

Nature-inspired platform nanotechnology for RNA delivery to immune cells

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*Annual Meeting of the Controlled Release Society
Philadelphia PA, US, July 14-18 2025*

Team

Leadership



Roy



Ewelina



Willem



Yohana



Thijs



Postdocs



Matt



Chiara

Ph.D. students



Anne



Stijn



Robby



Ayla



Koen



Jari



Jeroen



Tom



Mirre



Daniek



Merel



Senna



Sjoerd



Rianne



Yuri

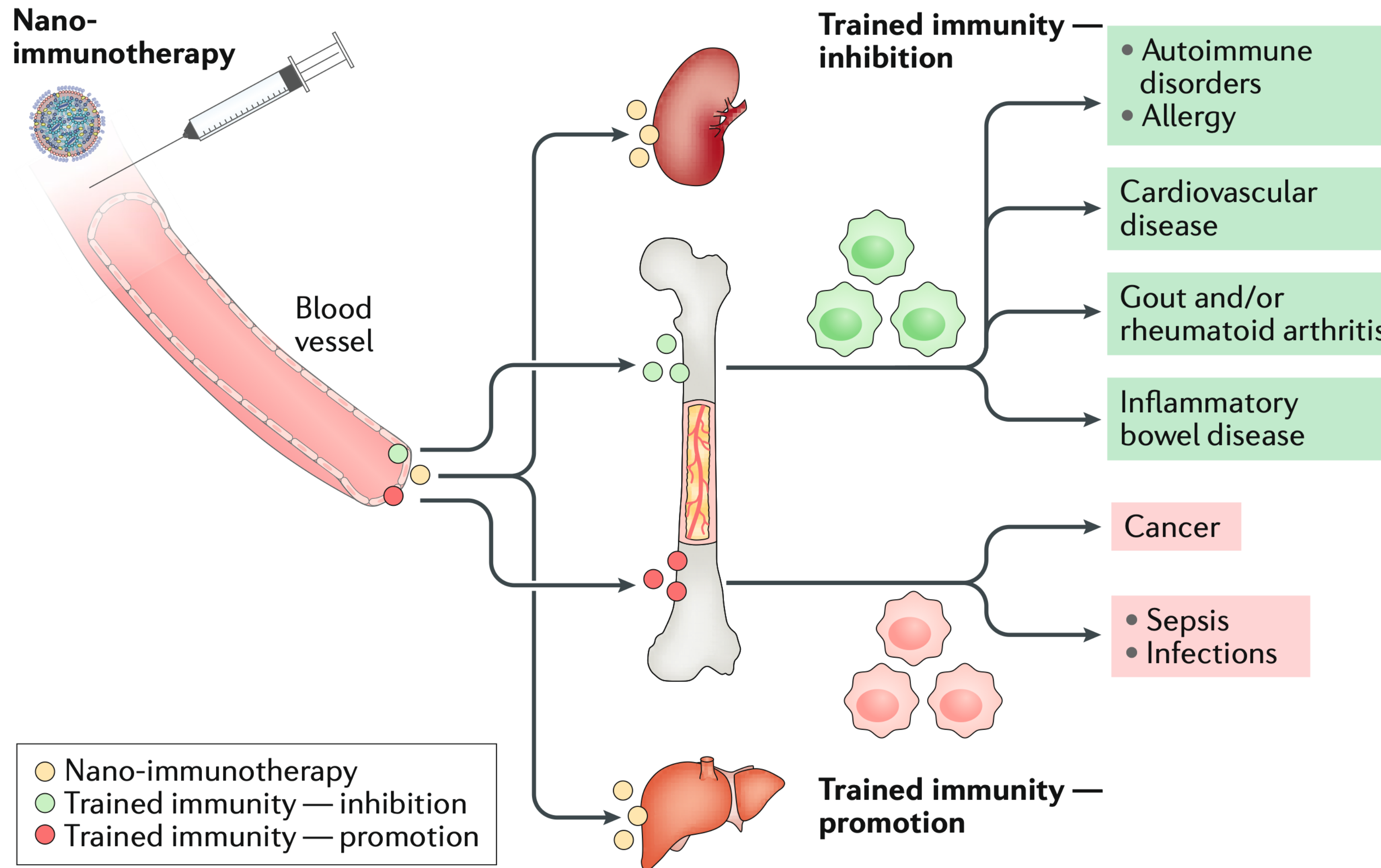


Iris

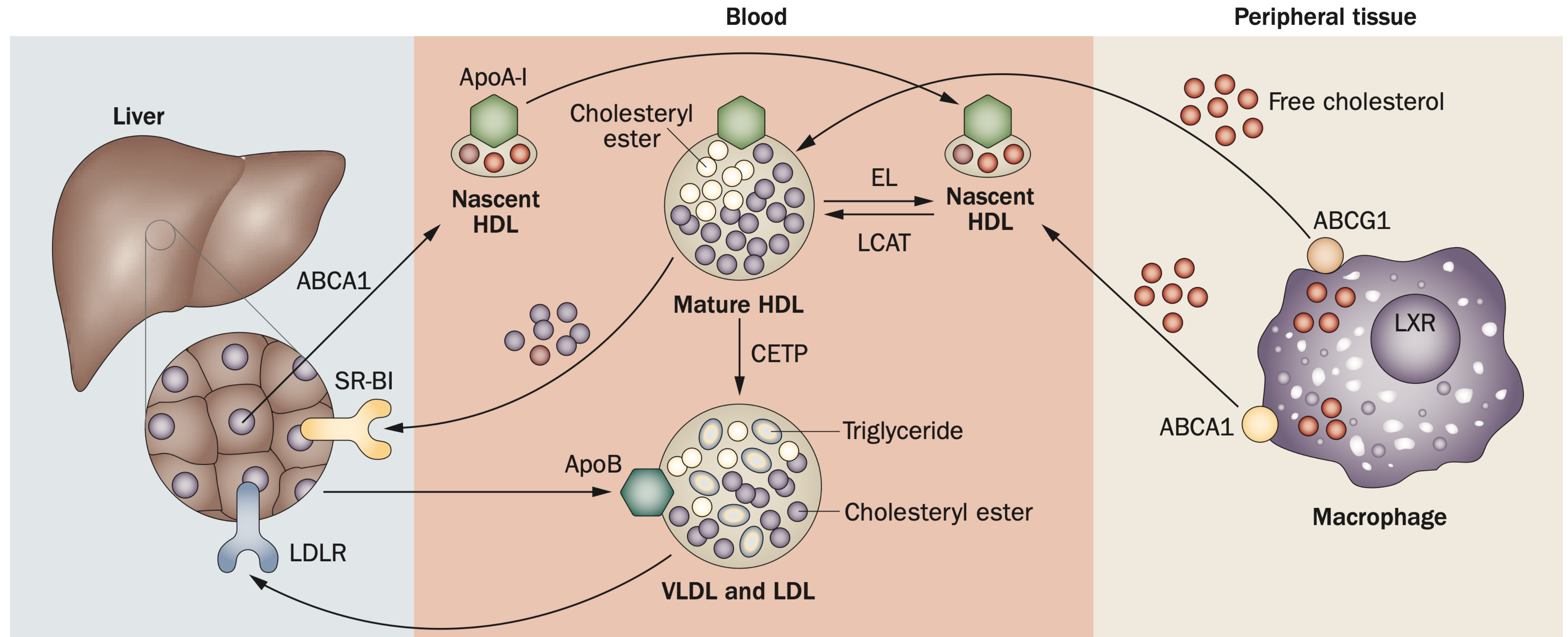
Engaging hematopoietic organs



Mihai Netea
Radboudumc

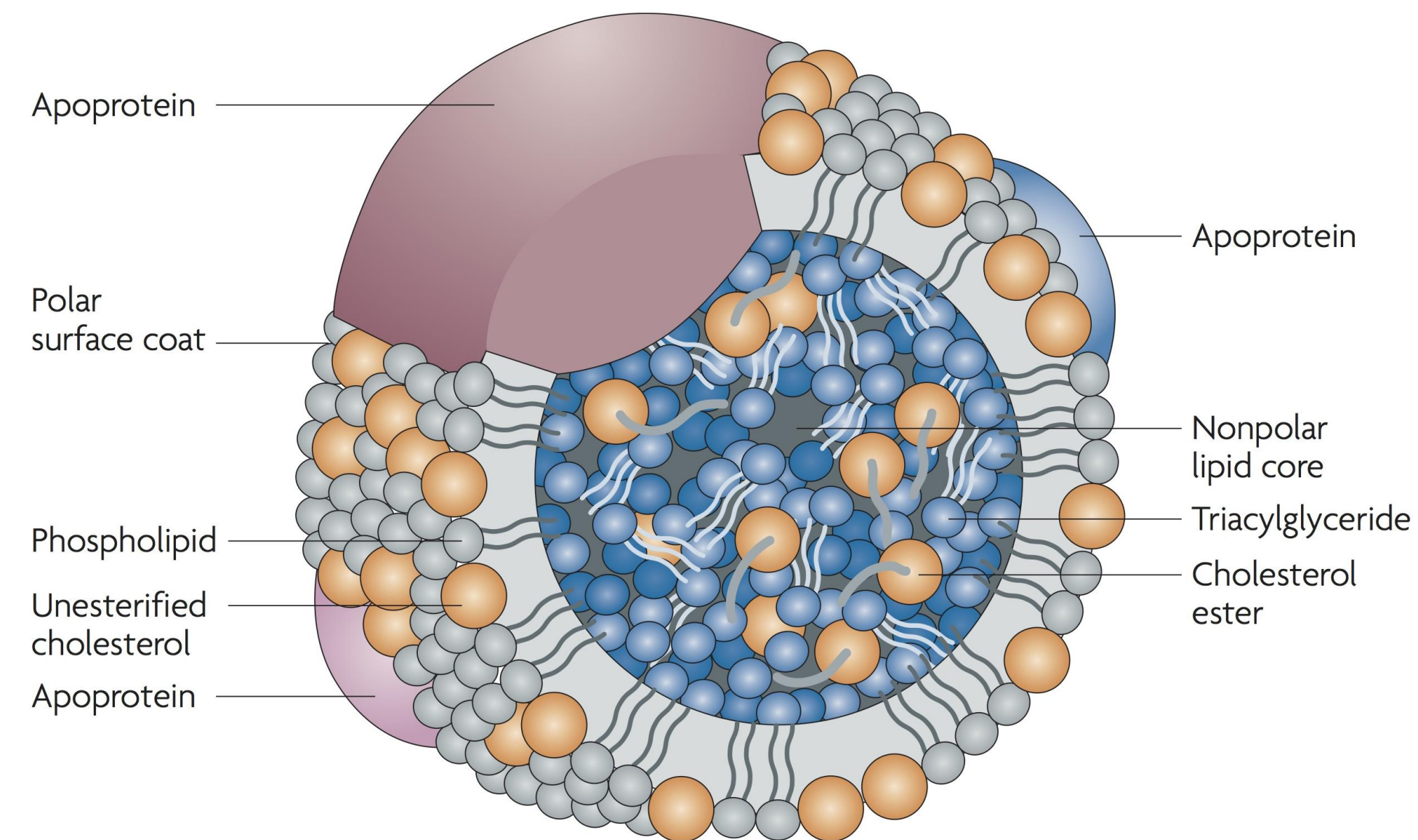


What does our body offer naturally?



