Hepatic Gene Disruption In Vivo After Liposomal Delivery of Cas9 mRNA and Chemically Modified Guide RNAs

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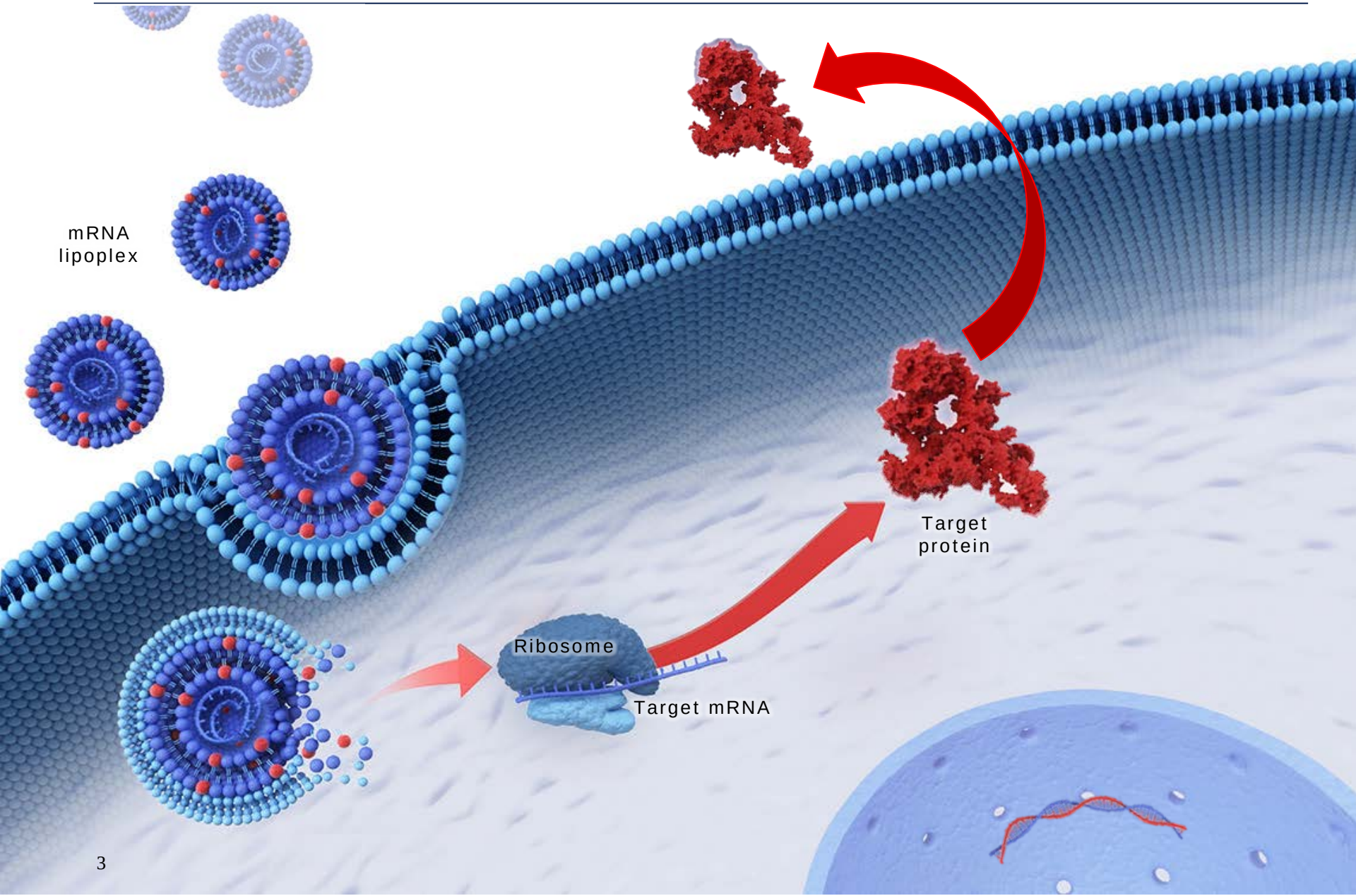
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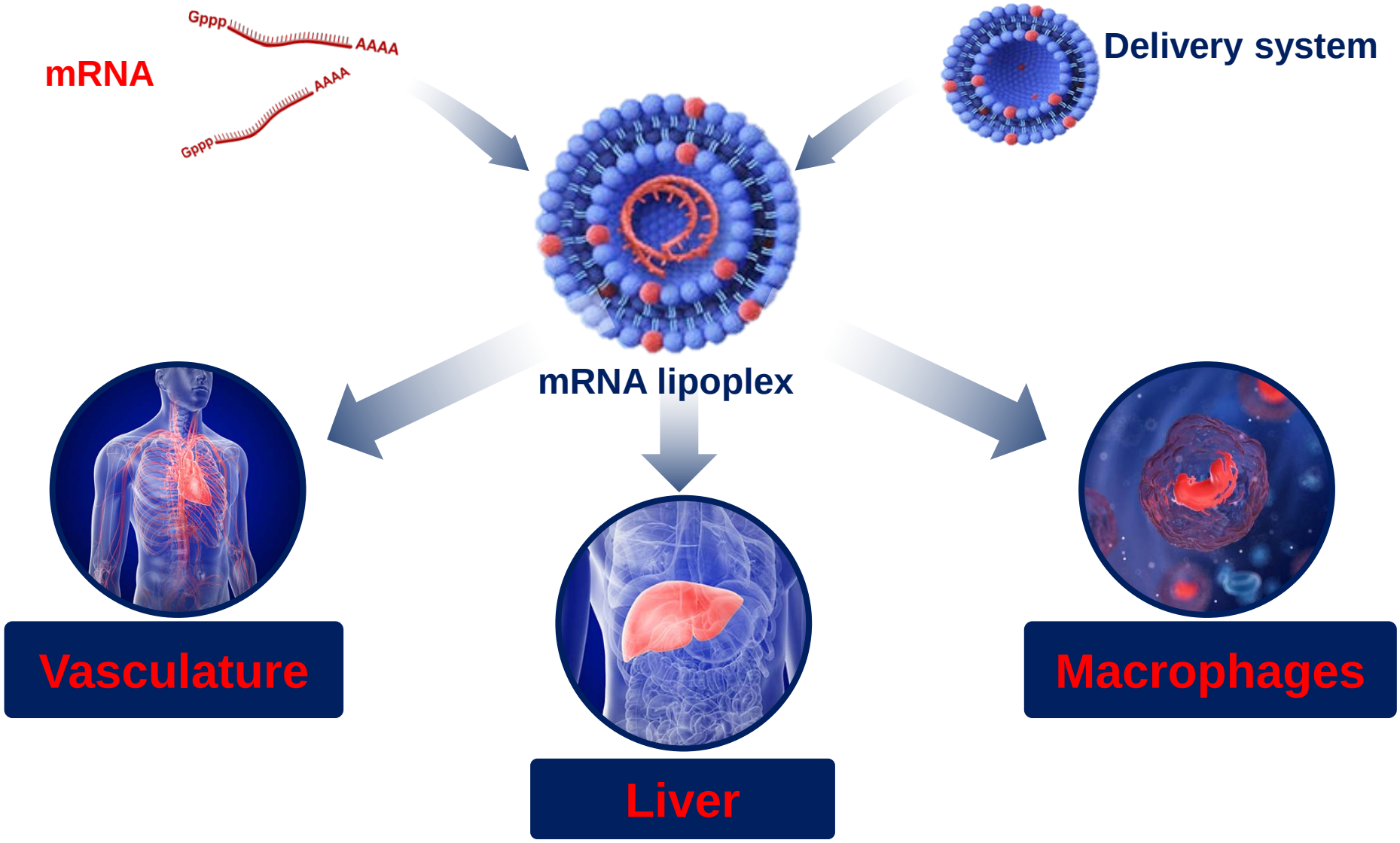
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mRNA Delivery

