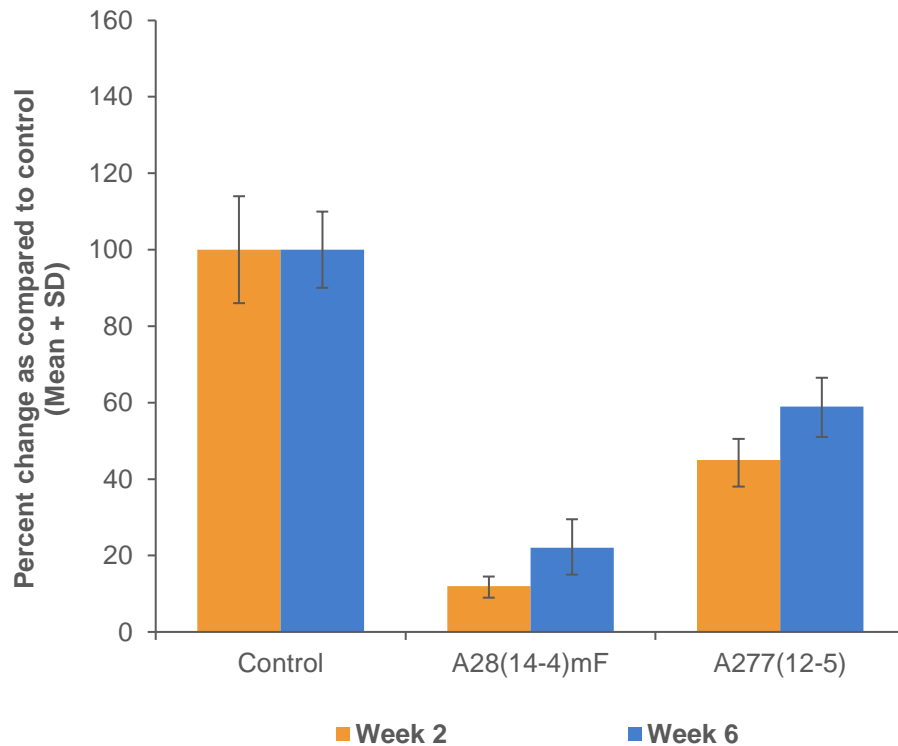
- qPCR (mRNA)
- ELISA (protein)

STP125G: Dose response in vivo (Week 2)

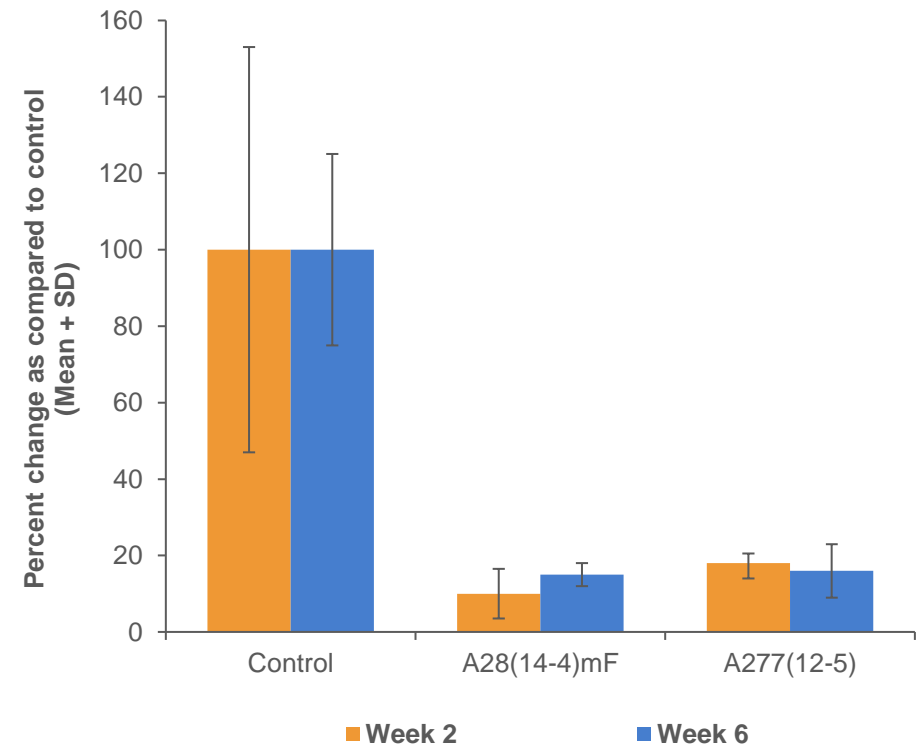


STP125G: Knockdown duration

mRNA levels in liver tissues



Protein levels in plasma (ELISA)



