Therapeutic RNA delivery: into hepatocytes and beyond

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Our mission: Establish a clinically viable technology platform for therapeutic RNAs

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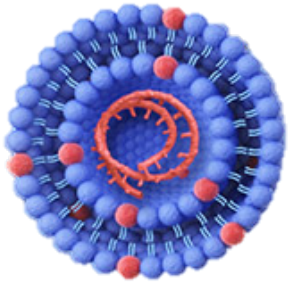
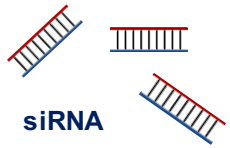
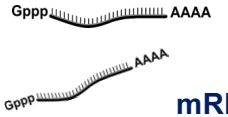


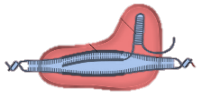
Particle approach



siRNA



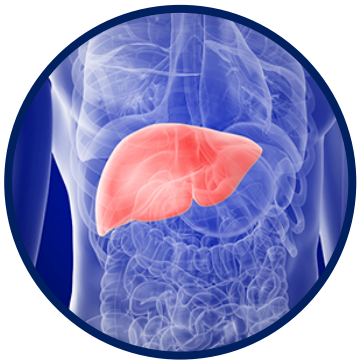
mRNA



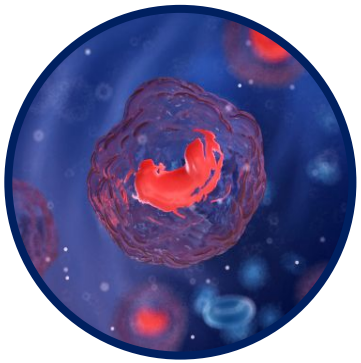
Gene editing payloads (CRISPR/Cas9)



Vasculature

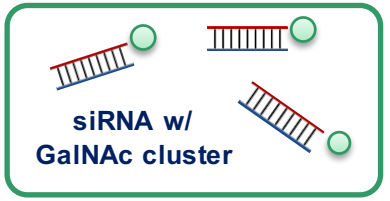


Liver

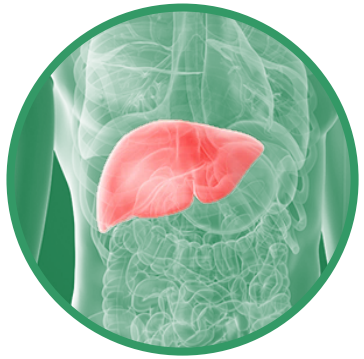


Macrophages

Conjugation approach



siRNA w/ GalNAc cluster



Hepatocytes

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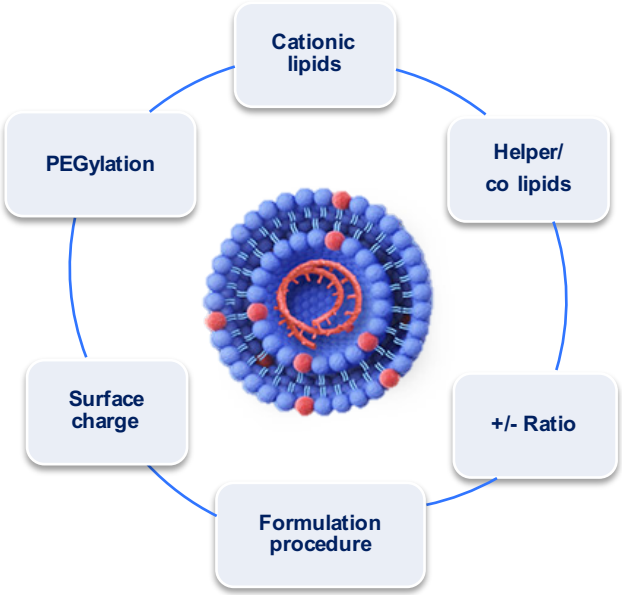
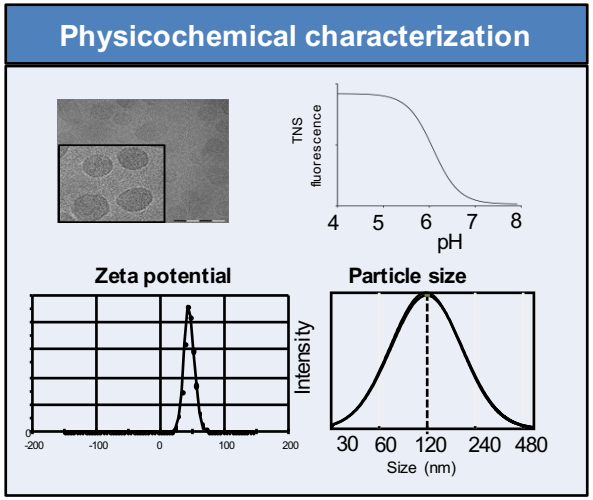
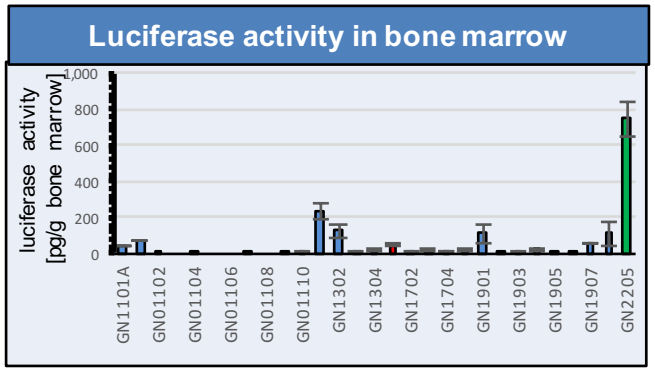
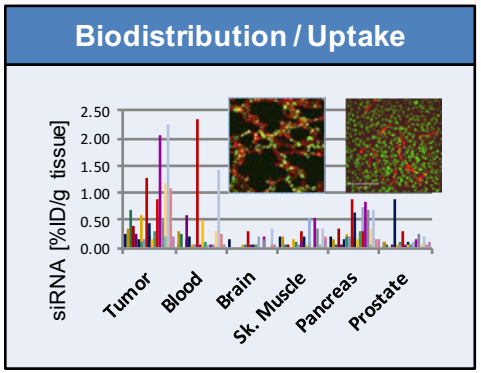
Technology platform to generate novel delivery systems