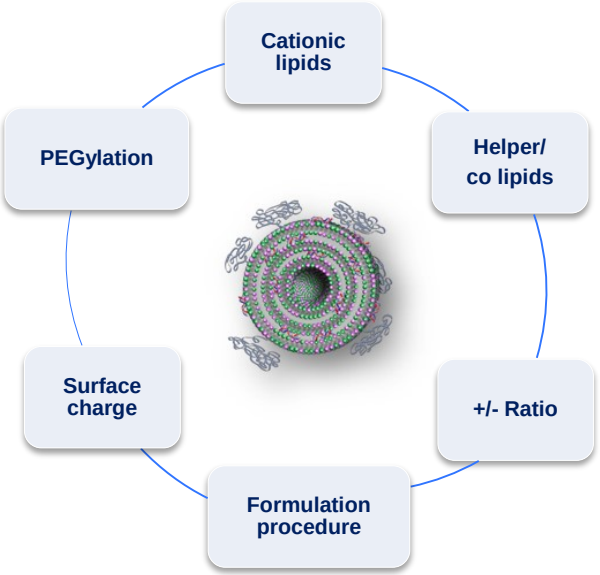


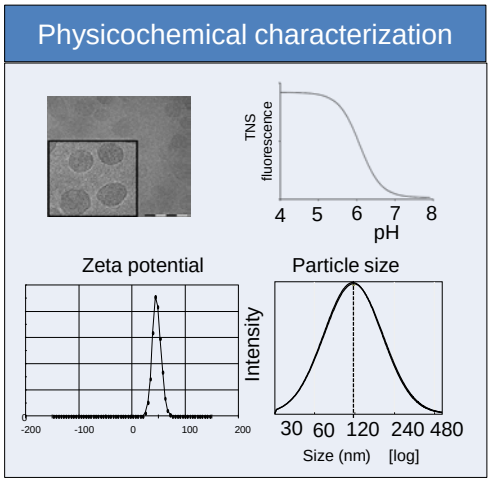
Our mission: Establish a clinically viable technology platform for therapeutic mRNAs