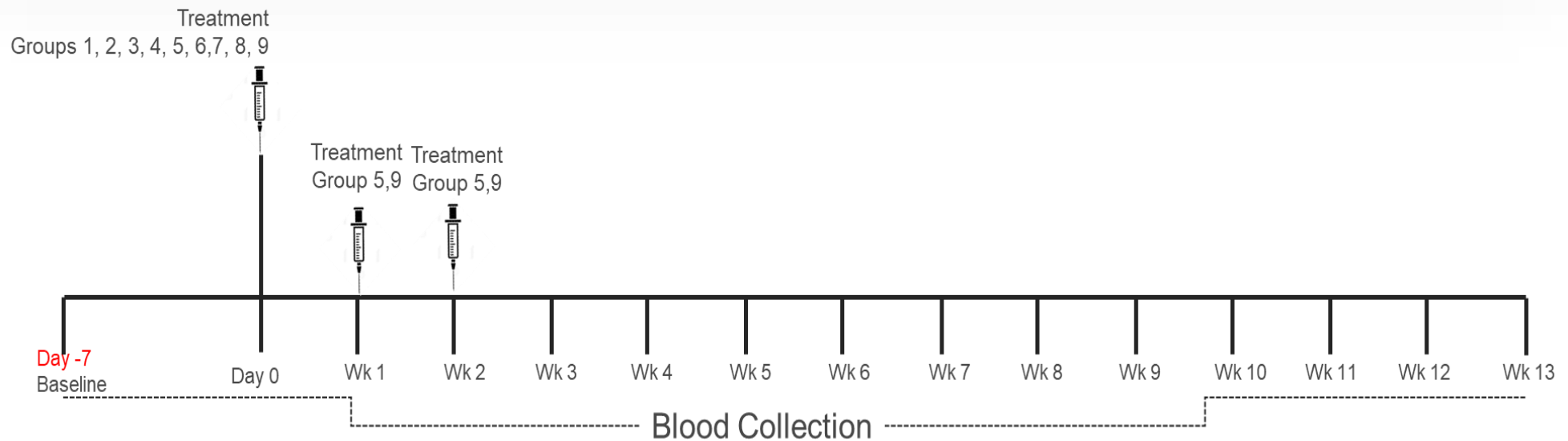
- A28(14-4)mF
 - 88% suppression at week 2 and maintained 78% at week 6
- A277(12-5)
 - 56% suppression at week 2 and maintained 42% at week 6
 - Excludes data from animal that was an outlier

- A28(14-4)mF
 - 90% reduction at week 2 that was sustained at 85% on week 6
- A277(12-5)
 - 83% reduction at week 2 that was sustained at 84% at week 6
 - Excludes data from animal that was an outlier



STP144G (Complement Factor B)

STP144G: Non-human primates (NHP) study design



Groups:

N = 36 NHP total

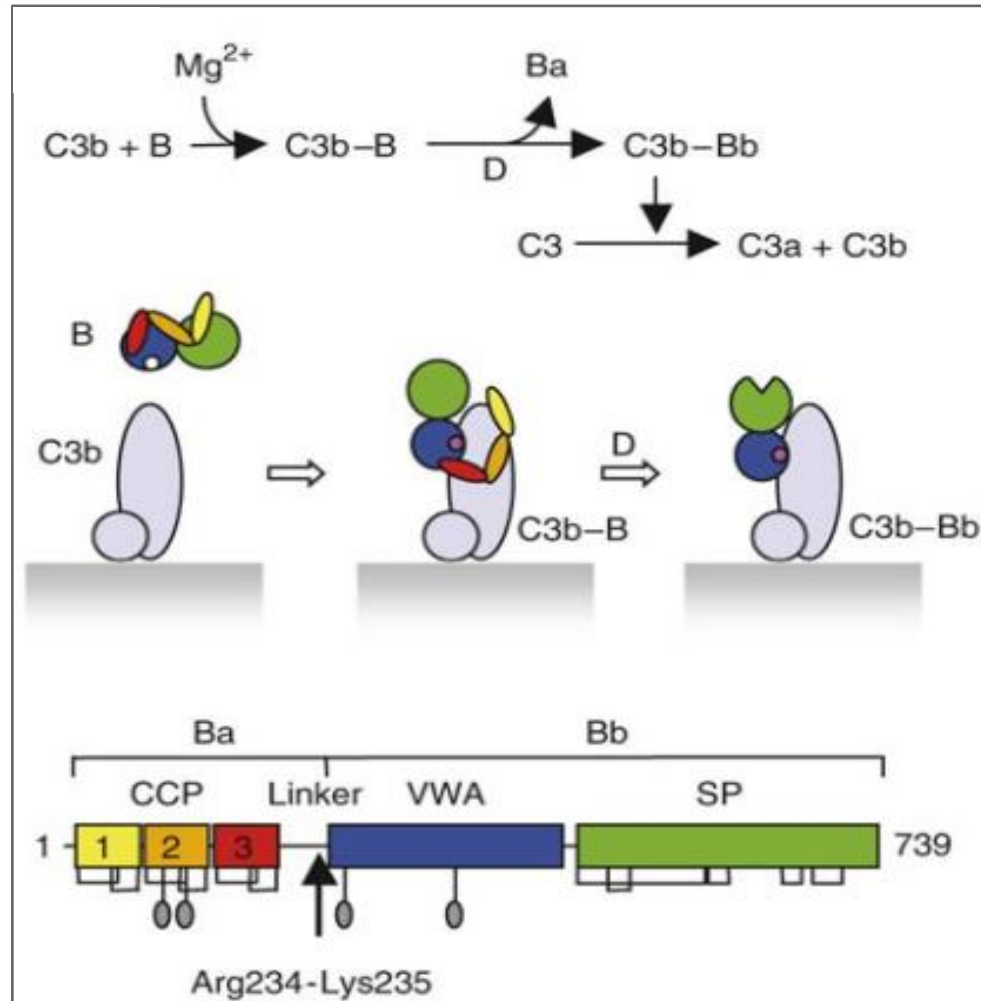
• N = 4 NHP/group

- 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)

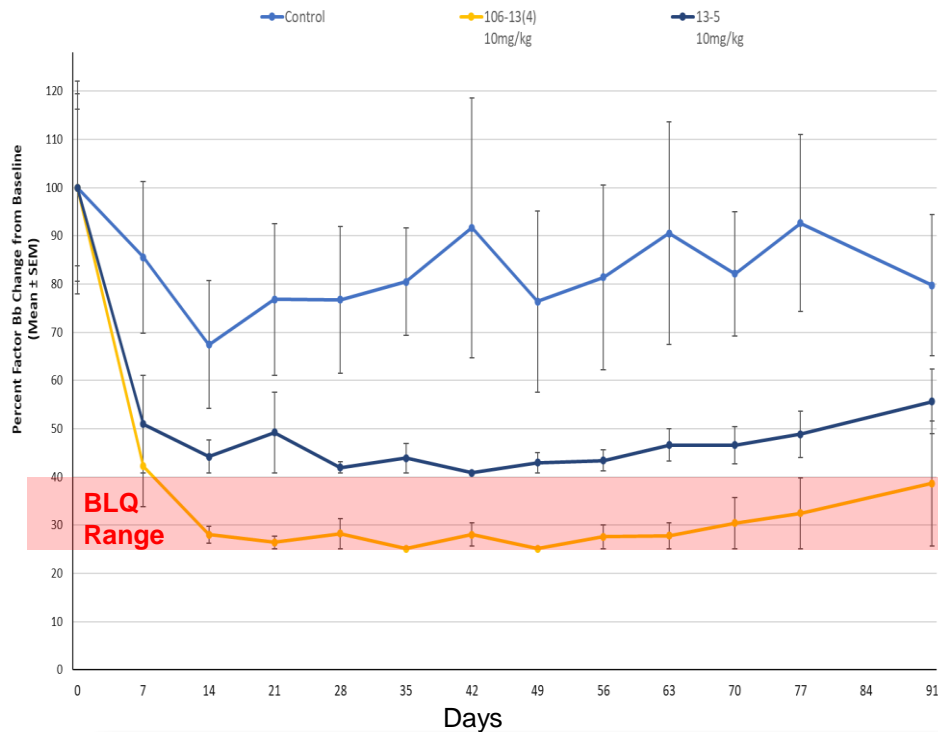
Complement Factor B: Bb assay background