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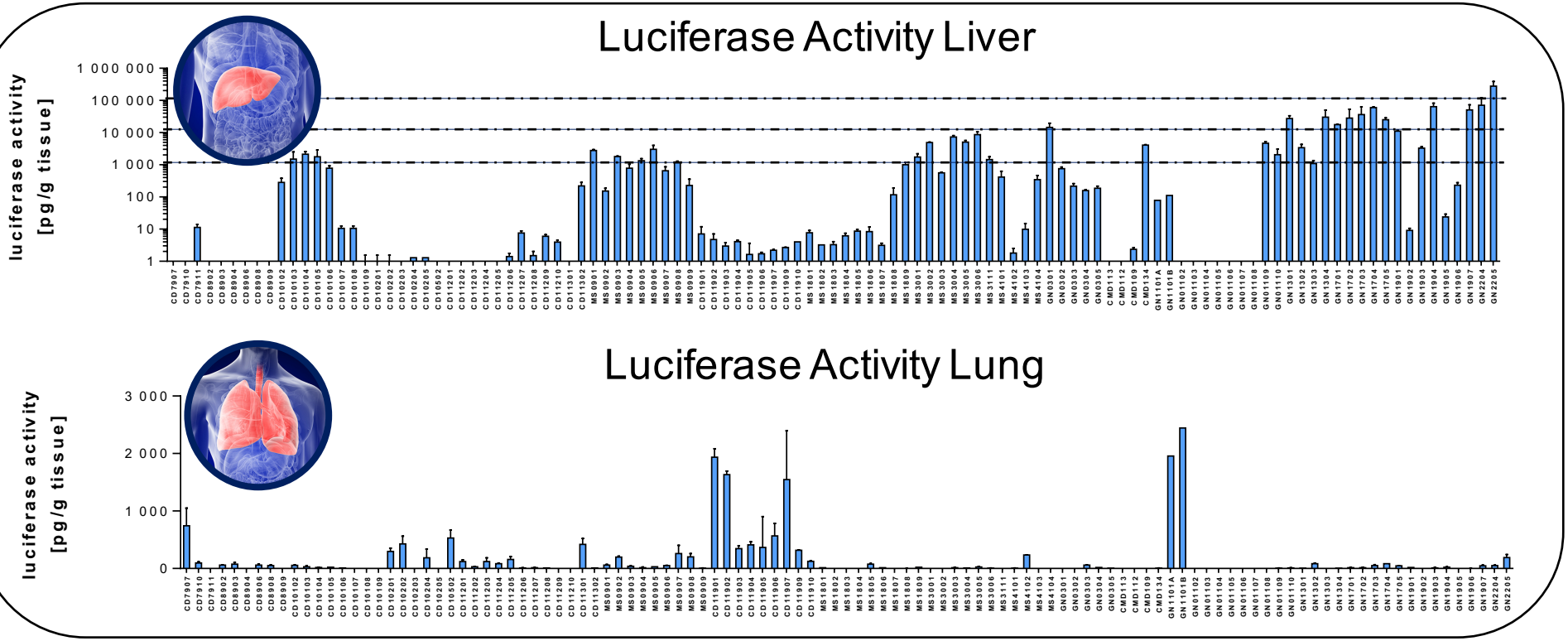
Screening for biodistribution of functional mRNA delivery *in vivo*

IV administration of
1mg/kg mRNA (FLuc; Ψ & 5MeC; TriLink)
C57BL/6 (n=2)



ex vivo quantification of luciferase activity in tissue lysates (liver, lung, spleen, kidney, bone marrow, brain, heart)



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Time course and biodistribution of GN2205 functional luciferase mRNA delivery



