Therapeutic RNA delivery

05/02/2017 – TIDES

Dr. Adrien Weingärtner

Head of Technology Development

SILENCE THERAPEUTICS

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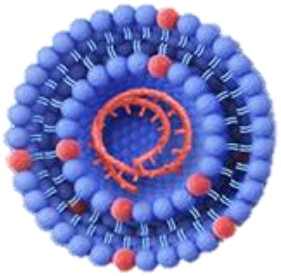
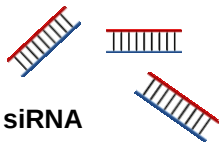
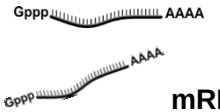
LNP delivery of RNA



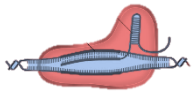
Lipid nanoparticle approach



siRNA



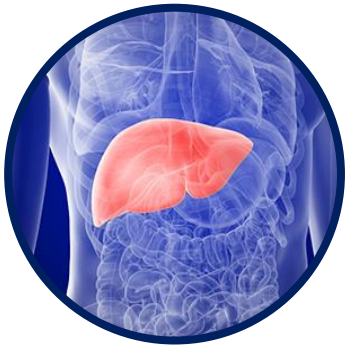
mRNA



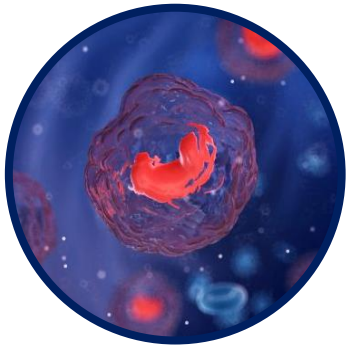
Gene editing payloads (CRISPR/Cas9)



Vasculature



Liver



Macrophages

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Time course and biodistribution of GN2205 functional luciferase mRNA delivery



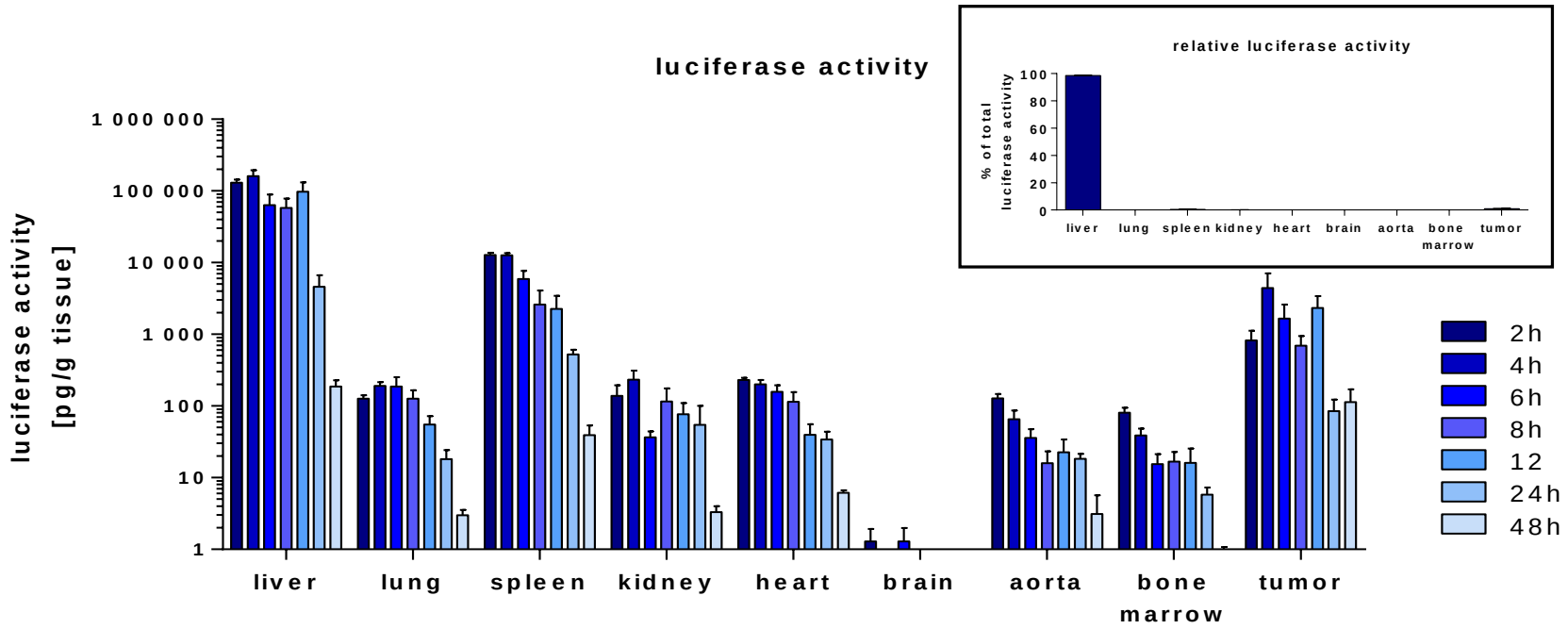
scid beige
Hep3B (5x10^6 cells s.c.)