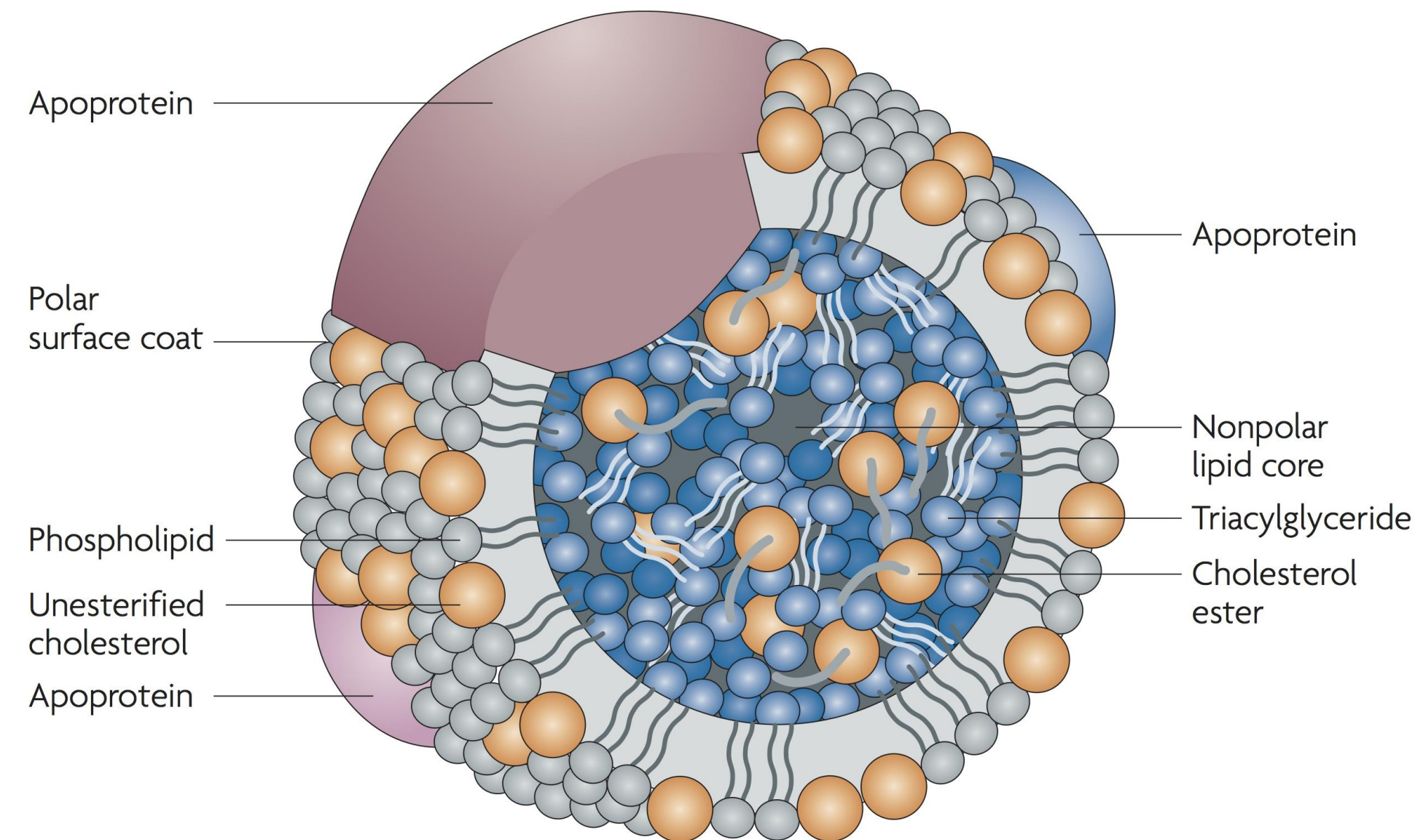
High density lipoprotein architecture

Lipoprotein morphology

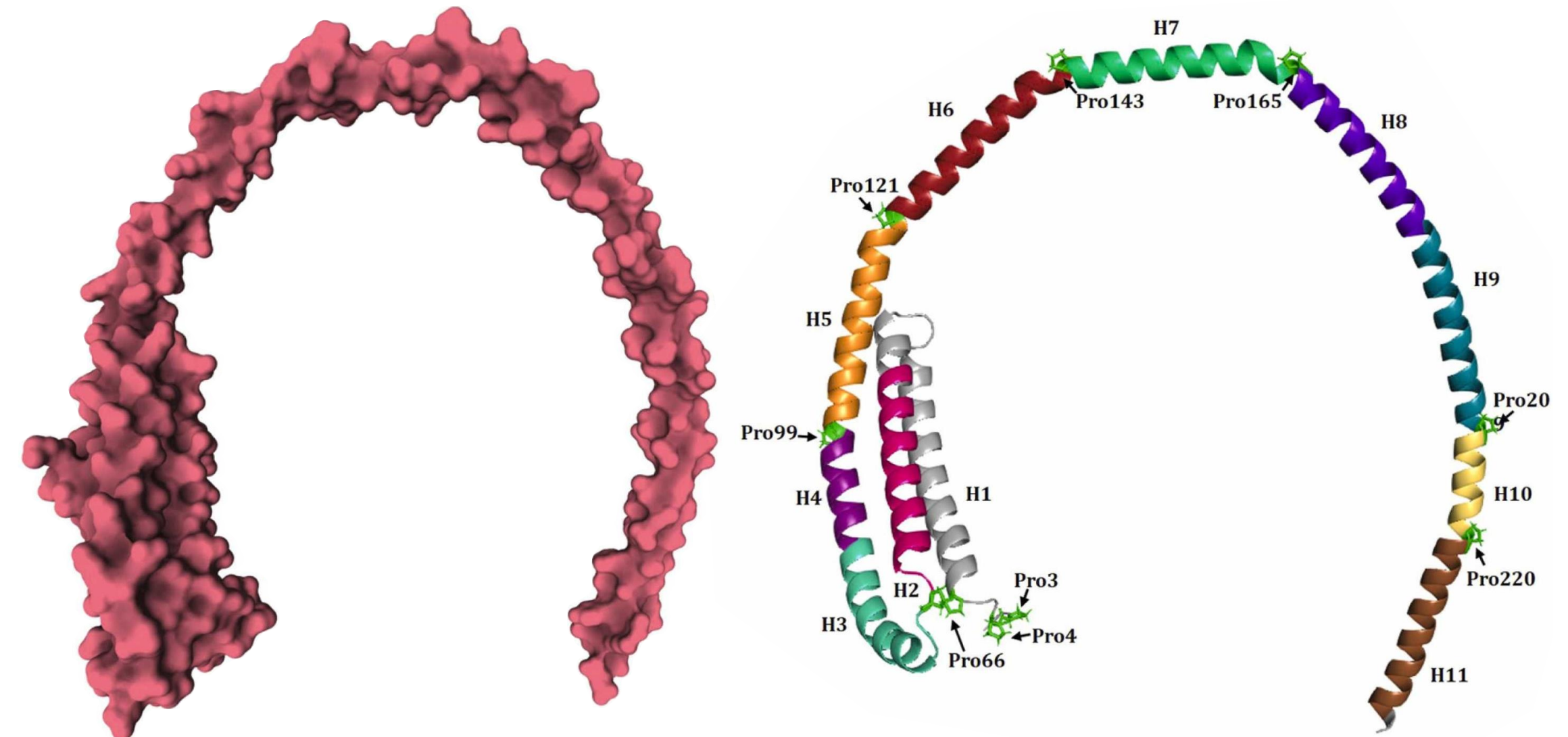


High density lipoprotein architecture

Lipoprotein morphology



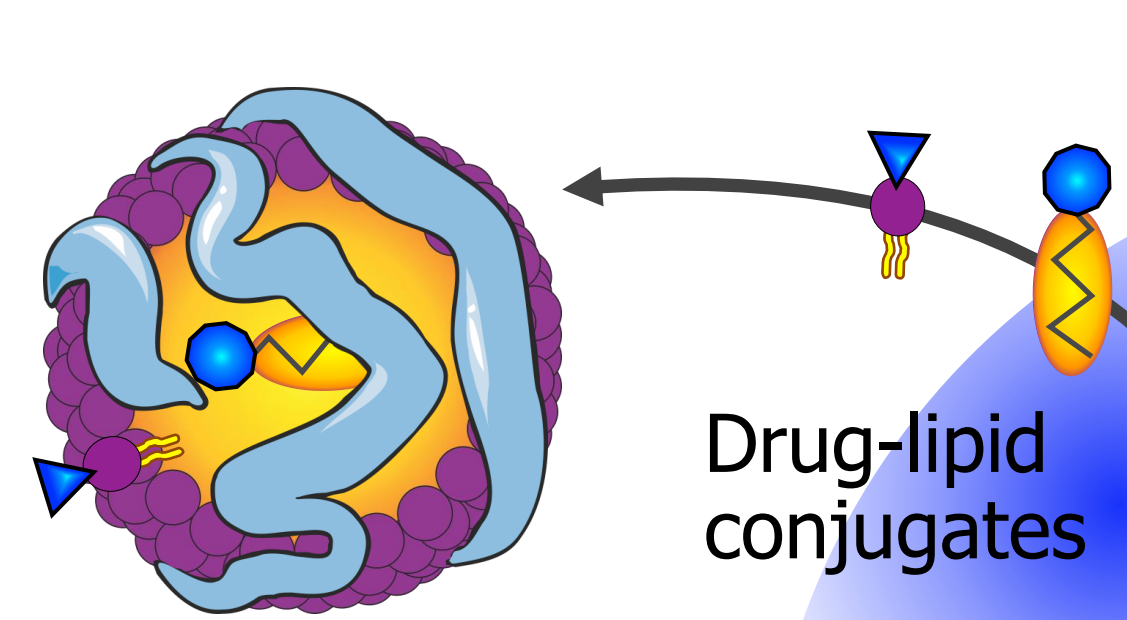
Apolipoprotein A1



- Structural integrity
- Natural stealth
- Natural affinity for immune cells
 - ABCA1, ABCG1, SRB1