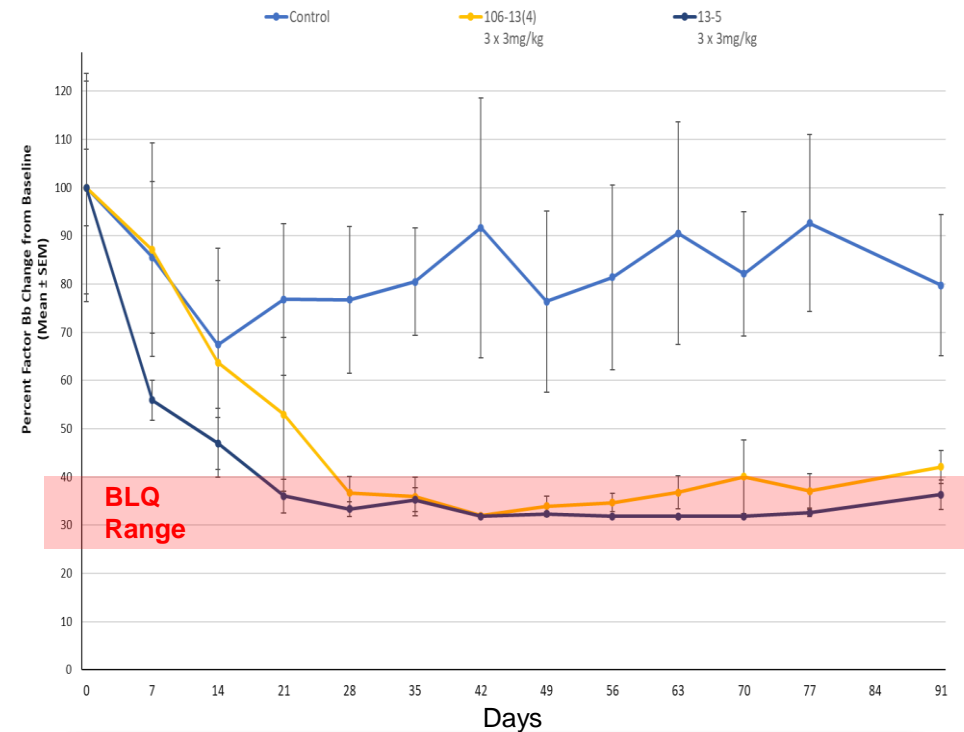
From Midler FJ et al (2007) *Nat Struct & Mol Biol* (14) 224-8

STP144G: Bb levels with lead compounds in NHP

Single Treatment Comparison



Multiple 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

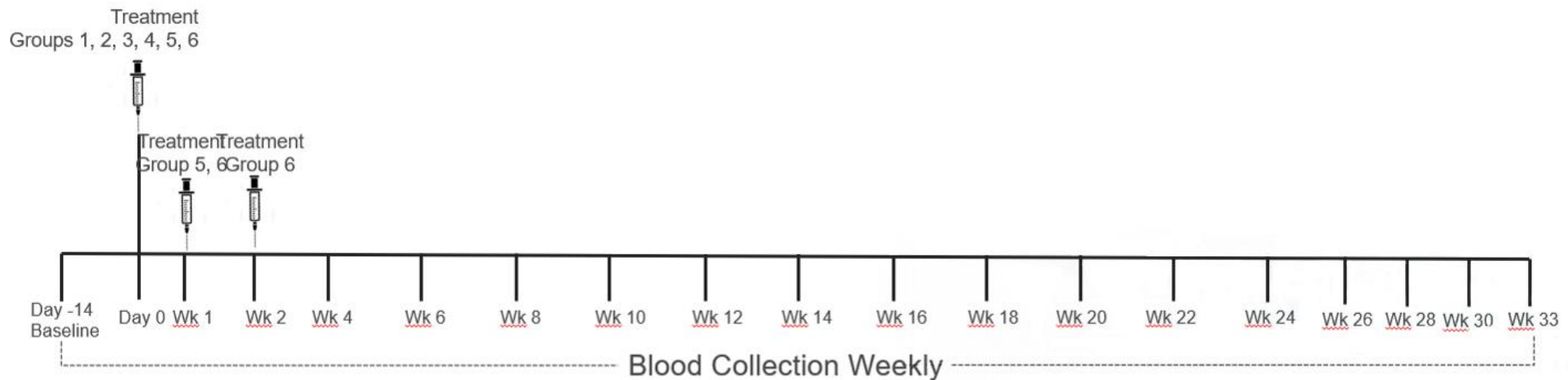
Max reduction of Factor Bb and duration of response