scid beige

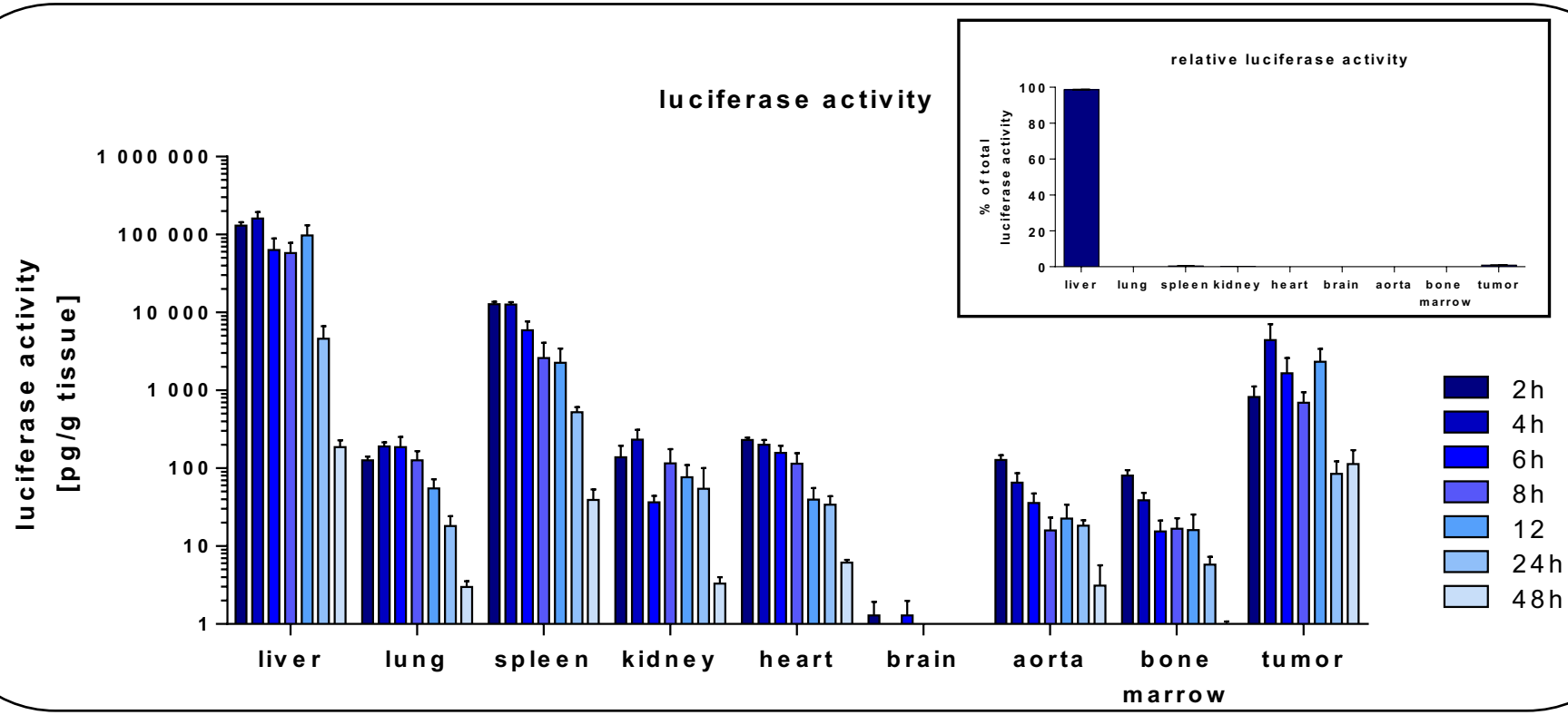
Hep3B (5x10^6 cells s.c.)

-19 days

IV administration of 1mg/kg mRNA
(FLuc; Ψ; 5MeC; TriLink)
(tumor size ~350mm³, n=6)

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

ex vivo quantification of luciferase activity in tissue lysates



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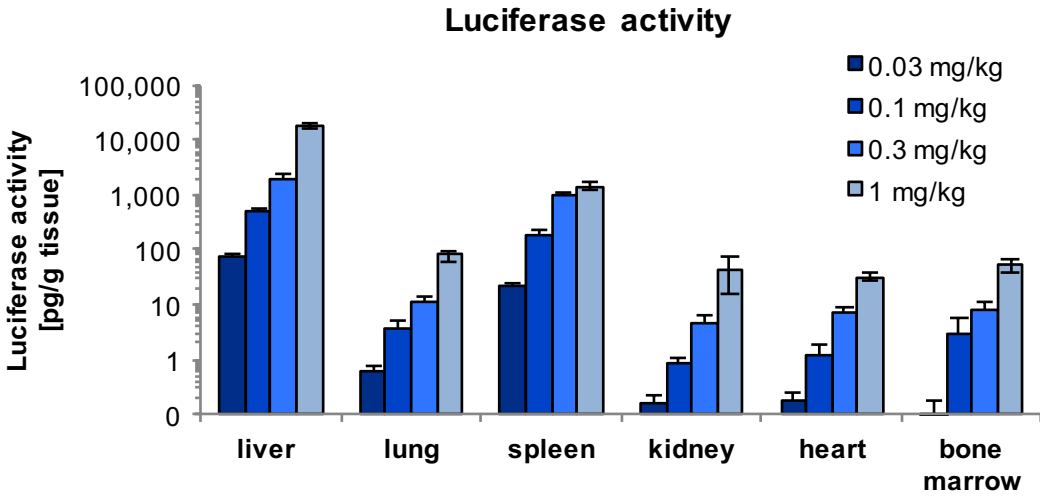
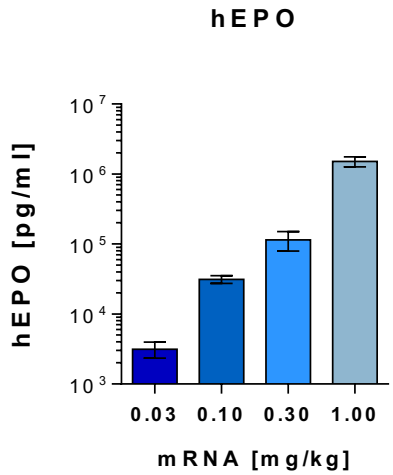
Dose response to GN2205 with hEPO and FLuc mRNA