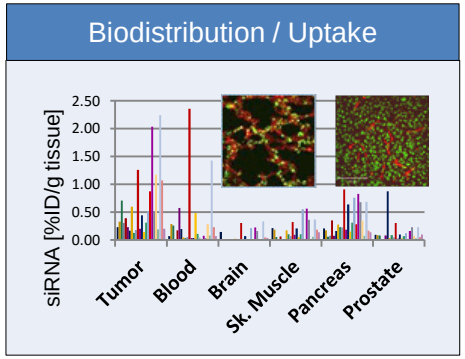


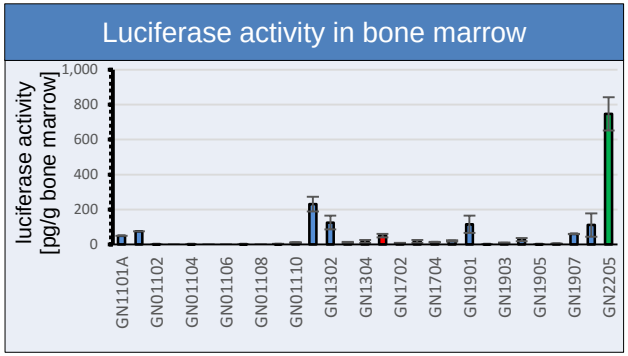
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Technology platform to generate novel delivery systems









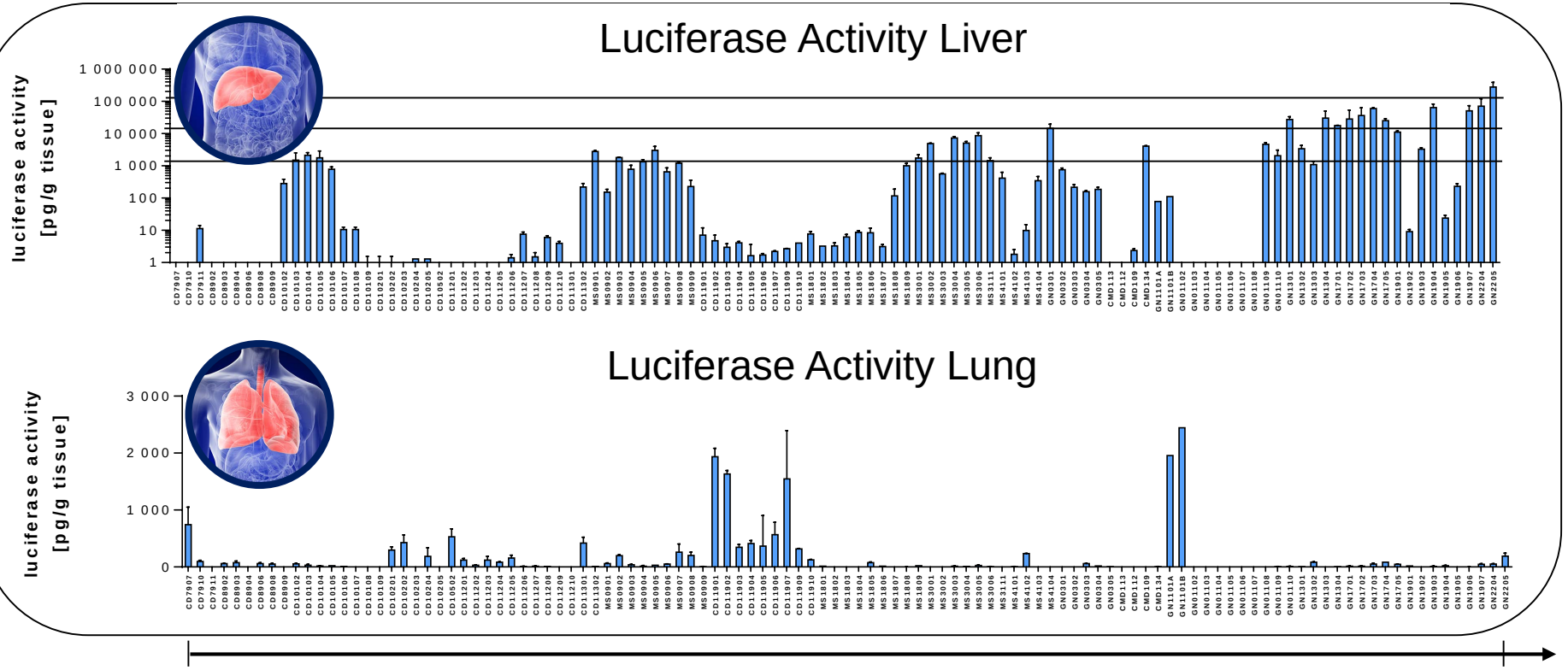
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Screening for biodistribution of functional mRNA delivery in vivo