-19 days

0h 2h 4h 6h 8h 12h 24h 48h

IV administration of
1mg/kg mRNA
(FLuc; Ψ; 5MeC; TriLink)
(tumor size ~350mm^3,
n=6)

ex vivo quantification of luciferase activity
in tissue lysates



→ **This formulation essentially targets the liver**

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GN2205 targets multiple cell types in the liver

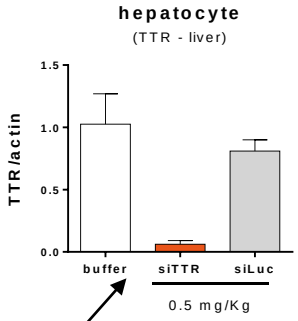


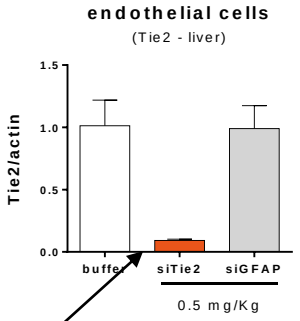
0h → 48h

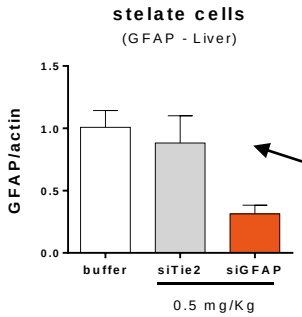
IV administration
0.5 mg/kg siRNA
(Silence)
C57BL/6 (n=4-6)