IV administration of 1mg/kg mRNA
(FLuc or hEPO; Ψ & 5MeC; TriLink)
C57BL/6 (n=6)



ex vivo quantification of luciferase activity in tissue lysates or hEPO in EDTA-plasma





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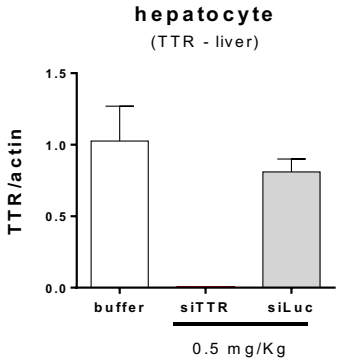
GN2205 siRNA delivery in the liver

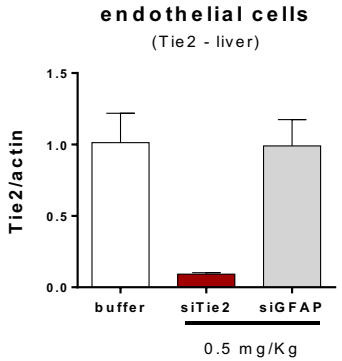
0h — 48h

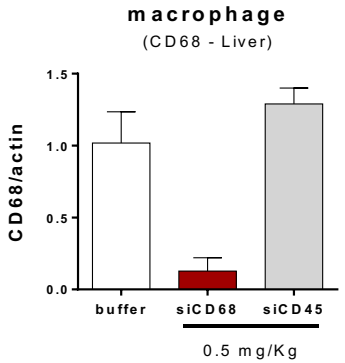


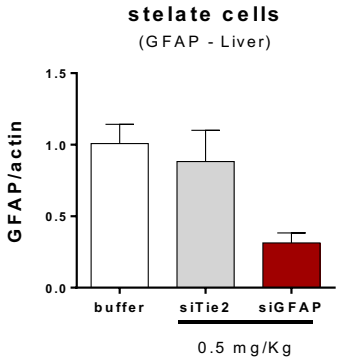
IV administration
0.5 or 1.0 mg/kg
siRNA (Silence)
C57BL/6 (n=4-6)

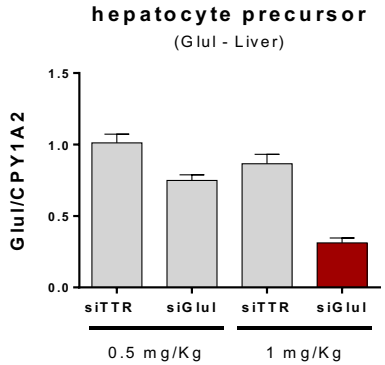
RT-PCR
quantification
of transcripts

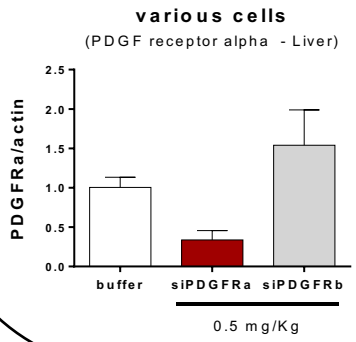


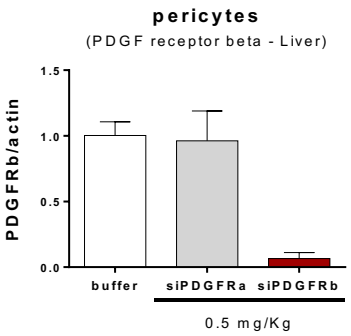


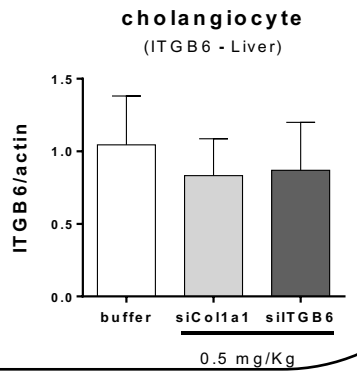












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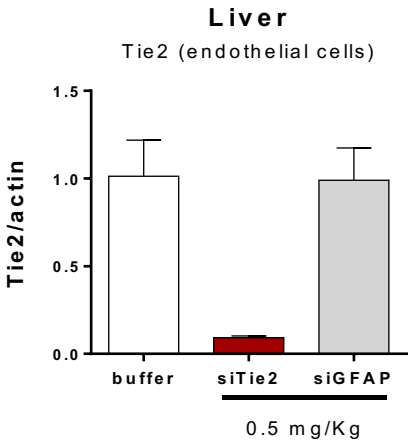
GN2205 targets vascular cells in liver