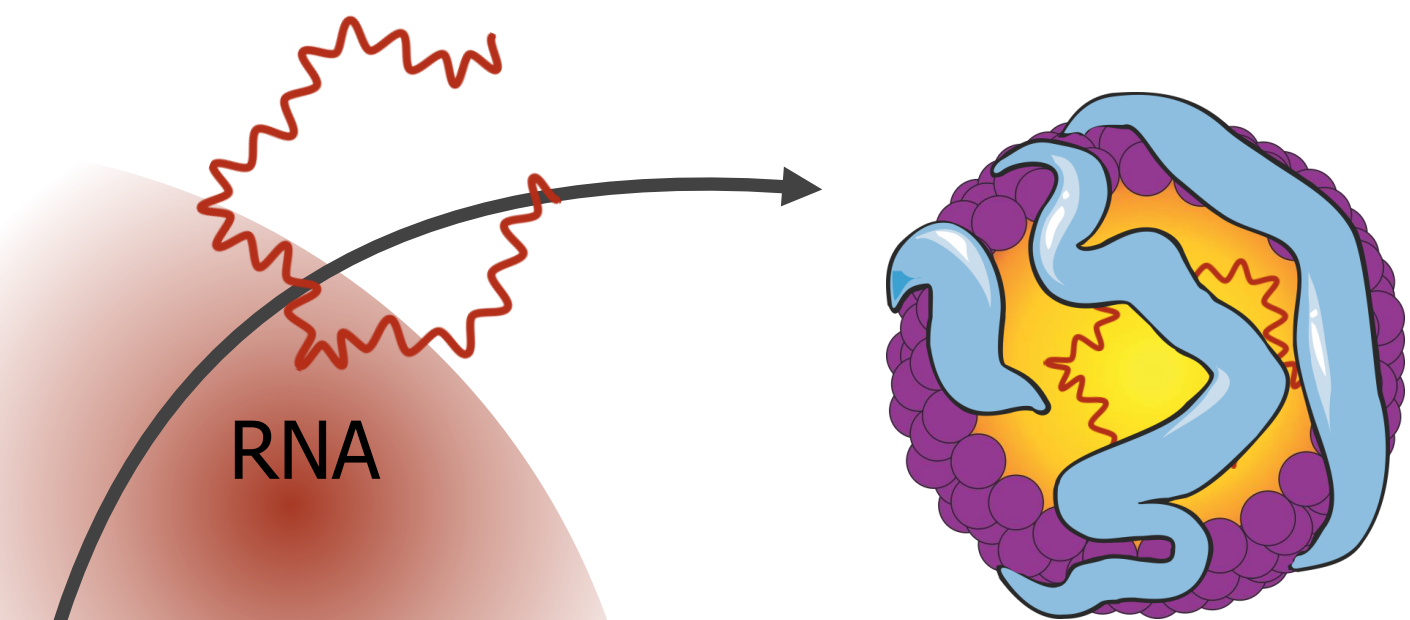
Modular aNP platform for delivery to immune cells

1 Small molecules



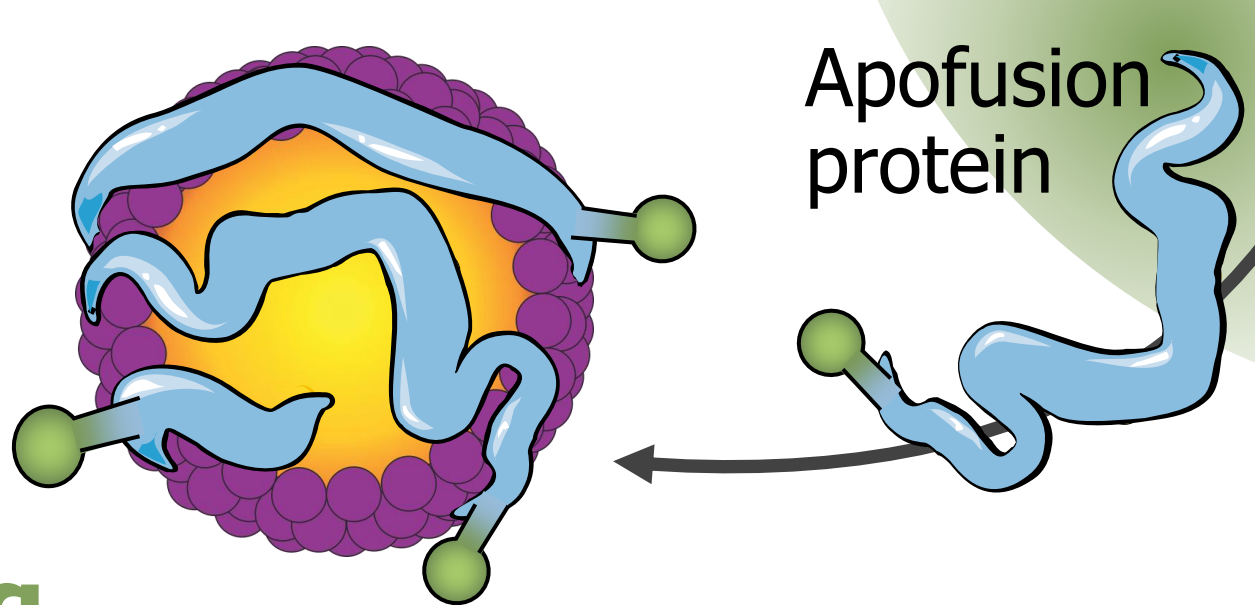
Priem *et al.*, Cell, 2020; Braza *et al.*, Immunity, 2018; Van Leent *et al.*, Sci Adv, 2021
Lameijer *et al.*, Nat Biomed Eng, 2018; Binderup *et al.*, Sci Transl Med, 2019