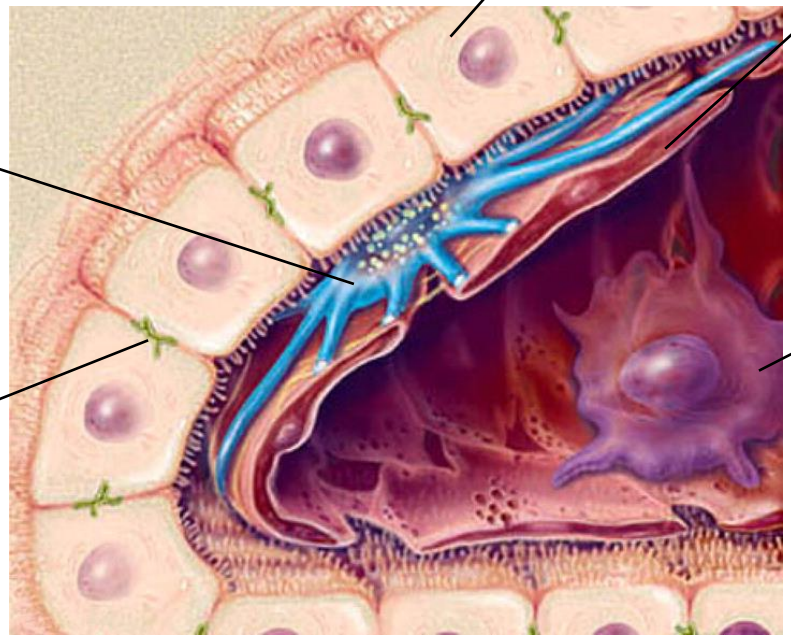


RT-PCR
quantification
of transcripts

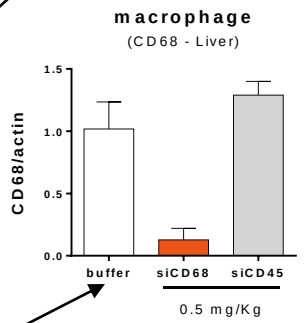


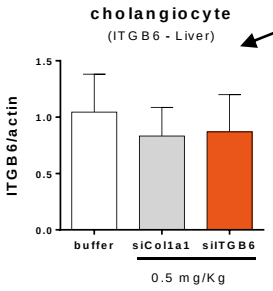


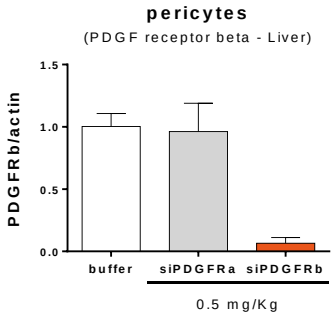




Physiol Rev 88: 125–172, 2008; doi:10.1152/physrev.00013.2007







→ **This formulation targets many cell types in the liver**

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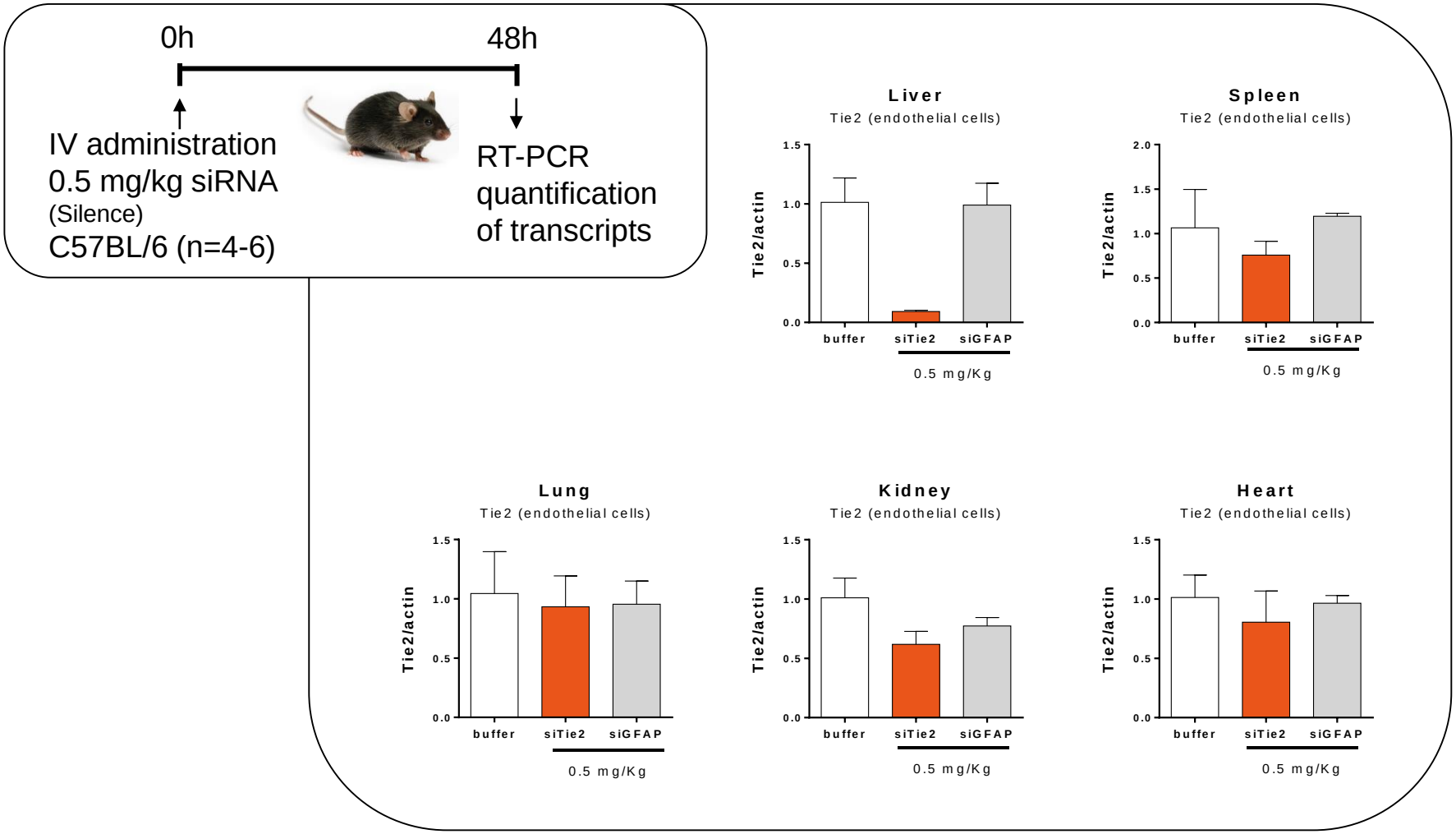
GN2205 targets vascular cells of liver only



→ **This formulation targets endothelial cells in liver only**

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GN2205 RNA delivery platform

Payloads:

- ✓ mRNA
- ✓ siRNA

Liver target cells:

- ✓ Hepatocytes
- ✓ Endothelial cells
- ✓ Stellate cells
- ✓ Macrophages
- ✓ Pericytes
- x Cholangiocytes

→ **The LNP is suitable for RNA payloads and targets multiple liver cell types.**

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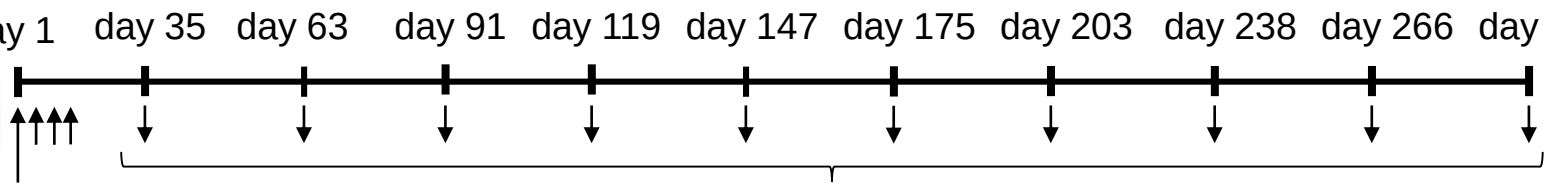
GN2205 co-delivery of guide RNA & spCas9-mRNA