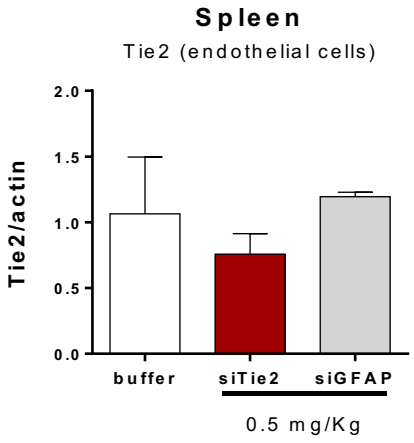
0h → 48h

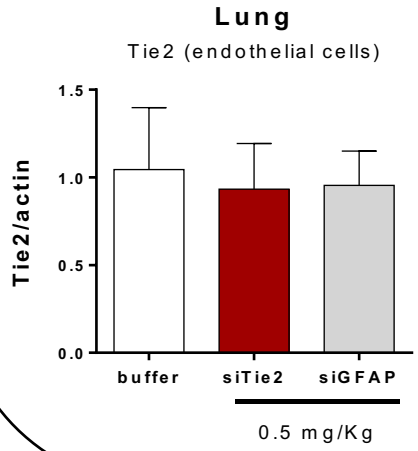


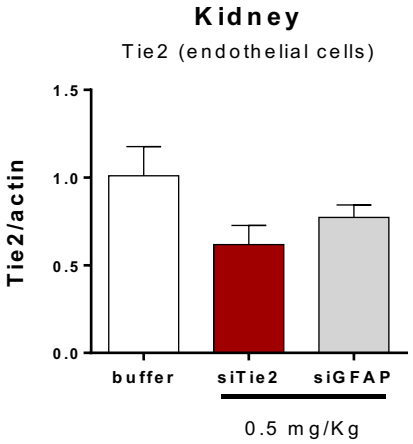
IV administration
0.5 mg/kg siRNA
(Silence)
C57BL/6 (n=4-6)

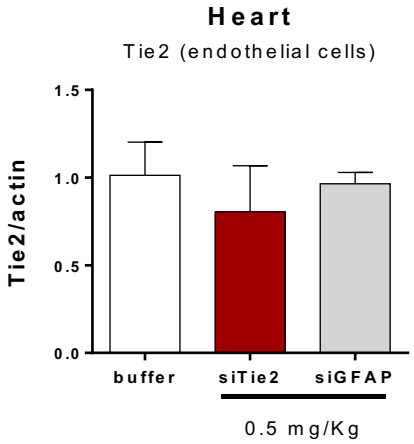
RT-PCR
quantification
of transcripts











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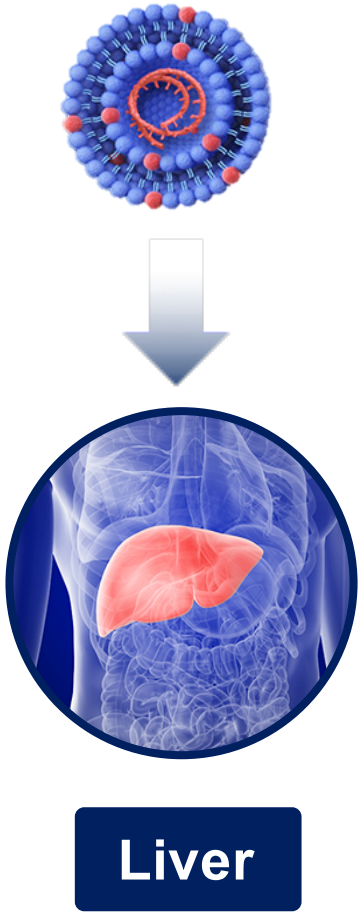
GN2205 RNA delivery platform



Liver:

- ✓ Hepatocytes & hepatocyte precursors
- ✓ Endothelial cells
- ✓ Stellate cells
- ✓ Macrophages
- ✓ Pericytes
- x Cholangiocytes

Spleen, Lung, heart & kidney:

- x Endothelial cells

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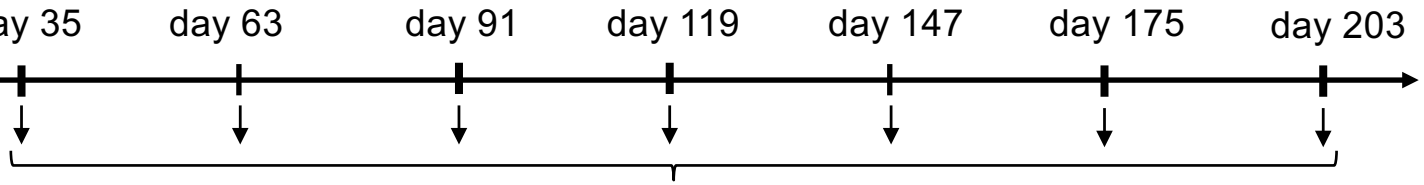
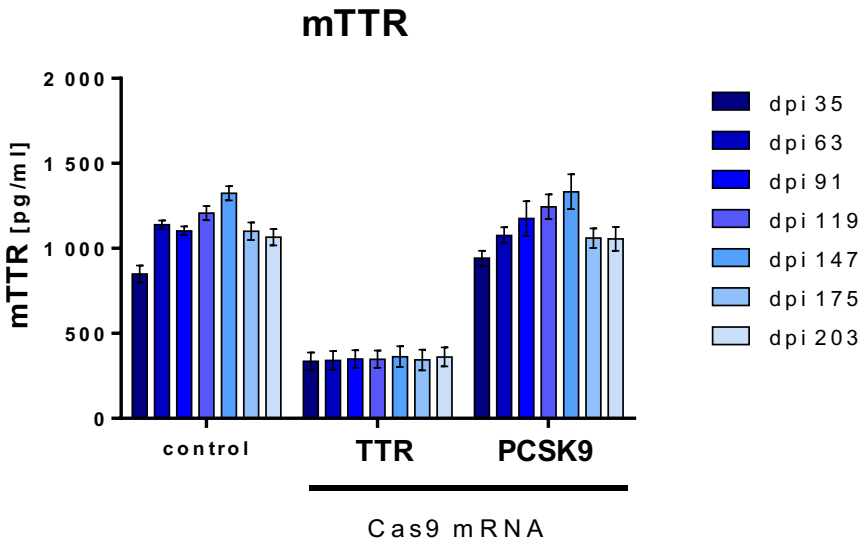
GN2205 co-delivery of guide RNA & spCas9-mRNA