2 RNA

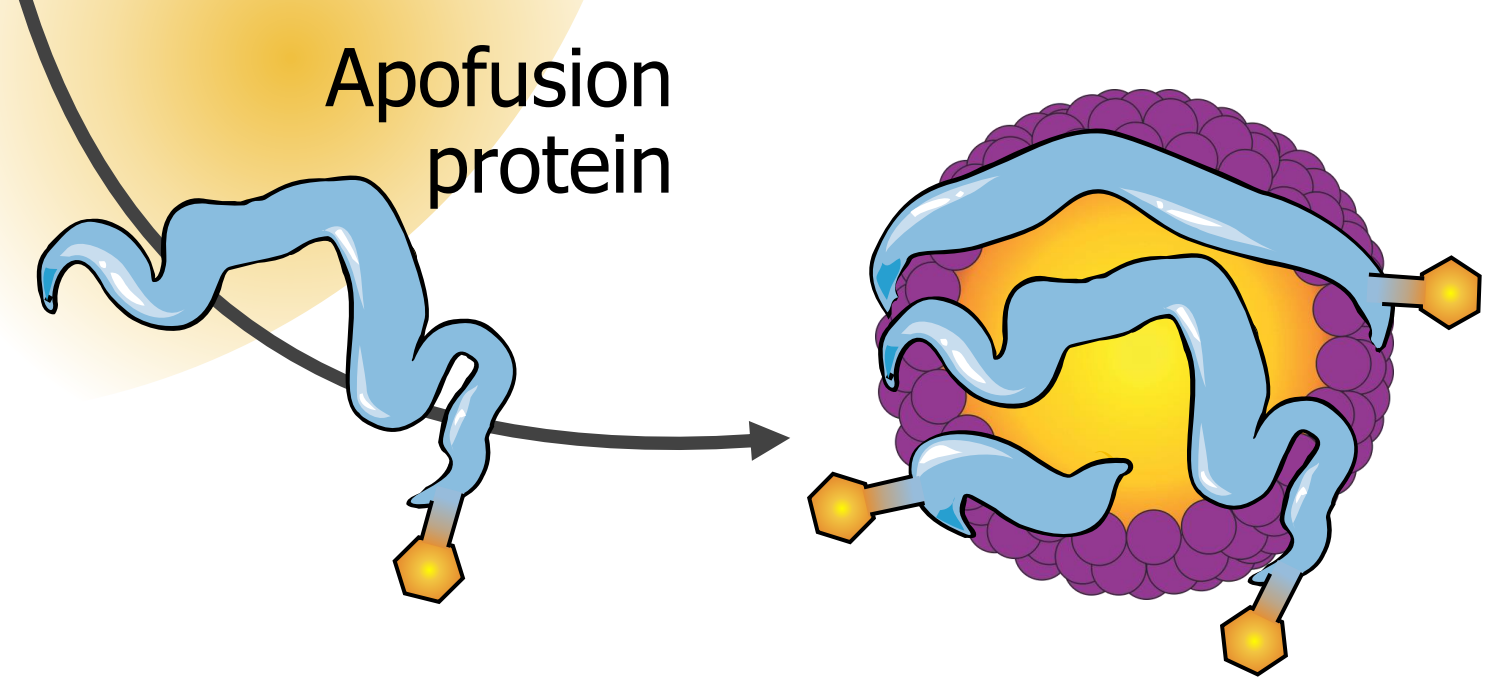


Hofstraat *et al.*, Nat Nanotechnol, 2025

3 Targeting

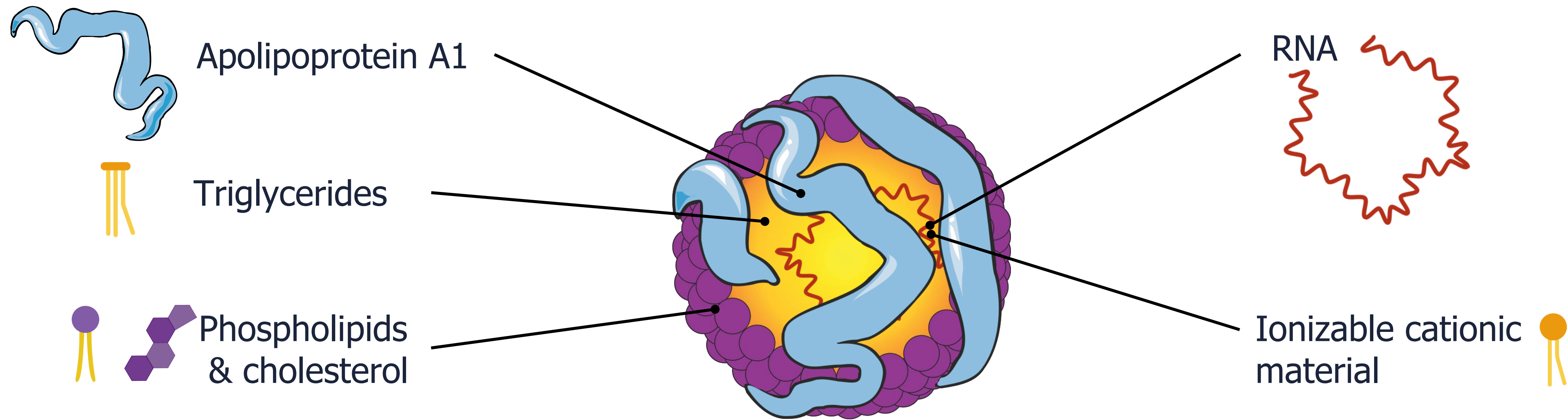


4 Proteins

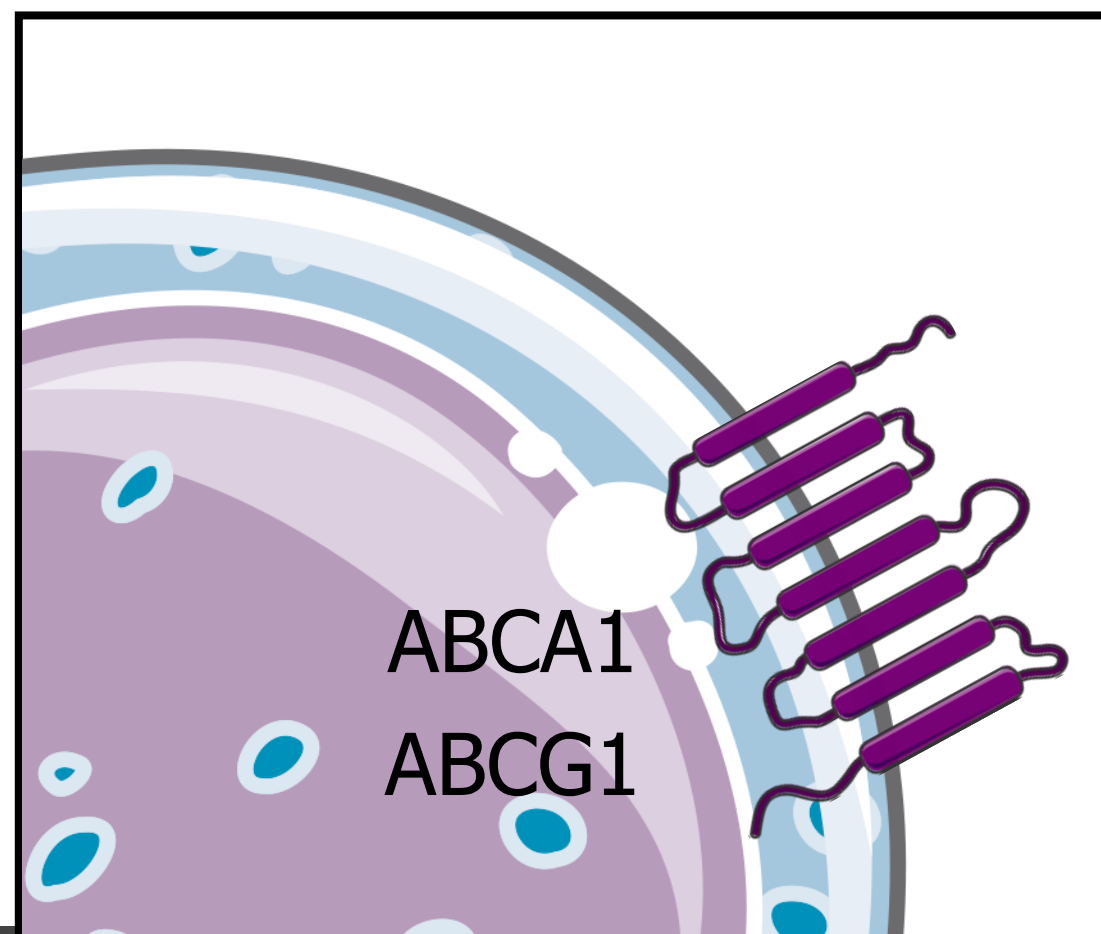


Schrijver *et al.*, Nat Biomed Eng, 2023