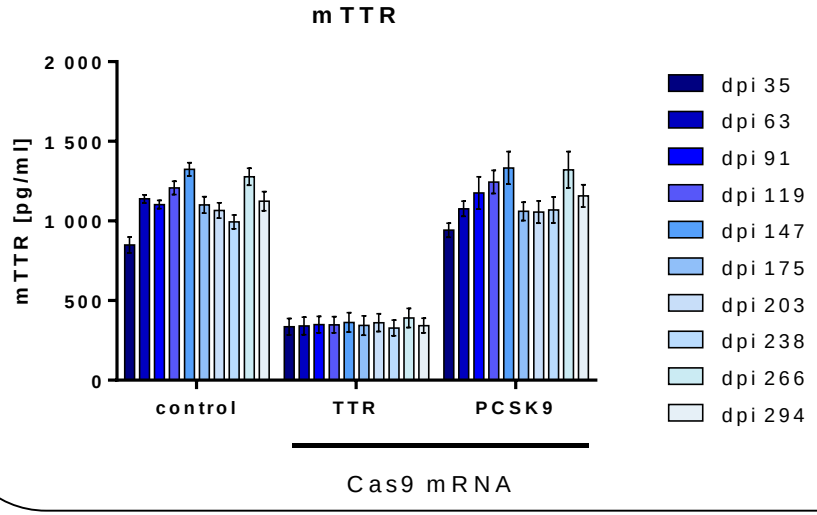


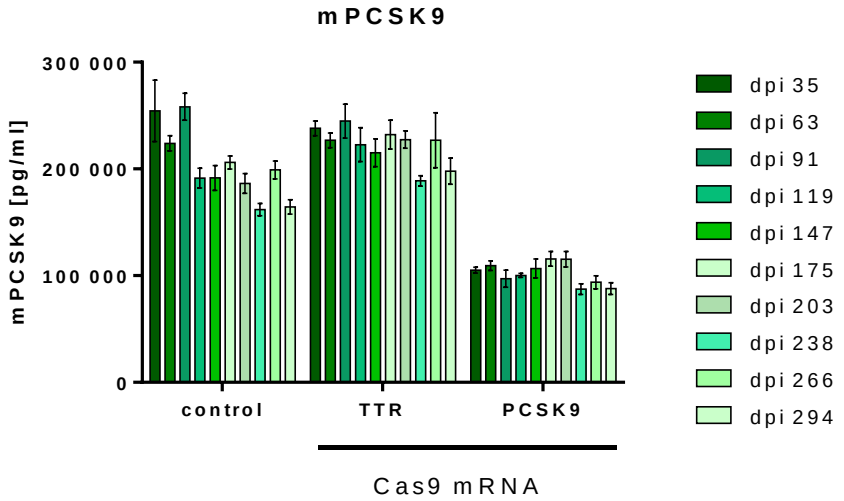




IV administration of 1mg/kg and 0.5 mg/kg mRNA & guide RNA
(Cas9-mRNA: Ψ & 5MeC, TriLink; guide RNA: Silence)
c57BL/6 (n=6)

quantification of serum protein at indicated time points by standardized ELISA & final genome analysis





→ **Long lasting partial knock out of liver expressed genes achieved with an entirely RNA based approach, using our LNP delivery system**

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Summary – LNP delivery approach



We have developed a liver targeting LNP-formulation that targets multiple cell types



Our LNP is suitable for efficient delivery of both siRNA and mRNA payloads



Co-delivery of Cas9 mRNA and guide RNA results in long lasting gene disruption *in vivo*

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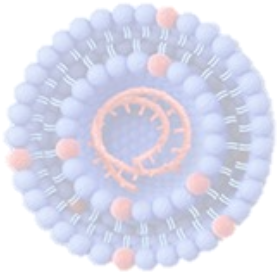
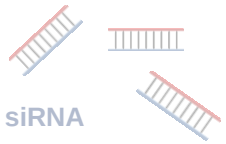
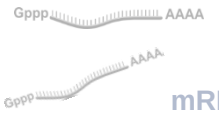
New Focus: siRNA conjugates



LNP approach



siRNA



mRNA



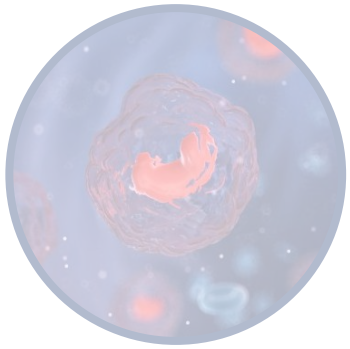
Gene editing payloads (CRISPR/Cas9)



Vasculature

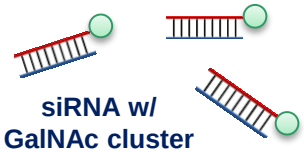


Liver



Macrophages

Conjugation approach



siRNA w/ GalNAc cluster



Hepatocytes

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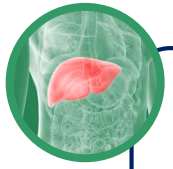
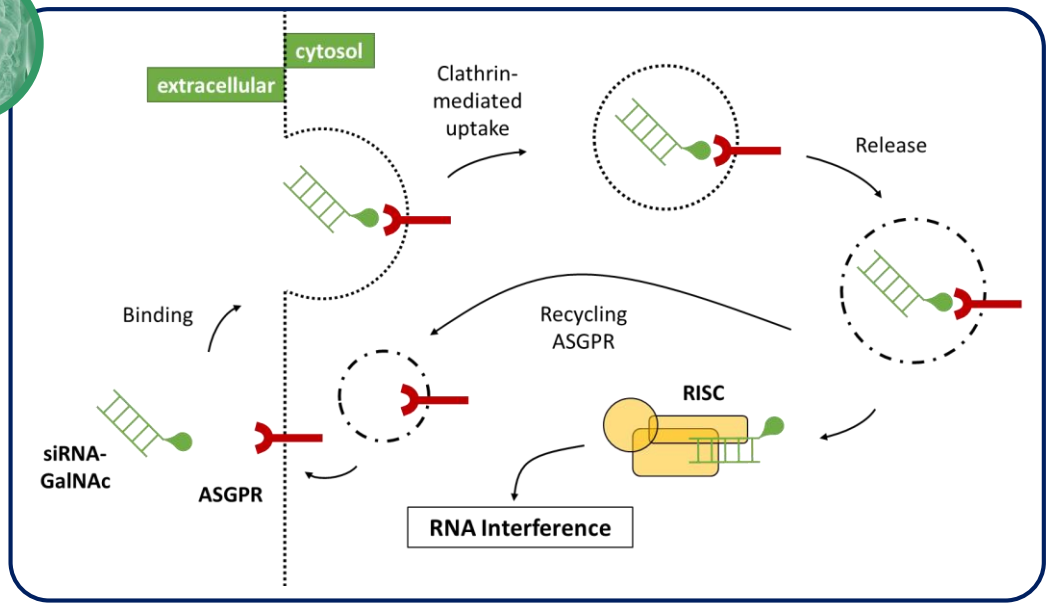
Hepatocyte delivery by GalNAc