- 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



STP122G (Coagulation Factor XI)

Factor XI: Knockdown in non-human primates (NHP) study design



N = 24 NHP total

- N = 4 NHP/group

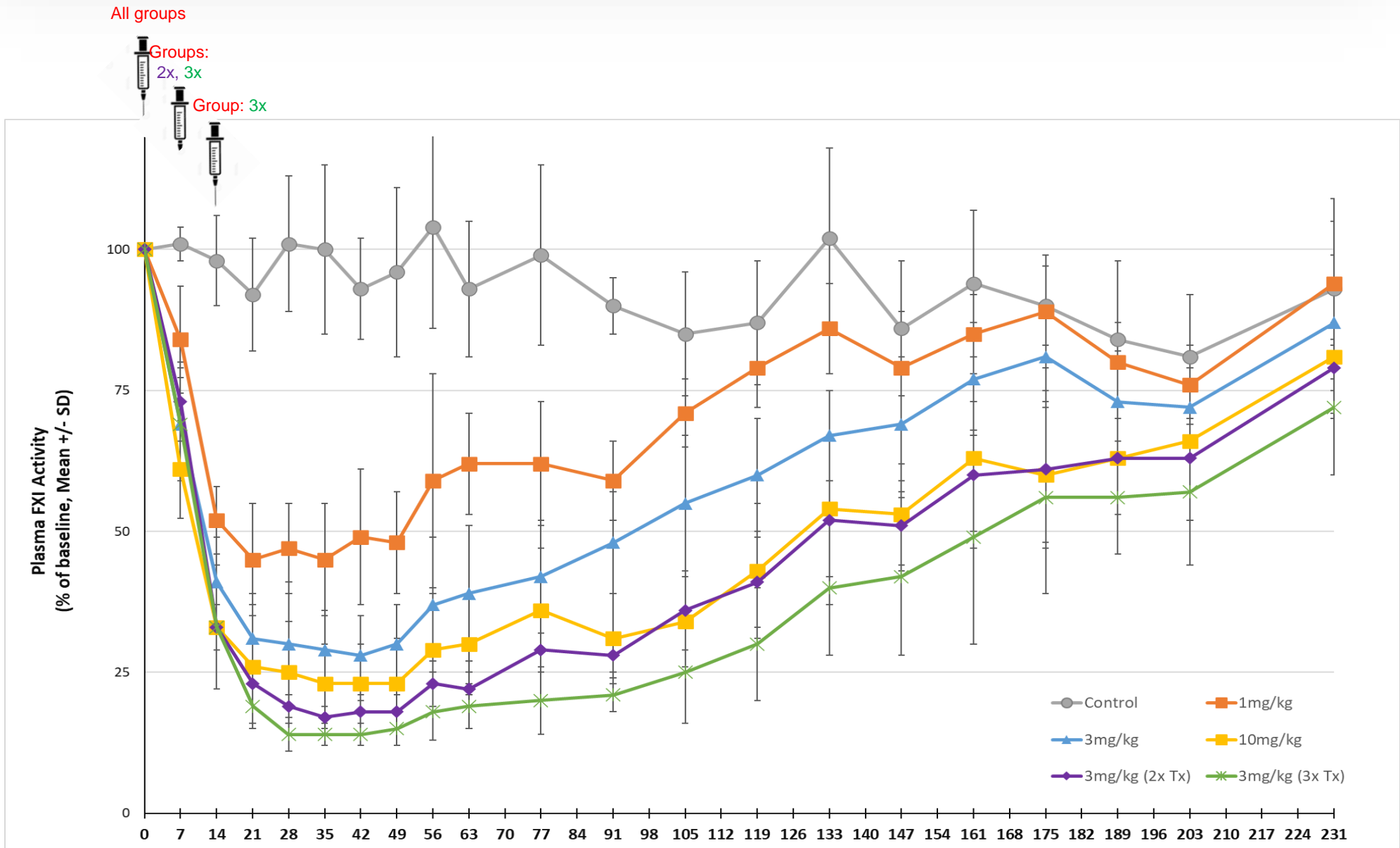
Groups:

- 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

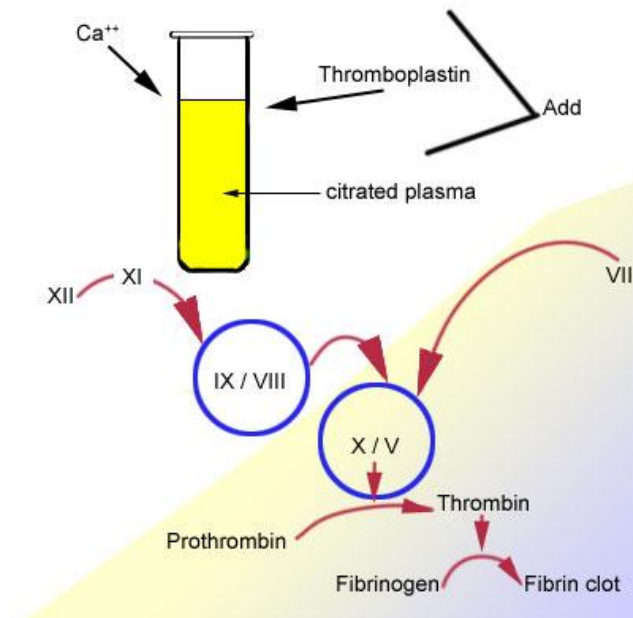
- Primary endpoint: Factor XI plasma activity
- APTT (activated partial thromboplastin time , PT (prothrombin time)
- Hematology and clinical chemistry: baseline, Wk2, Wk6, Wk18

Factor XI (NHP): Primary activity readout (up to week 33)

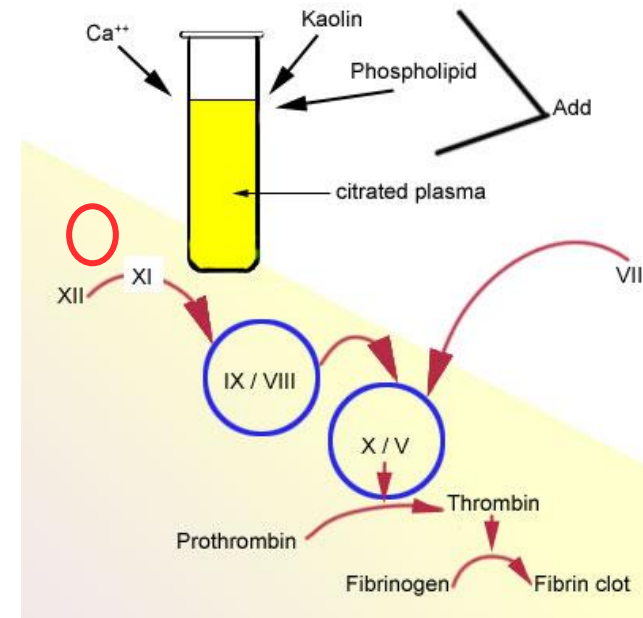


Factor XI (NHP): Secondary activity readout and pathway specificity

Extrinsic Pathway: Prothrombin time test (PT)



Intrinsic Pathway: Activated Partial Thromboplastin Time test (APTT)