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

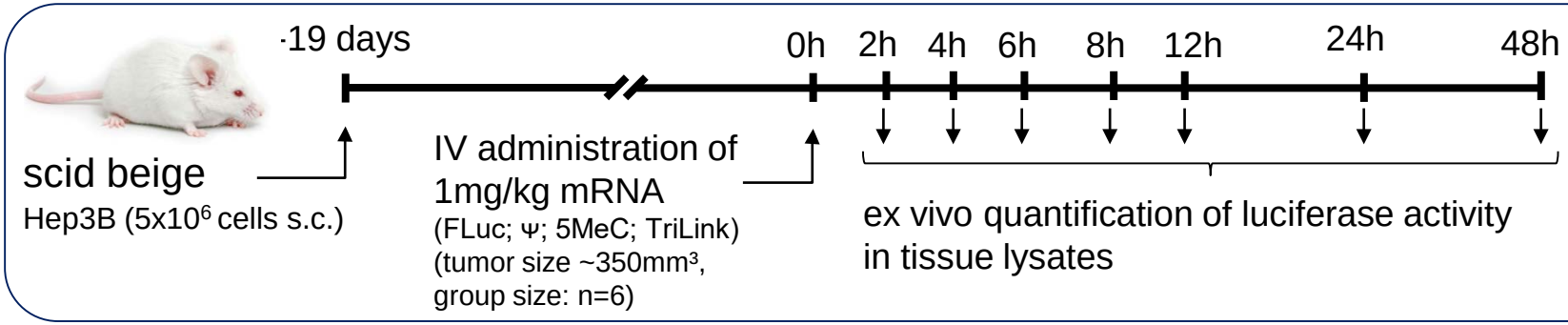


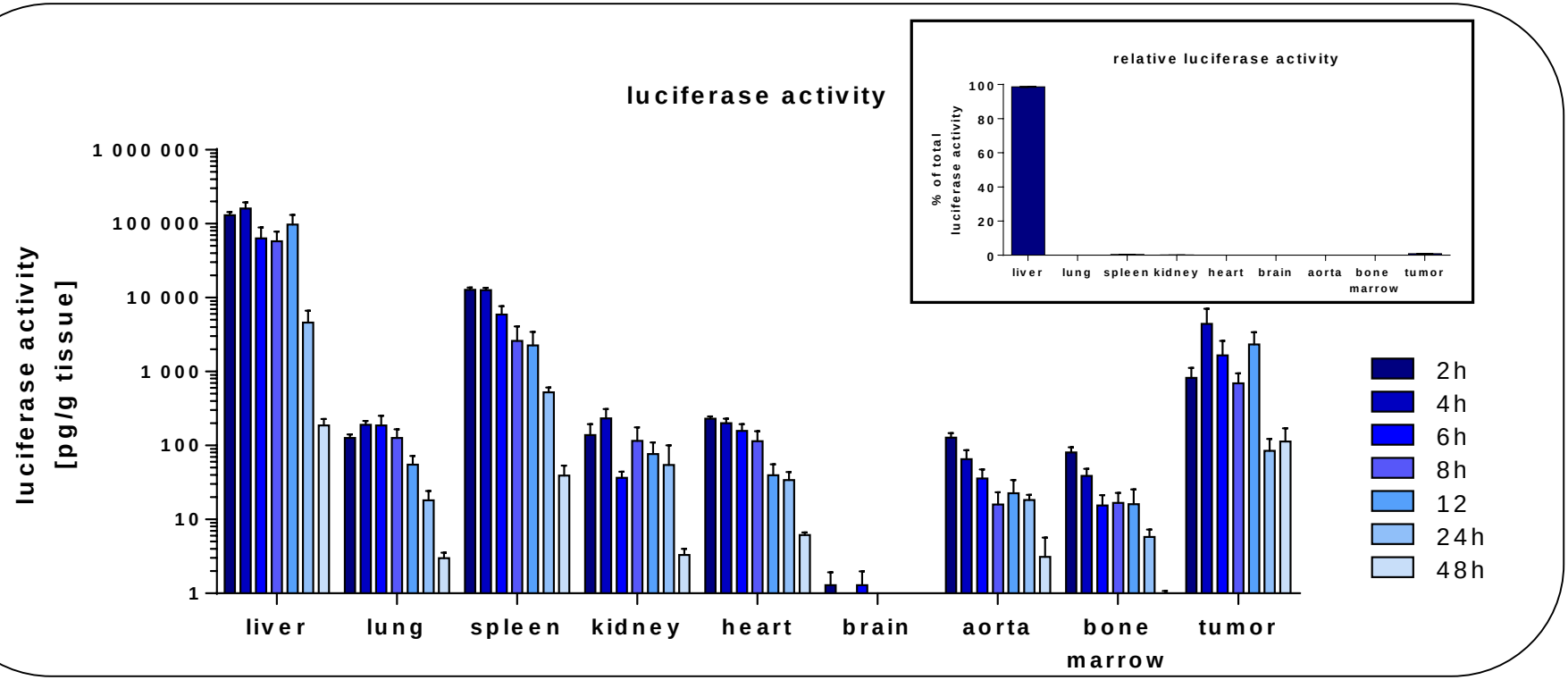
ex vivo quantification of luciferase activity in tissue lysates (liver, lung, spleen, kidney, bone marrow, brain, heart)