Modular aNP-RNA platform technology



Myeloid cells & HPSCs



Stijn

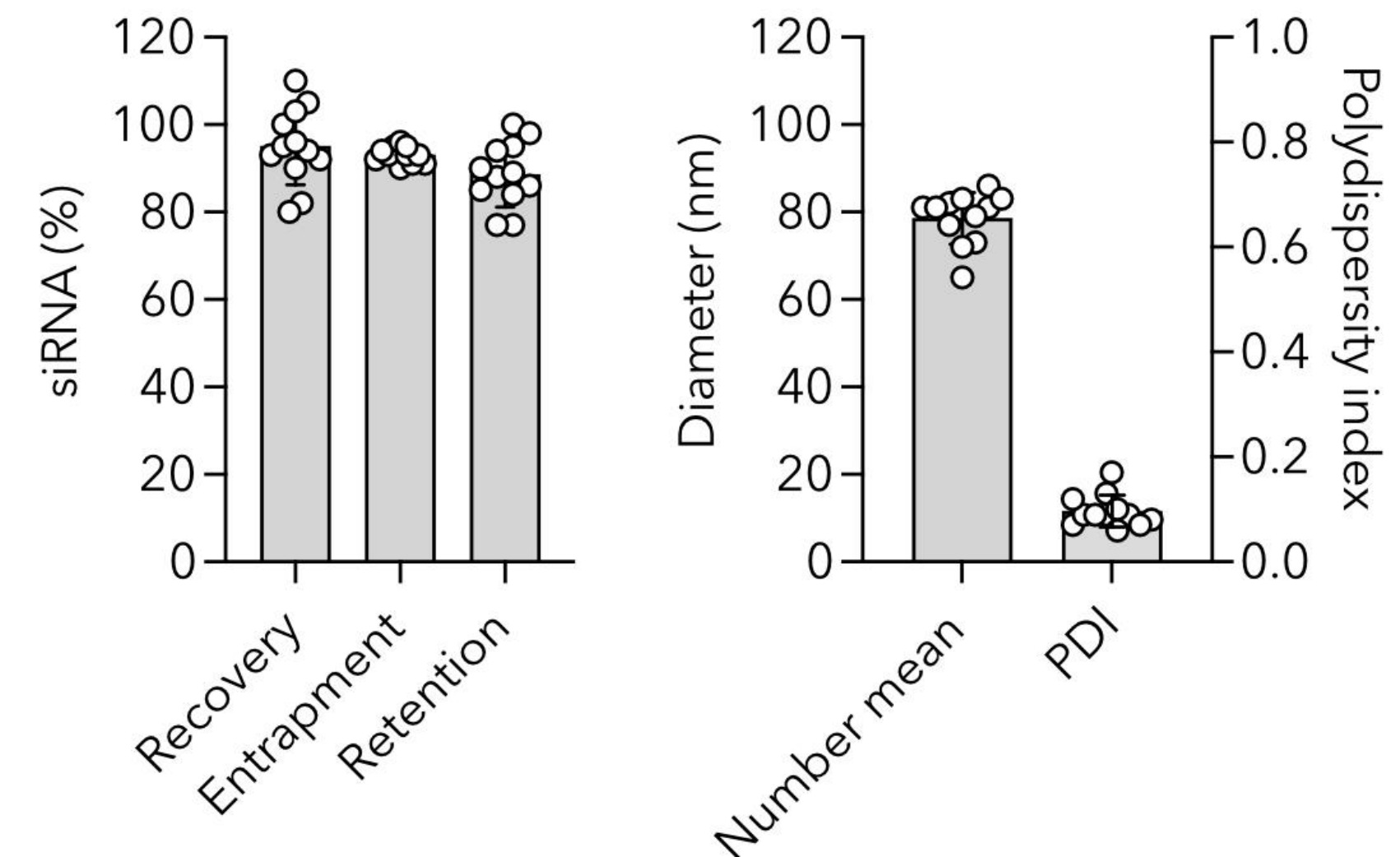
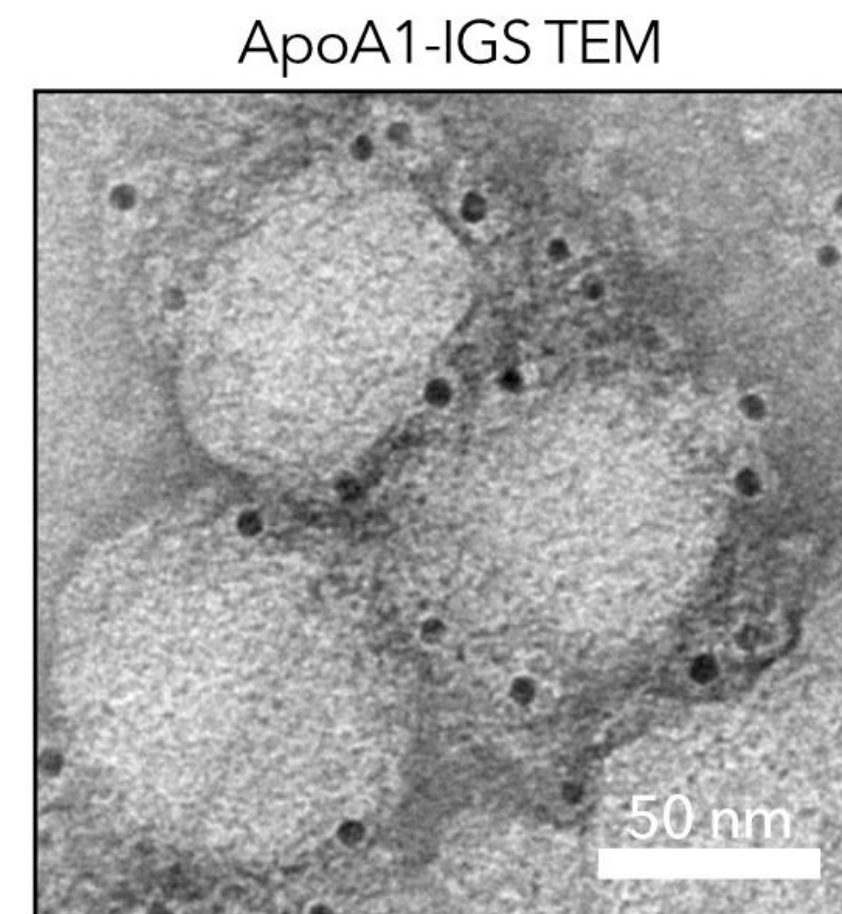
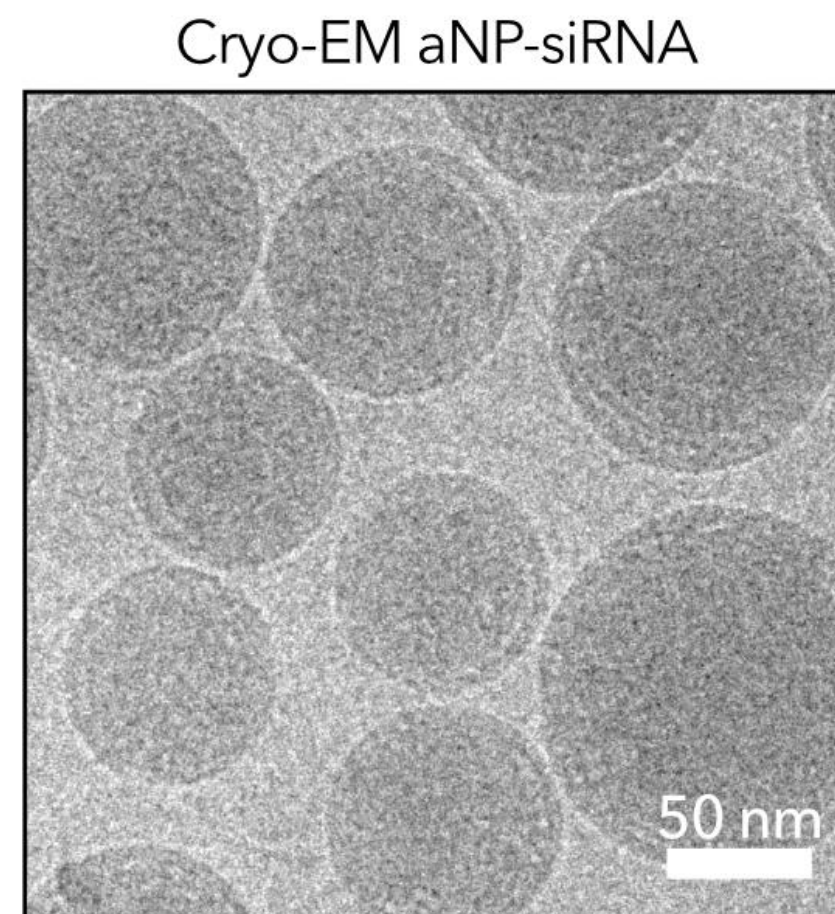
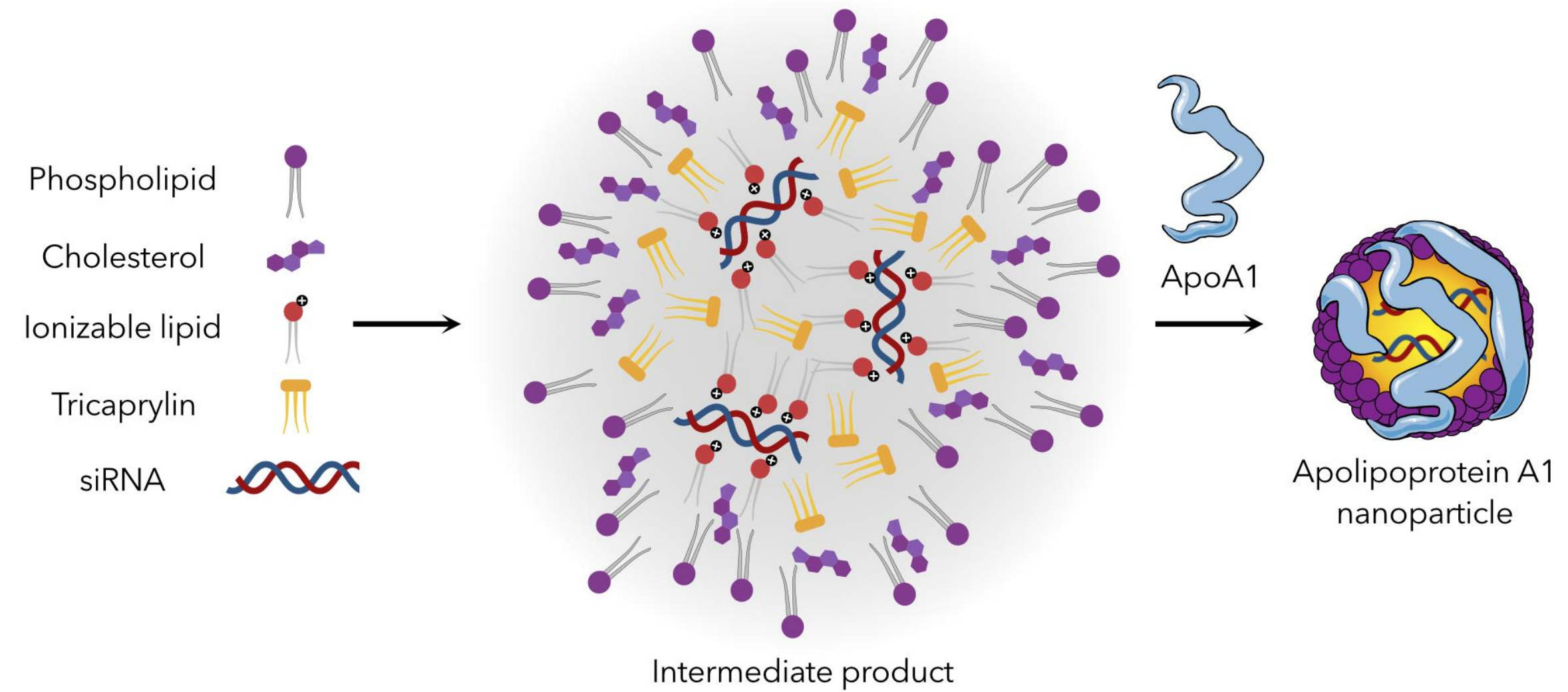
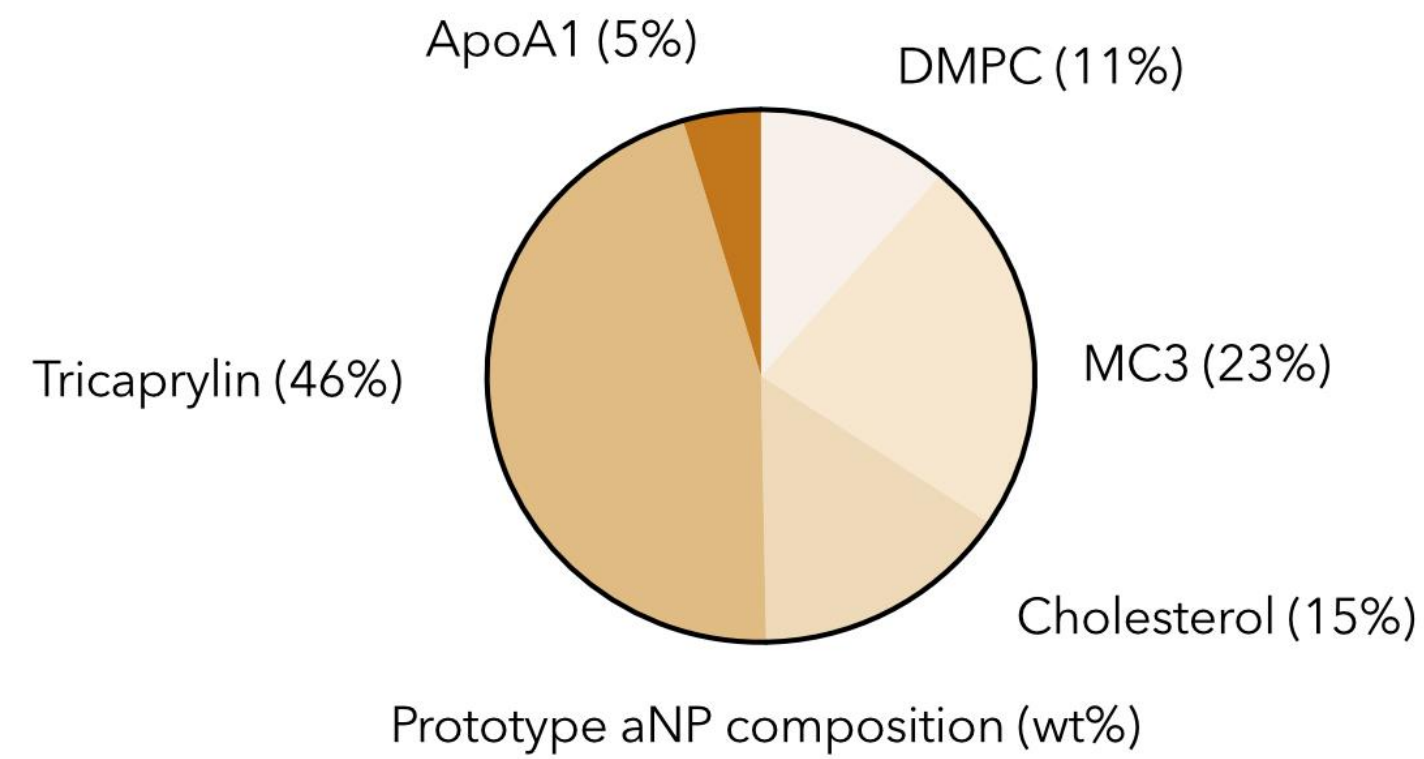