Scheme based on information provided by **Essentials of Glycobiology. 2nd edition. Varki A, Cummings RD, Esko JD, et al., editors. Cold Spring Harbor (NY): Cold Spring Harbor Laboratory Press; 2009.**

- **GalNAc** linked to **siRNA**
- GalNAc binds to **a highly expressed ASGP receptor in hepatocytes**, which is endocytosed and can shuttle cargo into the cytoplasm of the cell
- ASGPR is **conserved across species**
- GalNAc-siRNA conjugates can be administered by **subcutaneous administration**

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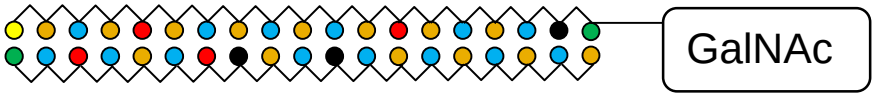
Key considerations for GalNAc-siRNA

siRNA payload extensively chemically modified

- with 2'-O-Me, 2'-F, PS & other
- to stabilized against nucleases in biofluids and cytoplasm
- to minimize immune stimulation
- to improve overall performance (therapeutic window)

Linker

- with optimized length and structure
- stabilized against degradation



GalNAc moiety

- polyvalent
- optimized for efficient transfer to the liver and hepatocytes

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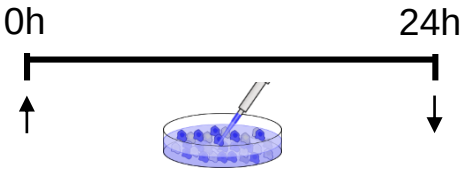
Knockdown of Target X using GalNAc-siRNA conjugates

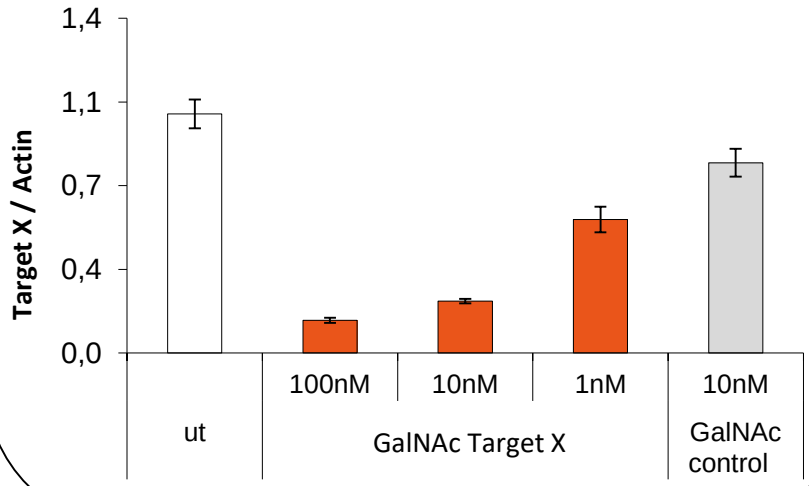
In vitro



Murine 1°Hepatocytes
GalNAc-siRNA conjugate

RT-PCR
quantification
of transcripts

Target X gene expression 24h post treatment (mean ± SD)



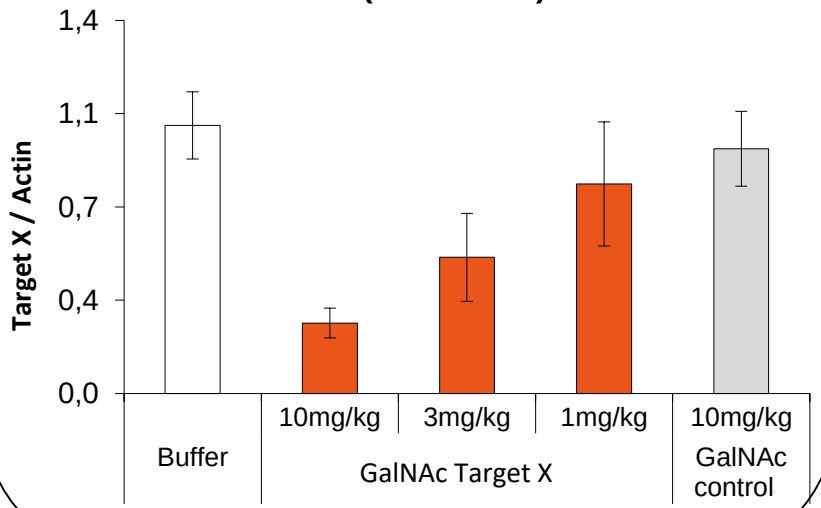
In vivo



s.c. administration
GalNAc-siRNA conjugate
c57BL/6 (n=4)

RT-PCR
quantification
of transcripts

Target X gene expression 48h post treatment (mean ± SD)