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Time course and biodistribution of GN2205 functional luciferase mRNA delivery





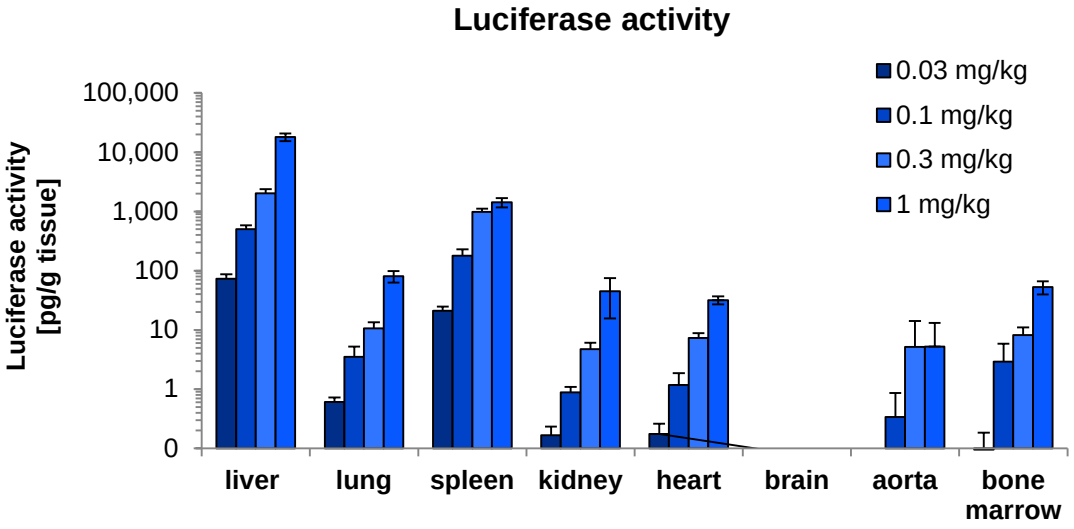
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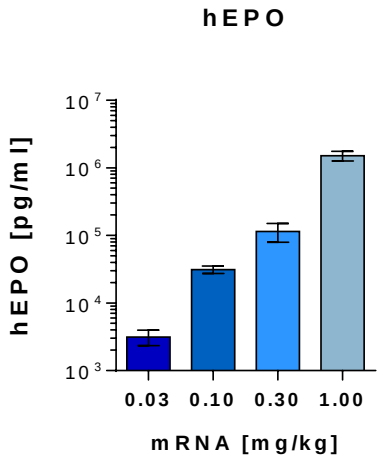
Dose response to GN2205 with hEPO and FLuc mRNA