Tom



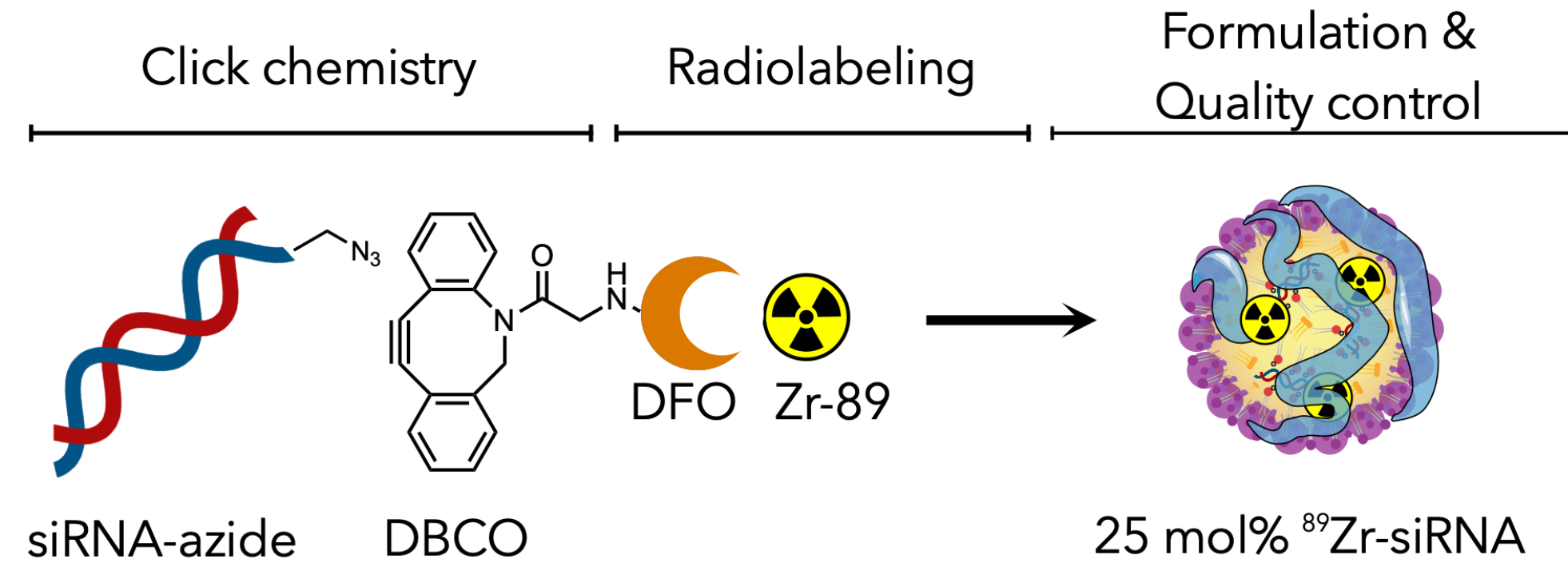
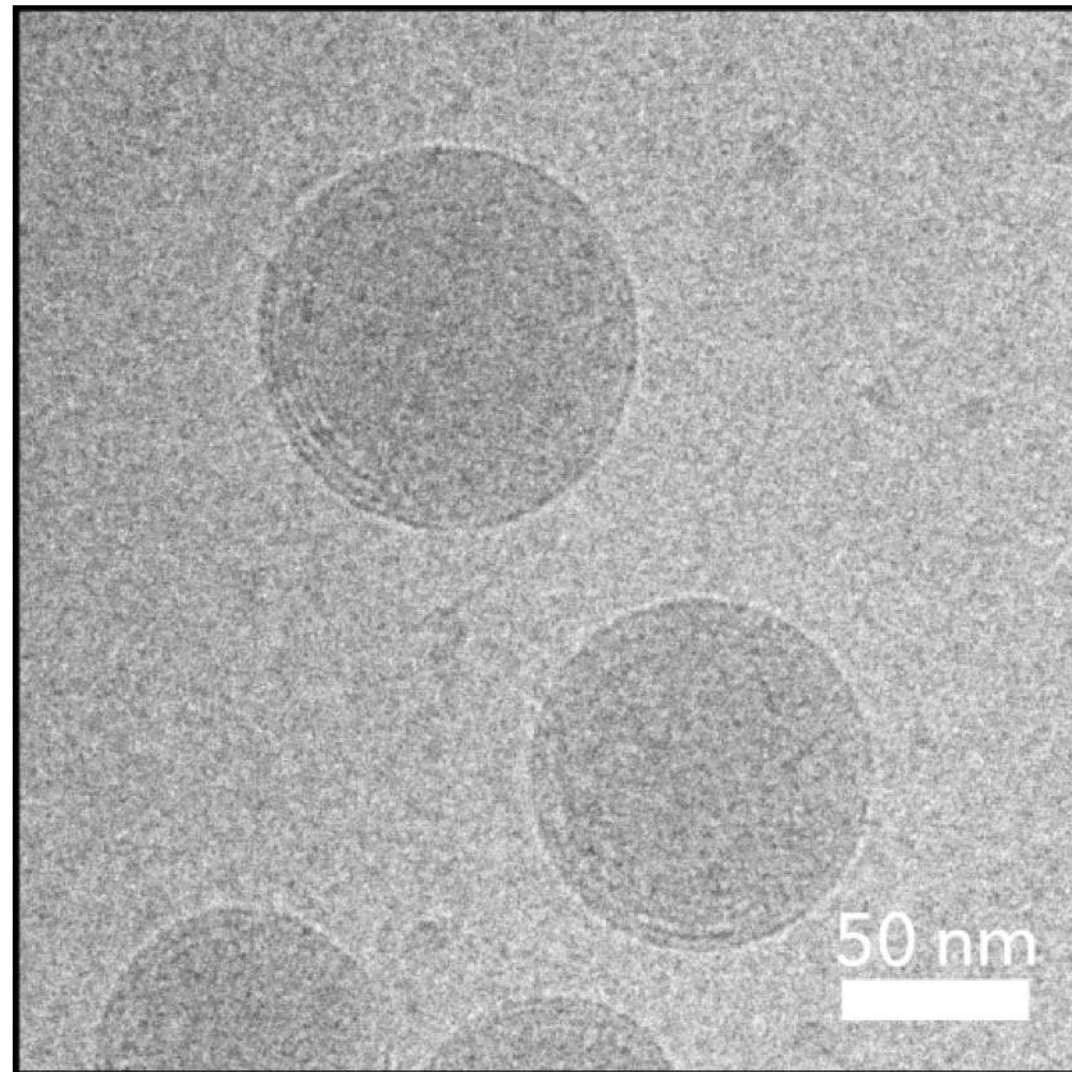
Robby