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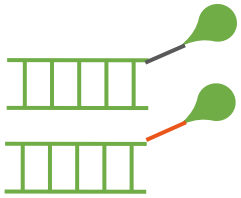
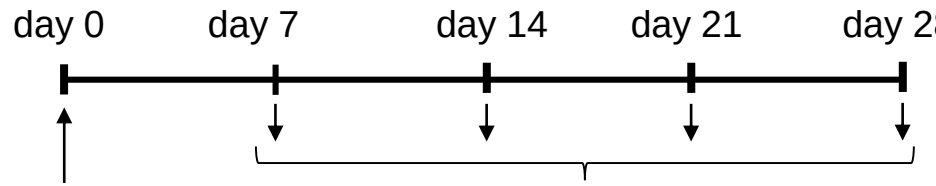
Duration of knockdown in mice (2nd vs 3rd gen. GalNAc)

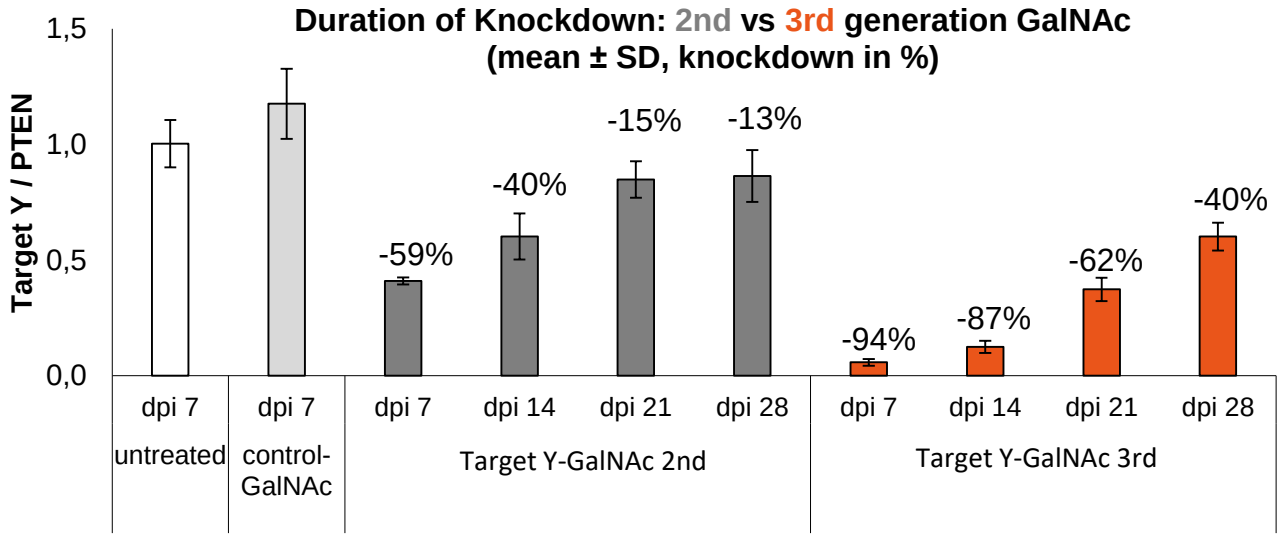






2nd & 3rd gen. GalNAc-siRNA, s.c., 2 mg/kg c57BL/6 (n=4)