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



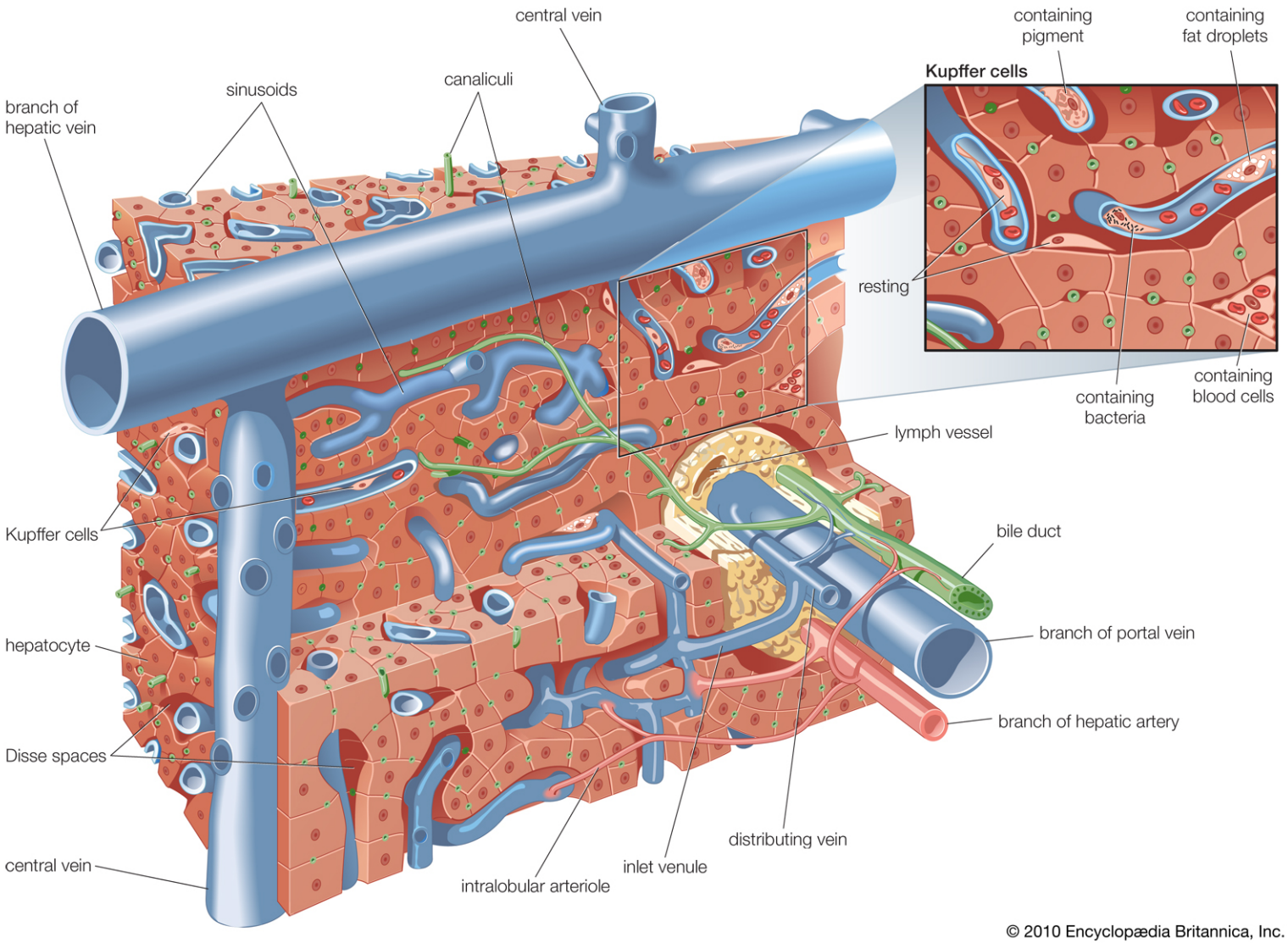
ex vivo quantification of luciferase activity in tissue lysates or hEPO in EDTA-plasma





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Topology of the liver



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GN2205 siRNA delivery in the liver

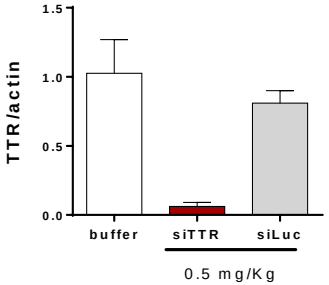
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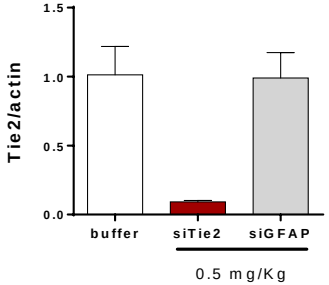
IV administration
0.5 or 1.0 mg/kg
siRNA (Silence)
C57BL/6 (n=4-6)

RT-PCR
quantification
of transcripts

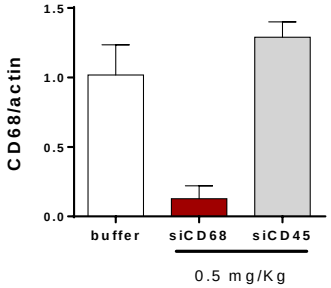
hepatocyte
(TTR - liver)



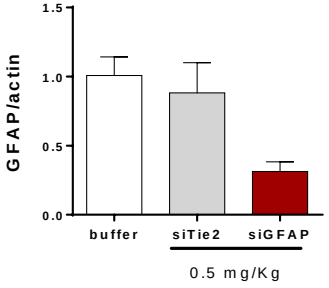
endothelial cells
(Tie2 - liver)



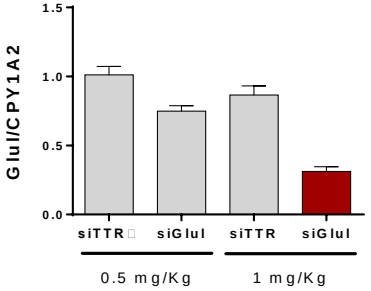
macrophage
(CD68 - Liver)