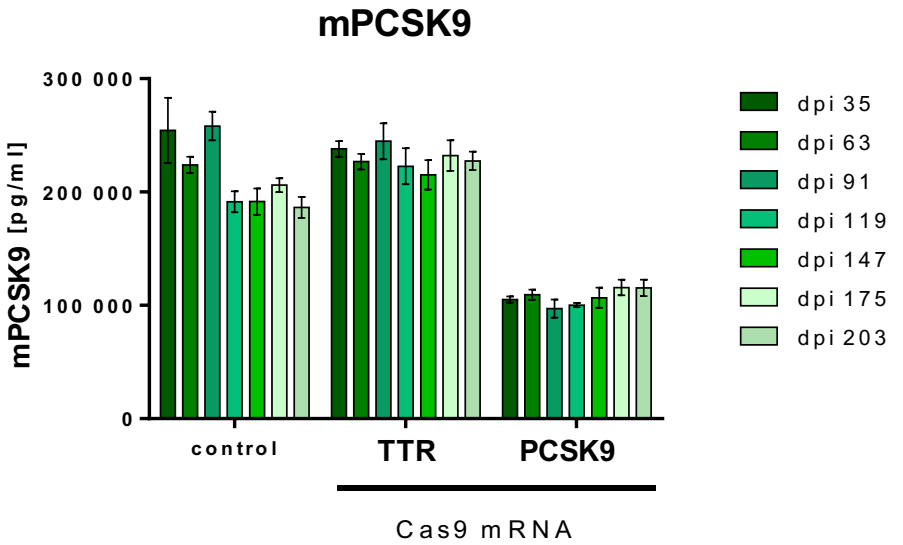




IV administration of 1mg/kg and 0.5 mg/kg mRNA & guide RNA
(Cas9-mRNA: Ψ & 5MeC, TriLink; guide RNA: Silence)
c57BL/6 (n=6)

quantification of serum protein at indicated time points by standardized ELISA





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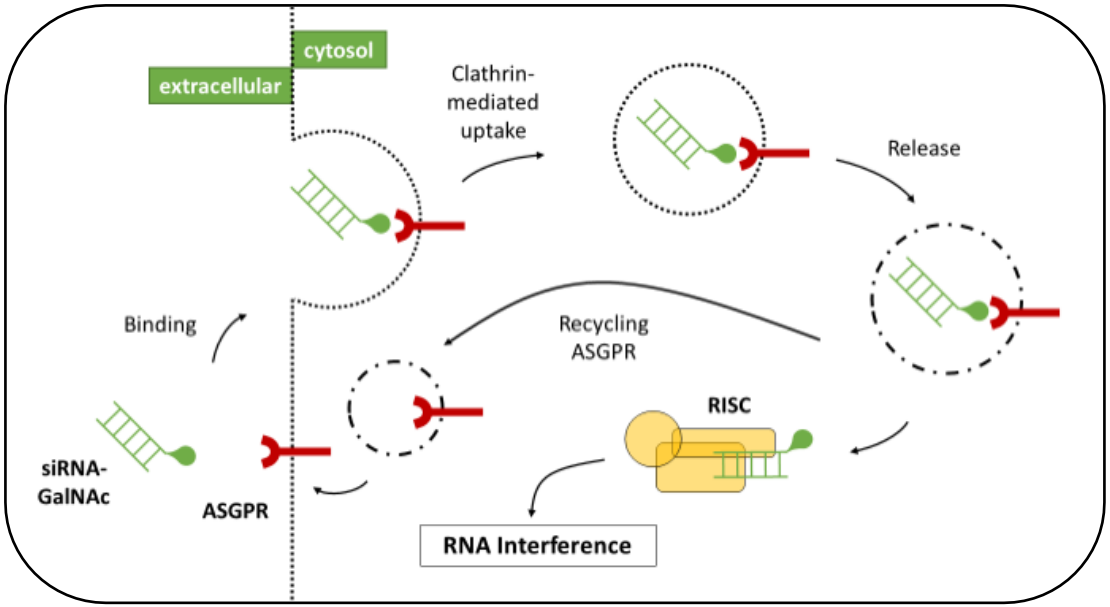
What are GalNAc-siRNA conjugates?



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-siRNA conjugate is a delivery platform

- contains **GalNAc cluster** linked to **siRNA**
- binds to **a highly expressed ASGP receptor in hepatocytes**, which is internalized and can shuttle cargo into the cell
- Receptor is **conserved across species**
- GalNAc-siRNA can be delivered **subcutaneously**