RT-PCR quantification of transcripts



→ **Improved knockdown achieved with 3rd generation GalNAc-linker**

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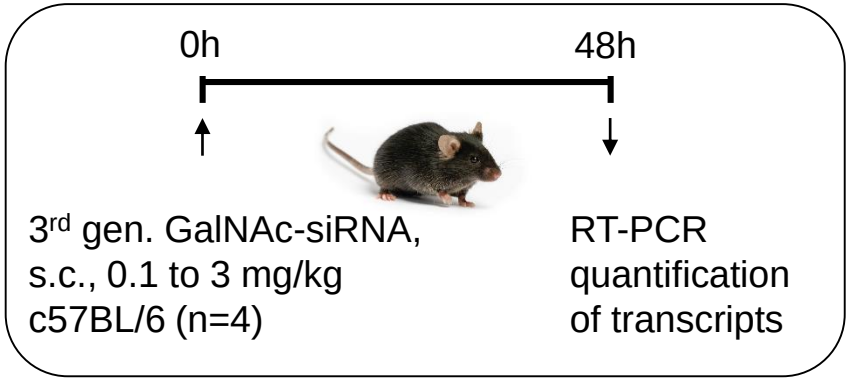
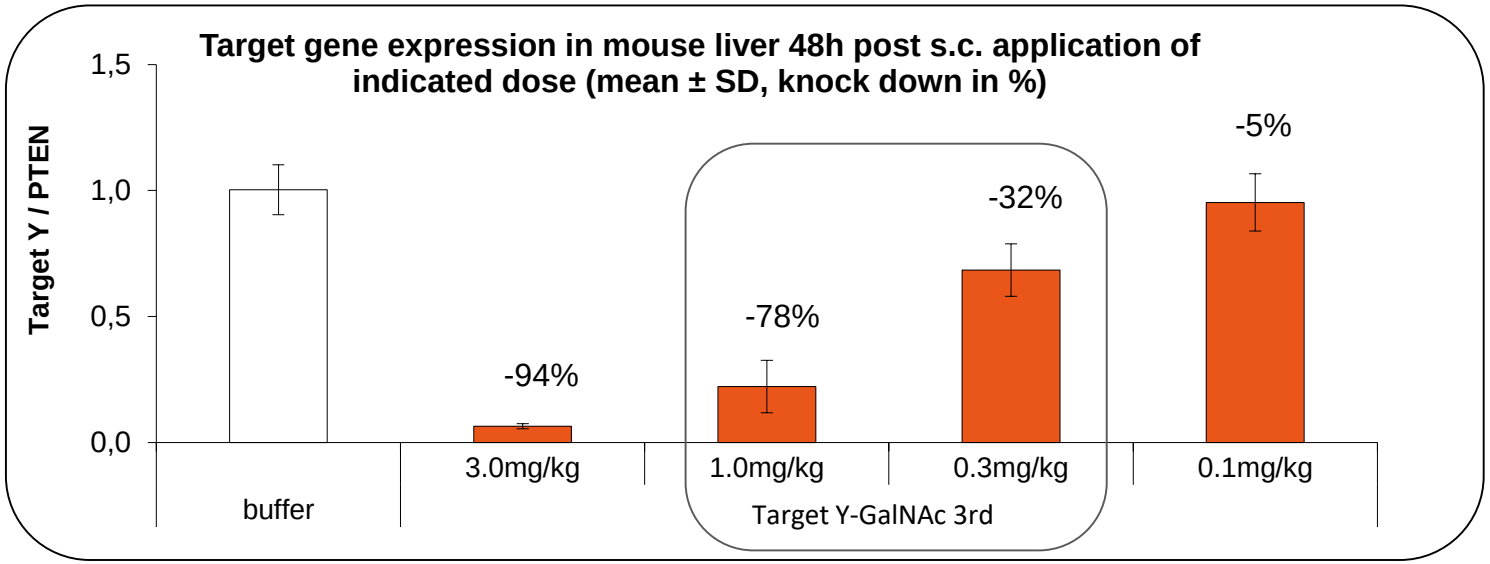
Dose Response to GalNAc-siRNA (3rd gen) in mice





→ **Decent dose response with 3rd generation GalNAc-linker**

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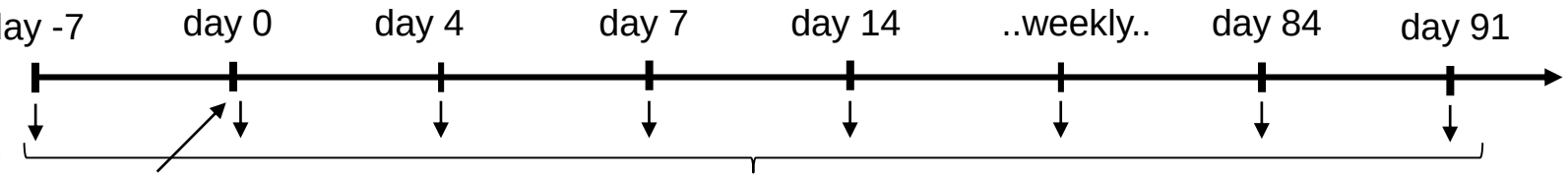
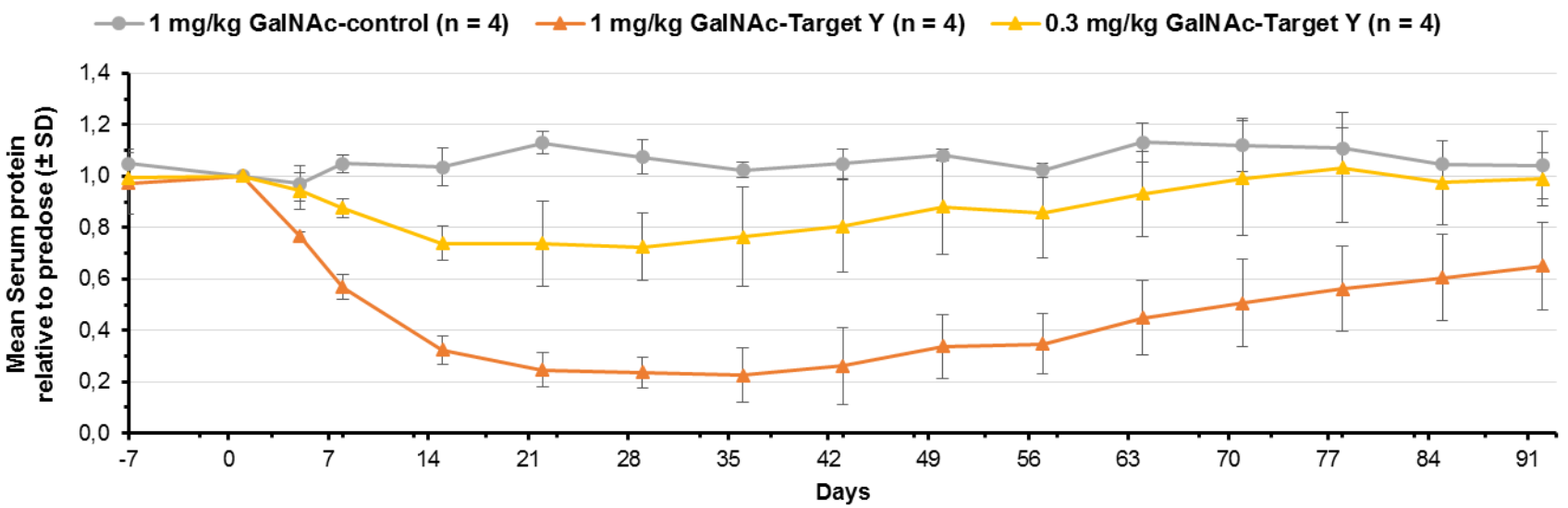
Long-lasting knockdown with 3rd gen. GalNAc siRNA conjugates in NHP