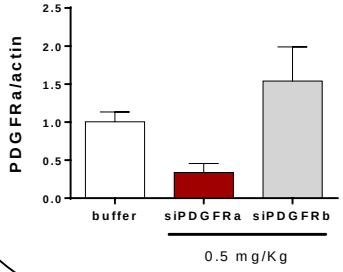
stelate cells
(GFAP - Liver)



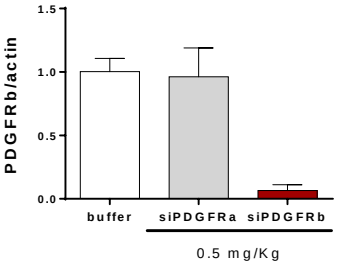
hepatocyte precursor
(Glul - Liver)



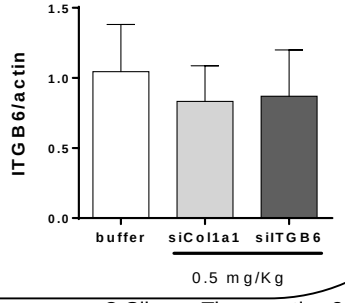
various cells
(PDGF receptor alpha - Liver)



pericytes
(PDGF receptor beta - Liver)



cholangiocyte
(ITGB6 - Liver)



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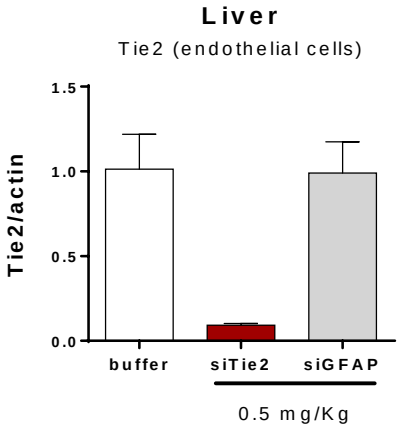
GN2205 targets vascular cells in liver

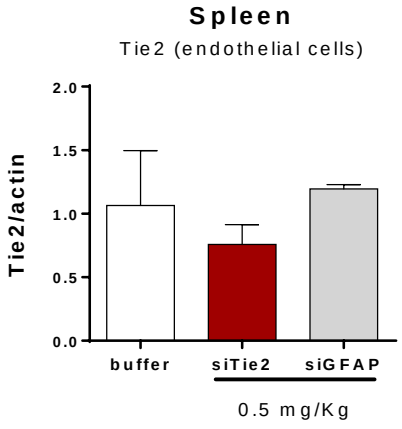
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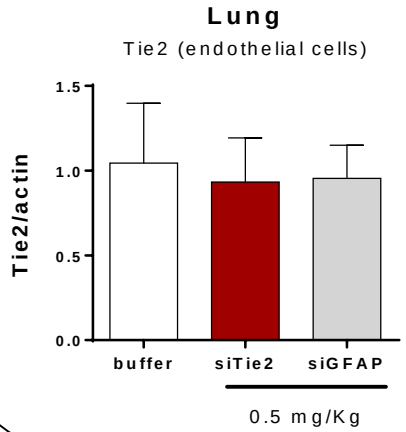


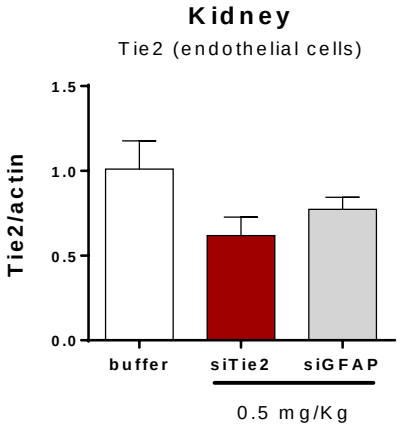
IV administration
0.5 mg/kg siRNA
(Silence)
C57BL/6 (n=4-6)

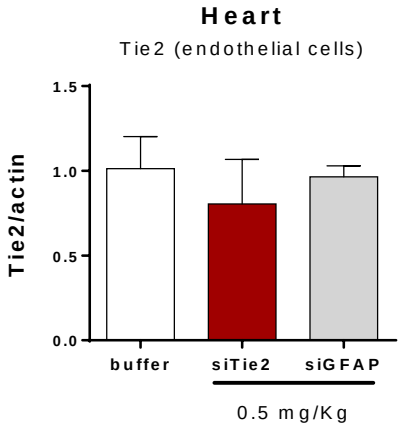
RT-PCR
quantification
of transcripts





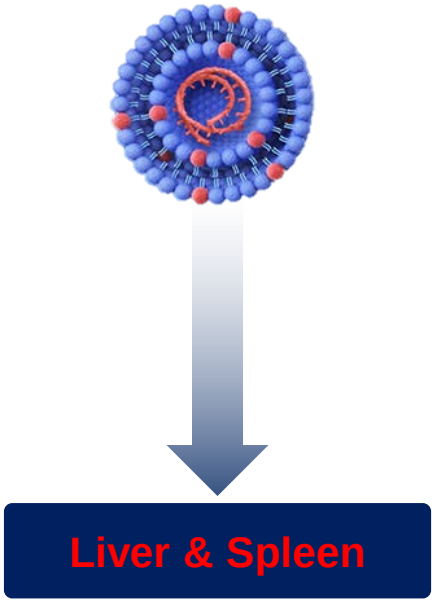






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GN2205 RNA delivery platform