aNP-siRNA prototype



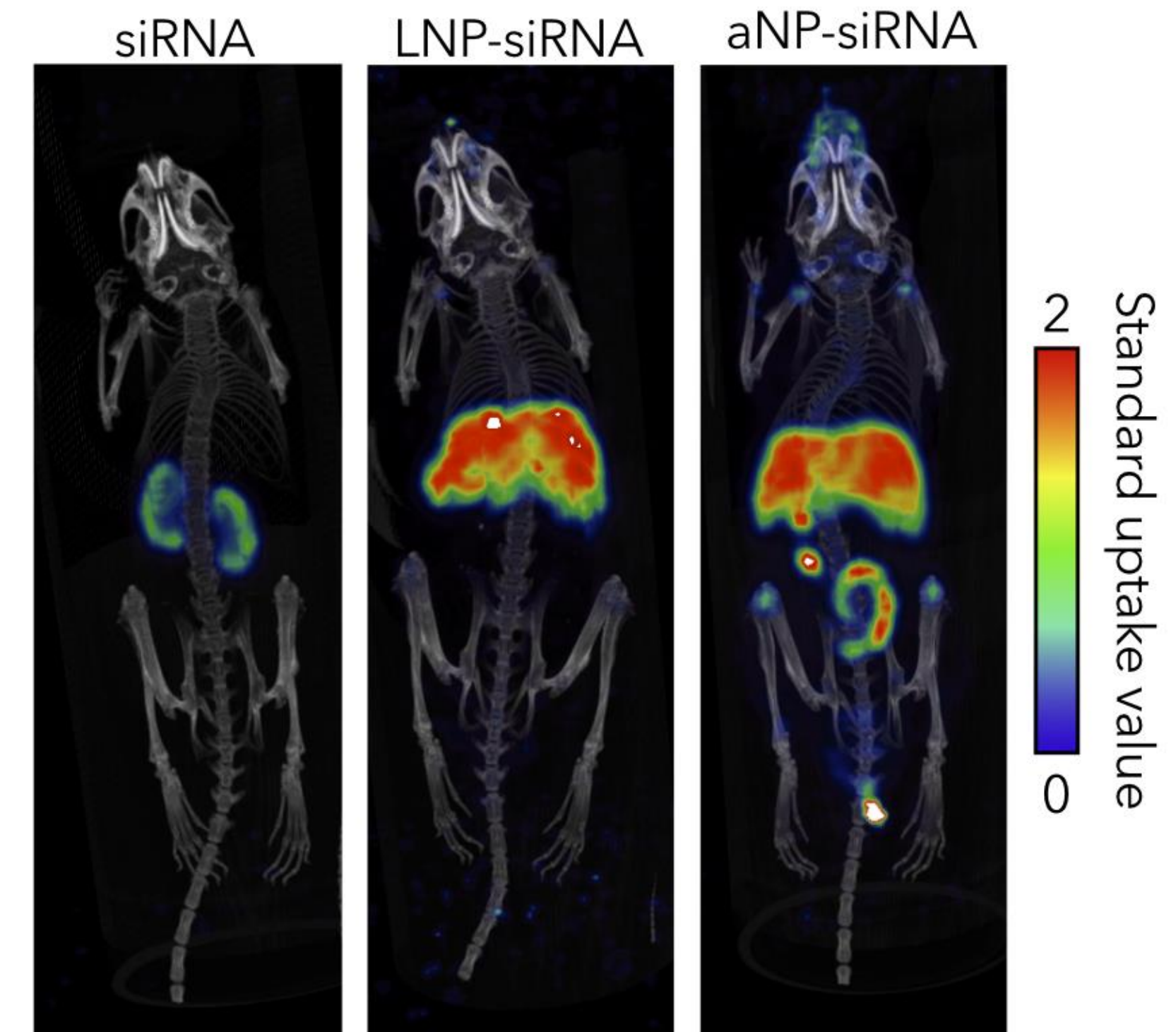
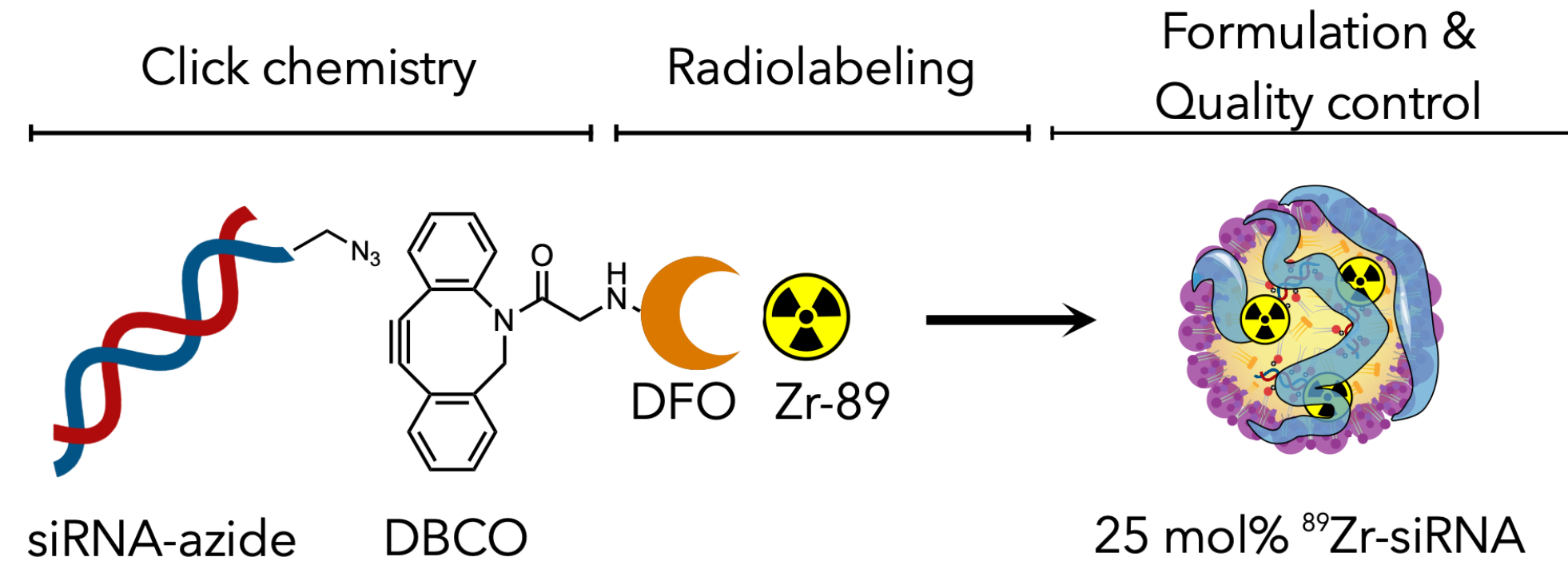
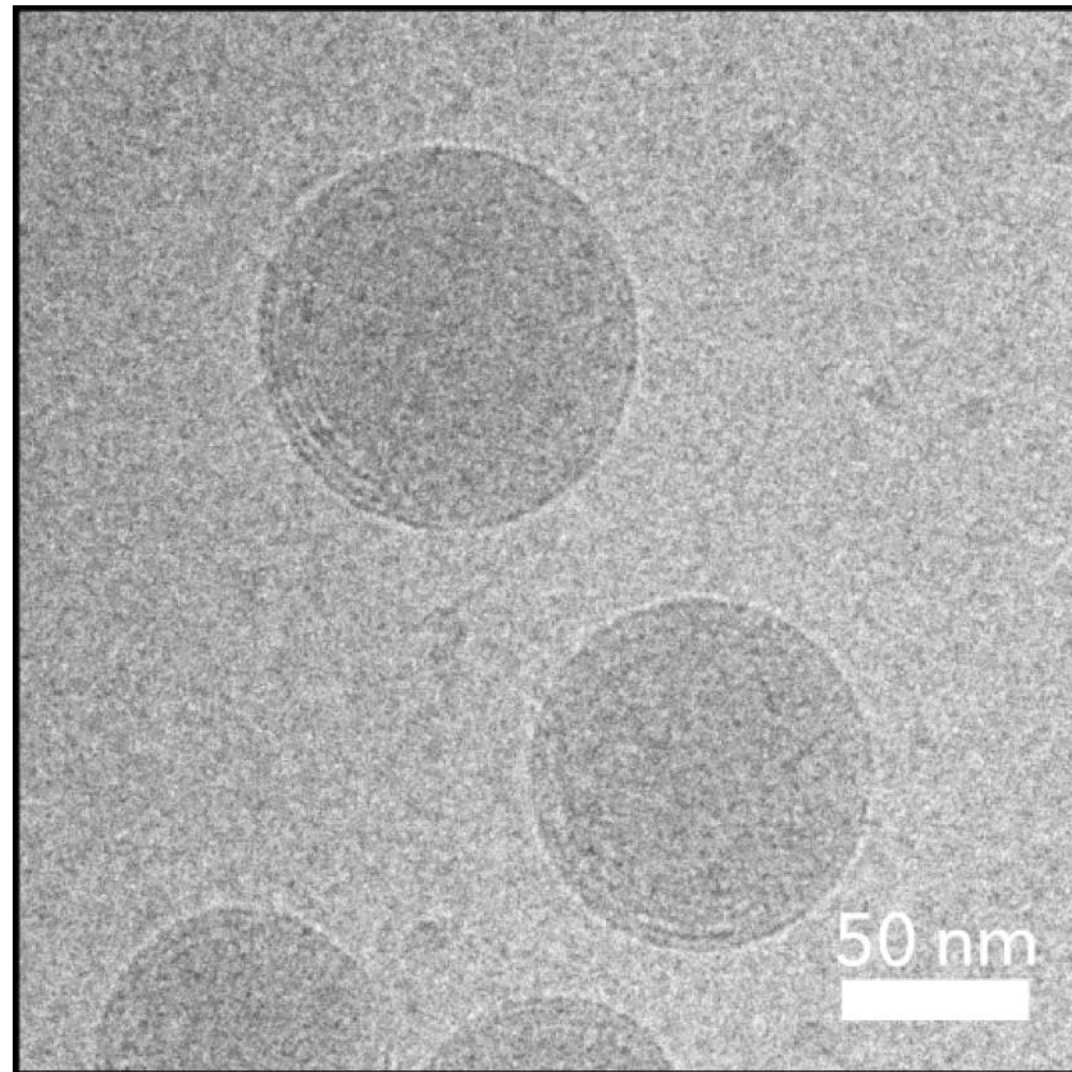
aNP-siRNA prototype