s.c. administration of 3rd gen. GalNAc-siRNA,1 and 0.3 mg/kg (n=4)

quantification of serum protein Target Y at indicated time points



→ **Duration and dose response of knockdown translates from mouse to NHP**

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Safety parameters of 3rd generation GalNAc conjugate in NHP

Changes in cytokine levels expressed as fold (×) of the predose group mean values

		Cytokine	GalNAc-Target Y				GalNAc-control	
			0.3 mg/kg b.w.		1.0 mg/kg b.w.		1.0 mg/kg b.w.	
			males	females	males	females	males	females
Day 1	2 h after s.c. administratio	IL-7	3	none	none	2	none	none
		IL-8	0.6	0.2	0.2	0.4	0.3	0.5
		MIP-1b	3	3	none	none	none	none
	6 h after s.c. administratio	IL-7	2	2	none	none	none	2
		MIP-1b	none	2	none	none	0.6	none
Day 2	24 h after administratio	IL-7	0.7	none	0.5	2	0.6	0.7
		IL-8	0.7	0.7	0.4	none	none	none
		MIP-1b	none	2	0.6	none	0.5	0.6
Day 4	72 h after administratio	IL-7	none	0.6	0.6	none	0.5	0.4
		IL-8	none	0.6	0.5	none	none	none
		MIP-1b	0.7	none	0.3	none	0.4	none

- no altered pro-inflammatory cytokines (IL-7, IL-8, MIP-1)
- no skin reaction
- no behavioral conspicuousness

→ **Well tolerated in higher species**

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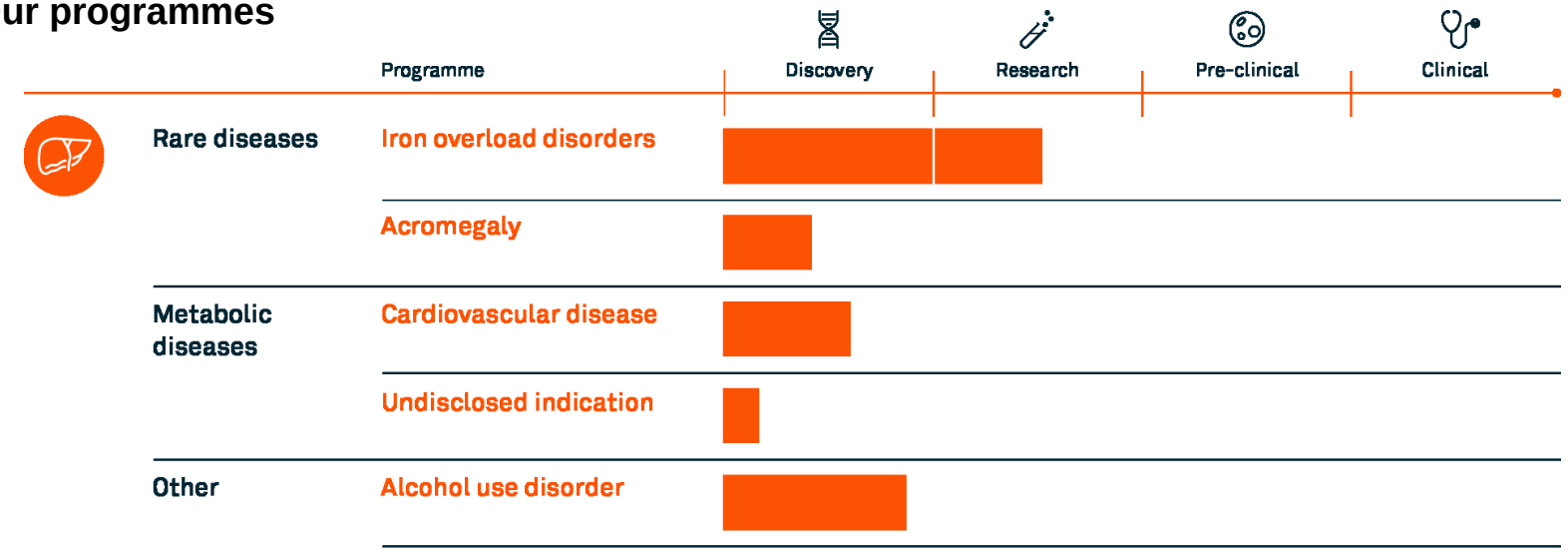
Our pipeline

Our programmes



Out-licensed programmes (AtuRNAi™)



Quark NOVARTIS

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Summary – GalNAc conjugates

Progress made in our new focus area:

- Improved GalNAc linker results in increased potency and duration of effect
- GalNAc-siRNA conjugates successfully translated from mouse to NHP
- Well tolerated in all species tested
- Established a GalNAc-siRNA based pipeline across several therapeutic areas (included rare and metabolic)

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Acknowledgements

Silence Berlin & London Team





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Thank you!

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