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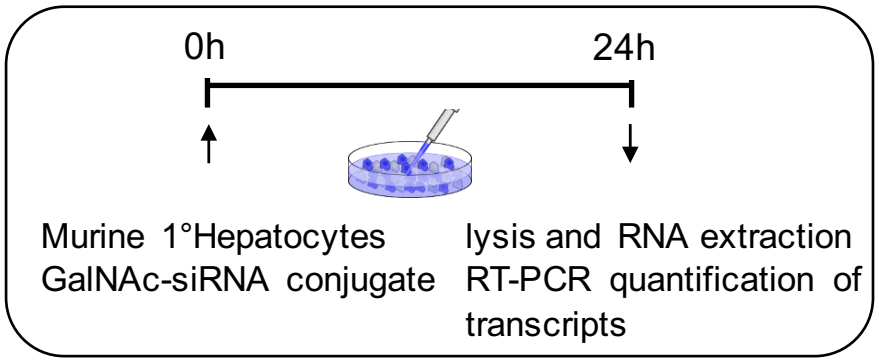
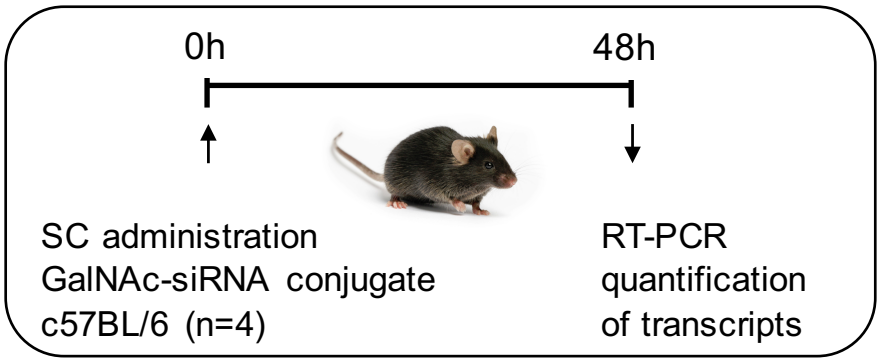
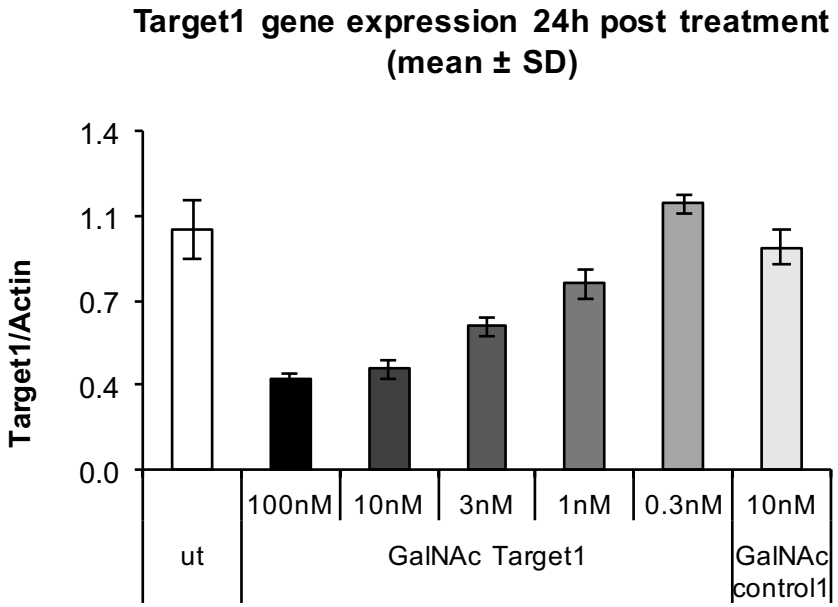
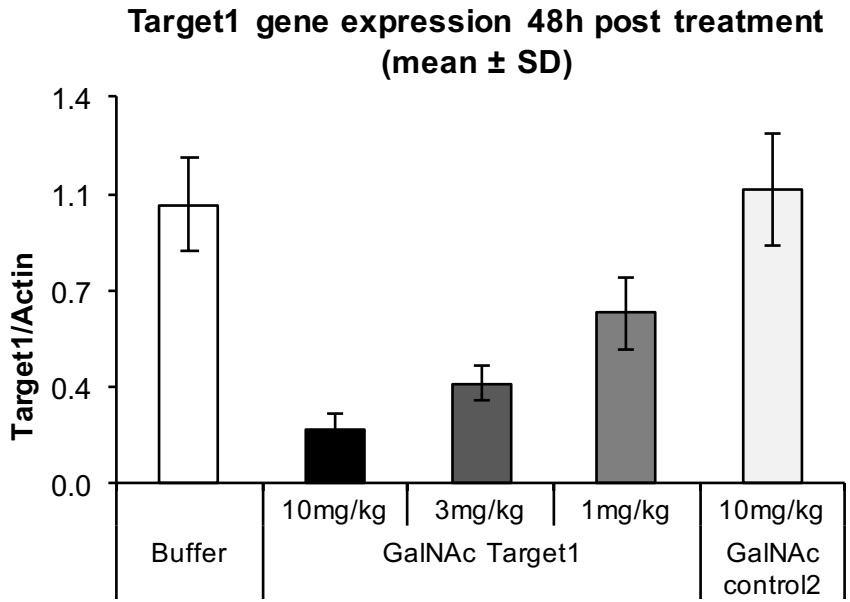
Knockdown of ubiquitous Target1 using GalNAc siRNA conjugates









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Knockdown of Target2 using GalNAc siRNA conjugates

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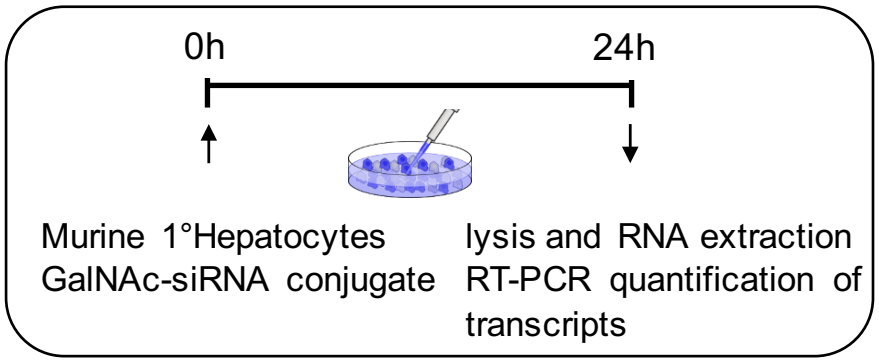