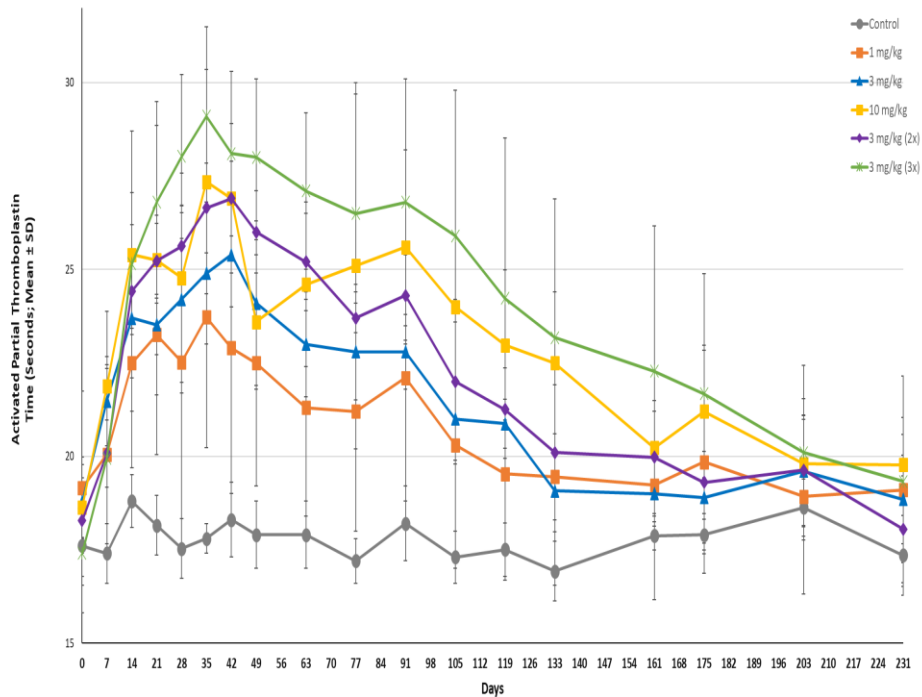


The prothrombin test specifically evaluates the presence of factors VII, V, and X, prothrombin, and fibrinogen

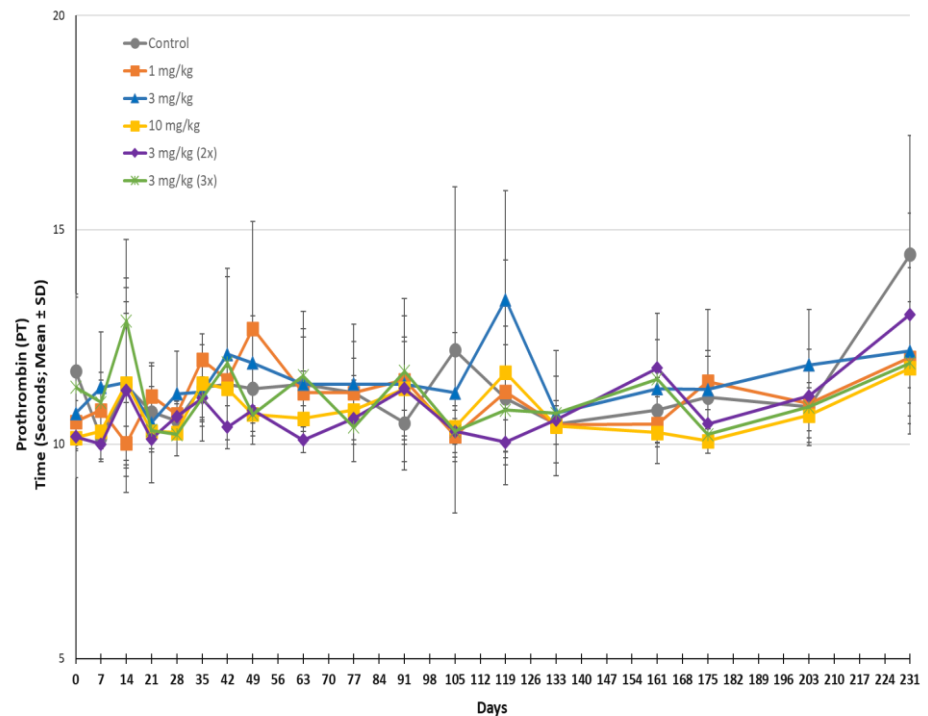
APTT measures the integrity of the intrinsic system (Factors XII, XI, VIII, IX) and common clotting pathways

Factor XI (NHP): Secondary activity readout and pathway specificity

APTT



PT



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







- No effect on PT values

Factor XI (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

GalAhead™ Programs: March 2022

Drug	Target	Indication	Bioinformatics	Discovery	Candidate Nomination	IND Enabling	IND
STP122G	Factor XI	Anticoagulation/Thrombosis					
STP125G	Non-disclosed	Hypertriglyceridemia					
STP144G	Complement Factor B	Complement-mediated diseases					
STP135G	Non-disclosed	Hypercholesterolemia					
STP145G	Non-disclosed	Complement-mediated diseases					
STP146G	Non-disclosed	Complement-mediated diseases					

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

Questions?