Liver:

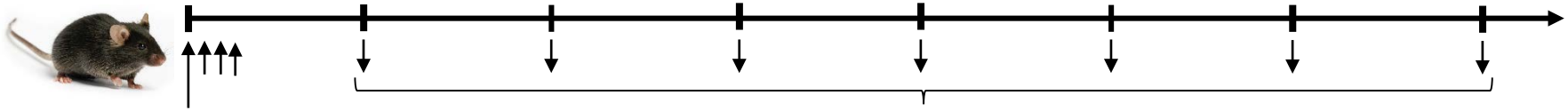
- ✓ Hepatocytes & hepatocyte precursors
- ✓ Endothelial cells
- ✓ Stellate cells
- ✓ Macrophages
- ✓ Pericytes
- x Cholangiocytes

Spleen, Lung, heart & kidney :

- x Endothelial cells

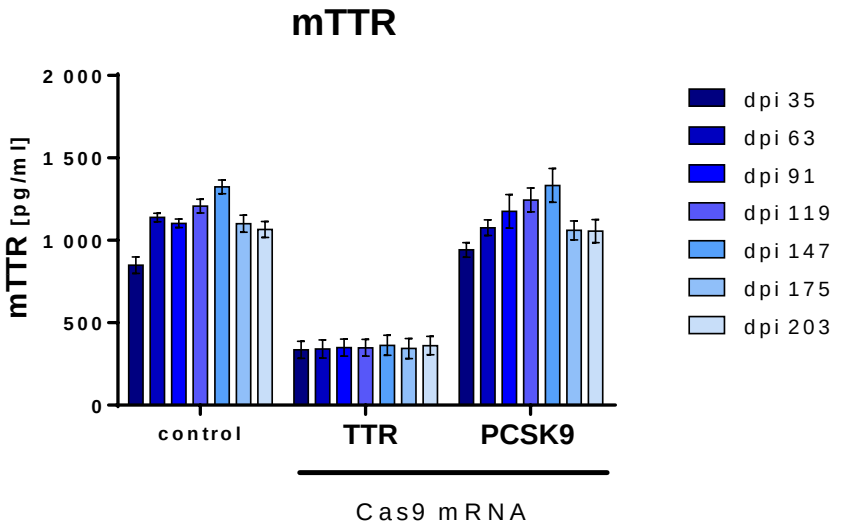
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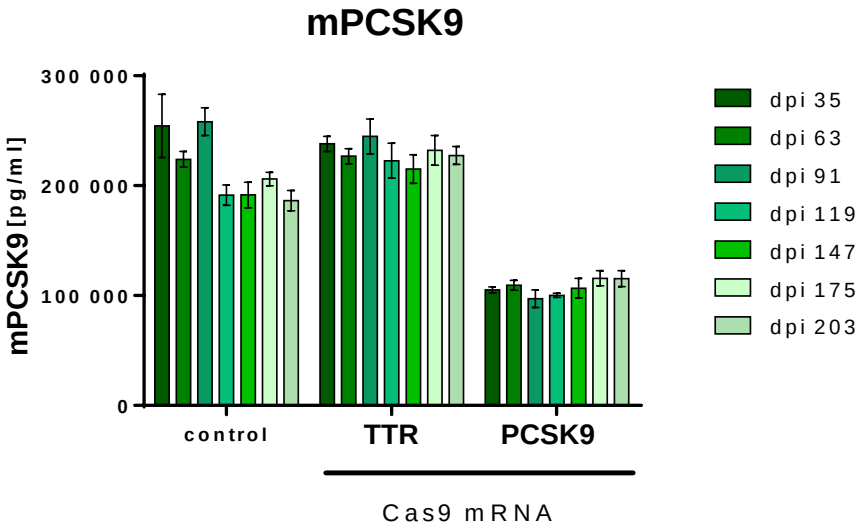
GN2205 co-delivery of guide RNA & spCas9-mRNA



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

quantification of serum protein at indicated time points by standardized ELISA





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Summary

- Identification of LNP with 100 fold Increased activity in liver
- Targeting multiple cell types in the liver
- Suitable for different RNA payloads

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

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Acknowledgement



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Thank you!

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