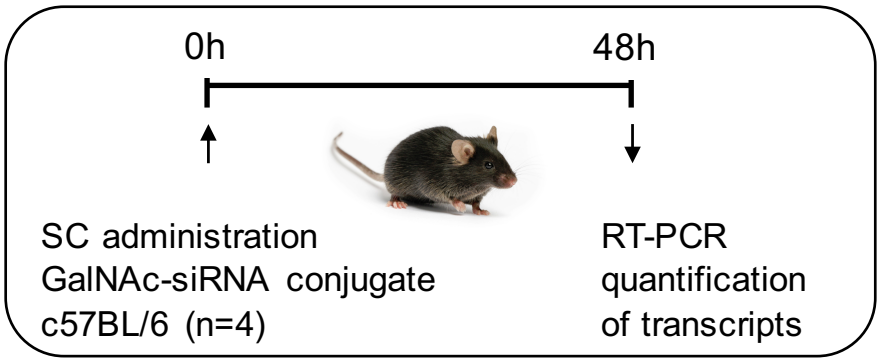

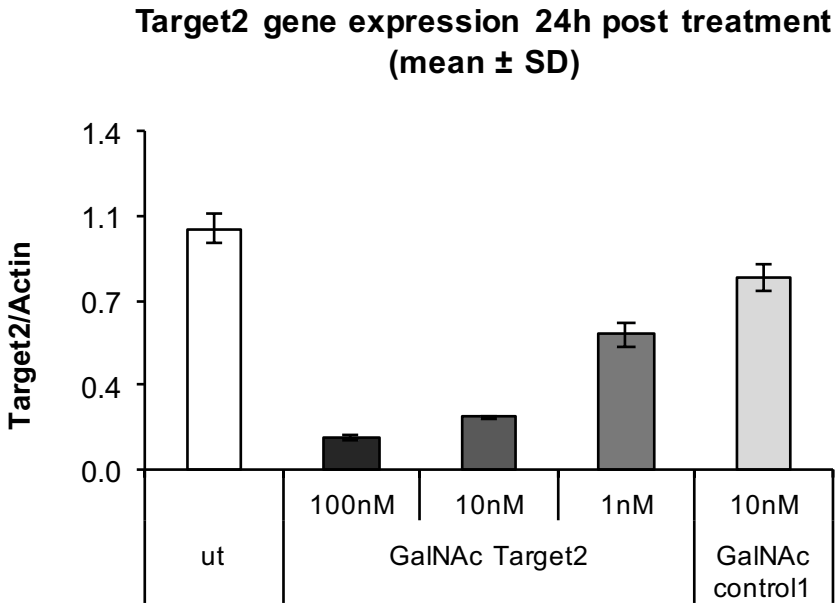

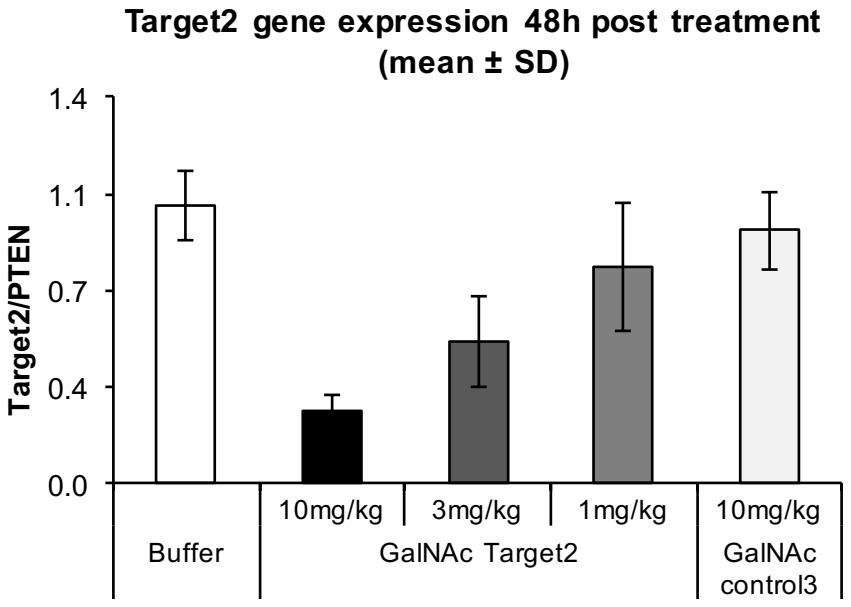

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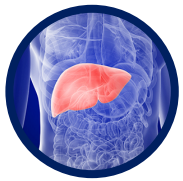
Summary



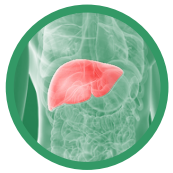
Experience to transfer siRNA formulation into mRNA delivery system



Identified LNP with 100 × fold activity in liver
Targeting multiple cell types in the liver



co-delivery of Cas9 mRNA and guide RNA results in long lasting gene disruption



Proprietary ST siRNA payload and ST GalNAc chemistry for delivery to hepatocytes

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Acknowledgement



Formulation team: Gemma Navarro

Biology Team: Ute Schaeper

Adrien Weingärtner

Vivarium: Birgit Durieux

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