Cryo-EM ^{89}Zr -siRNA-aNP



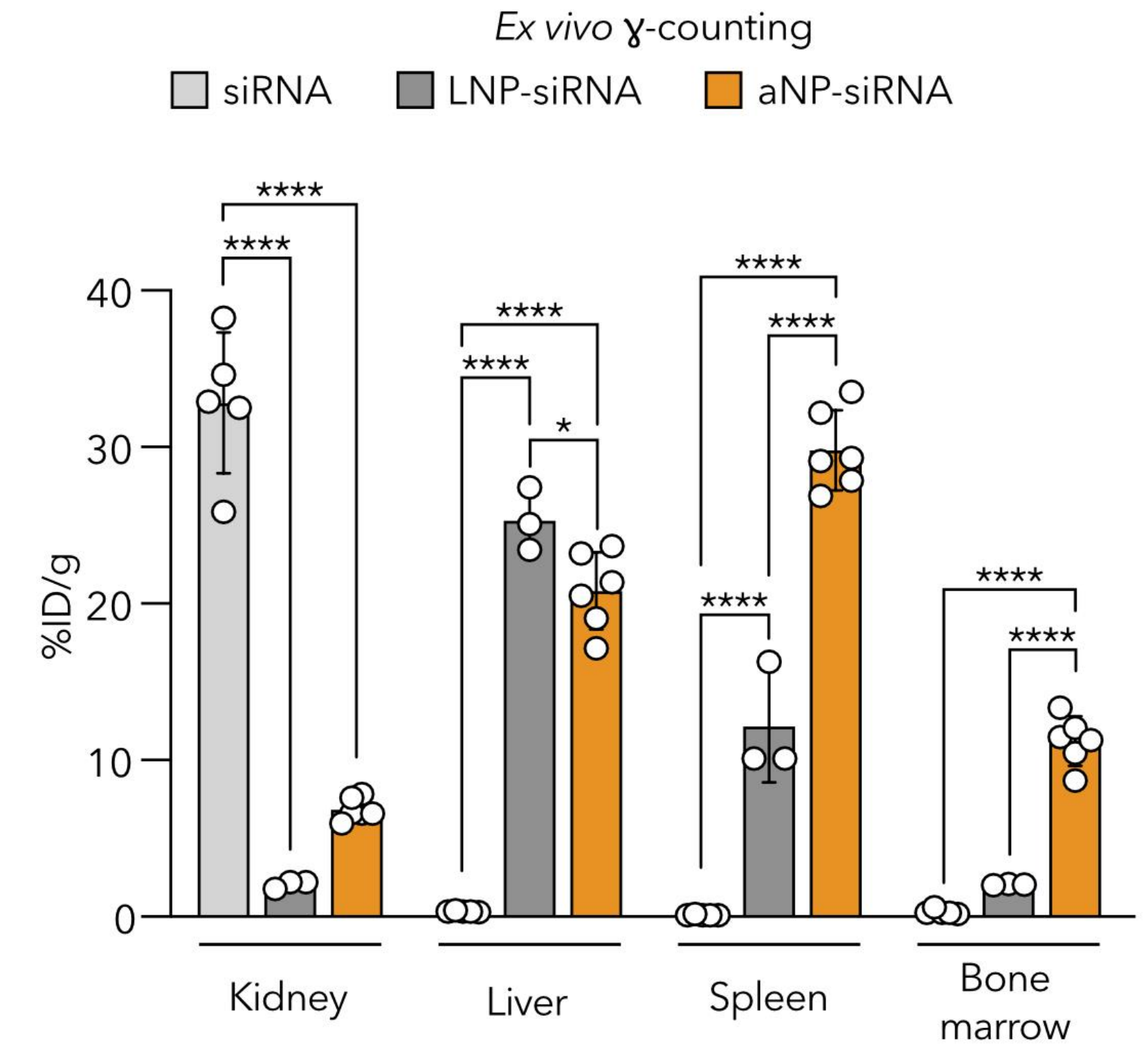
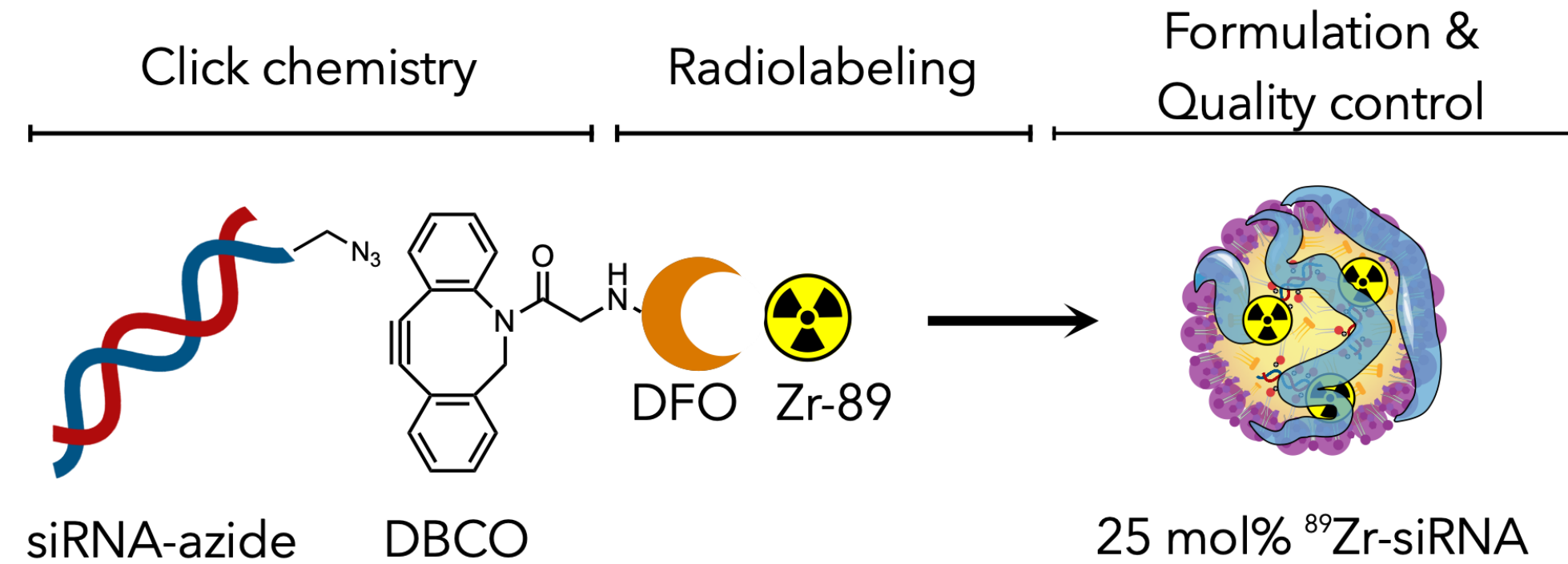
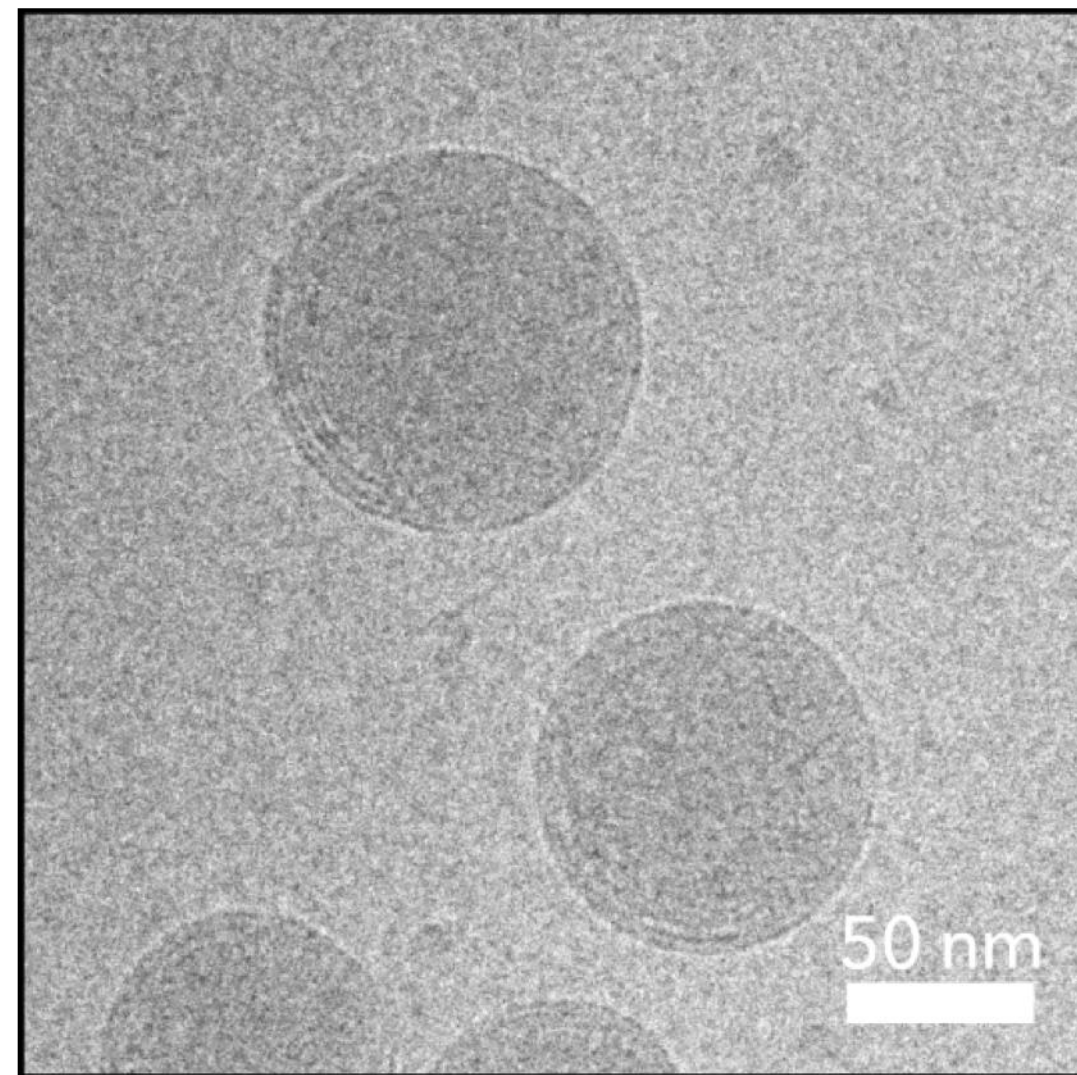
aNP-siRNA prototype

Cryo-EM ^{89}Zr -siRNA-aNP

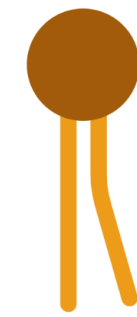
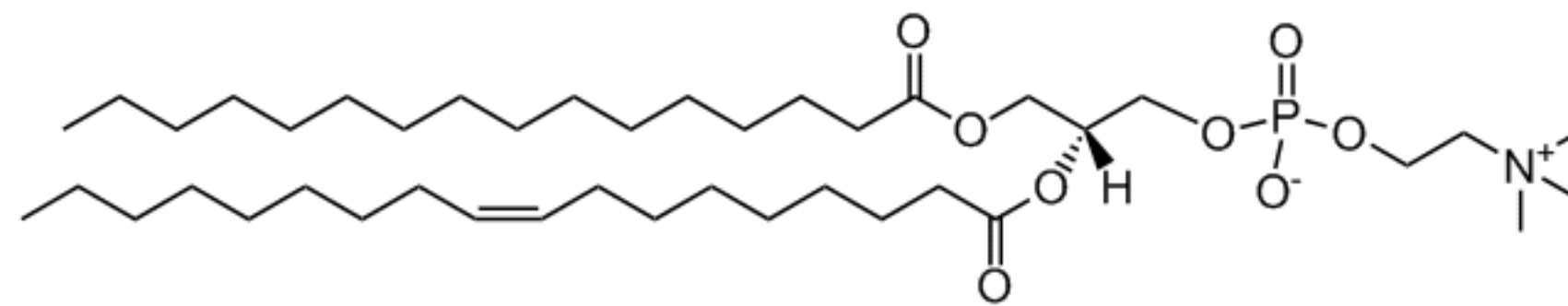


aNP-siRNA prototype

Cryo-EM ^{89}Zr -siRNA-aNP



aNP-siRNA library establishment



POPC-based aNPs

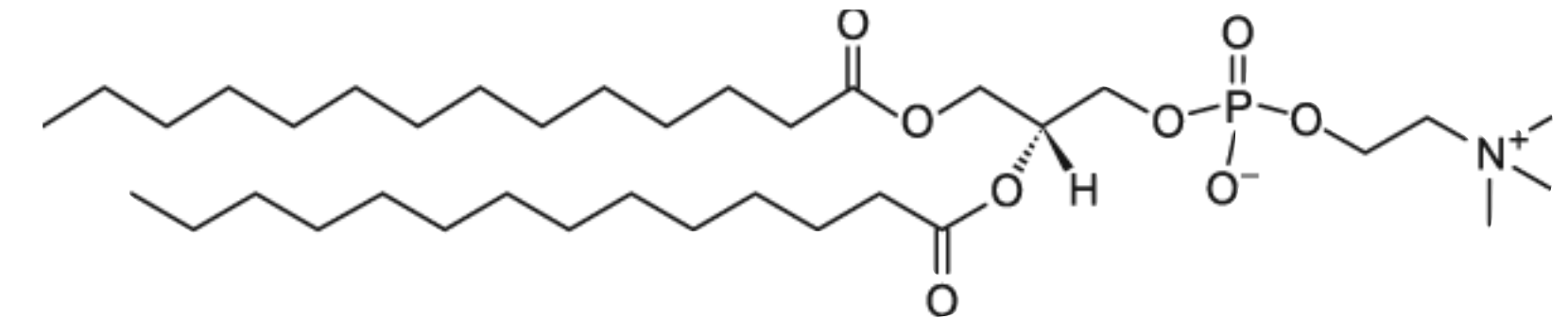
Nitrogen-to-Phosphate ratio

3 6 9 12

Tricaprylin	None	1	2	3	4	5	6	7	8	9	10	11	12
	Med	25	26	27	28	29	30	31	32	33	34	35	36
	Hi	49	50	51	52	53	54	55	56	57	58	59	60

Lo Med Hi →

Cholesterol

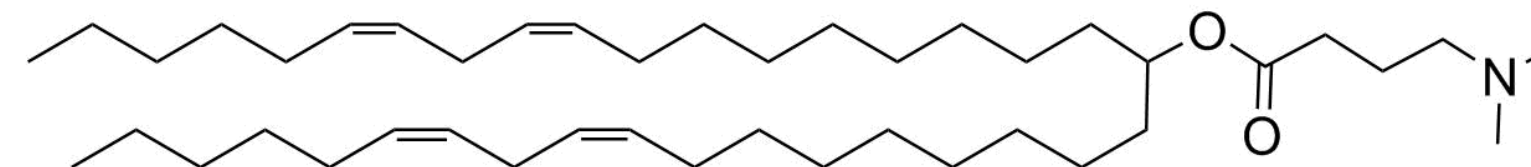


DMPC-based aNPs

Nitrogen-to-Phosphate ratio

3 6 9 12

13	14	15	16	17	18	19	20	21	22	23	24
37	38	39	40	41	42	43	44	45	46	47	48
61	62	63	64	65	66	67	68	69	70	71	72

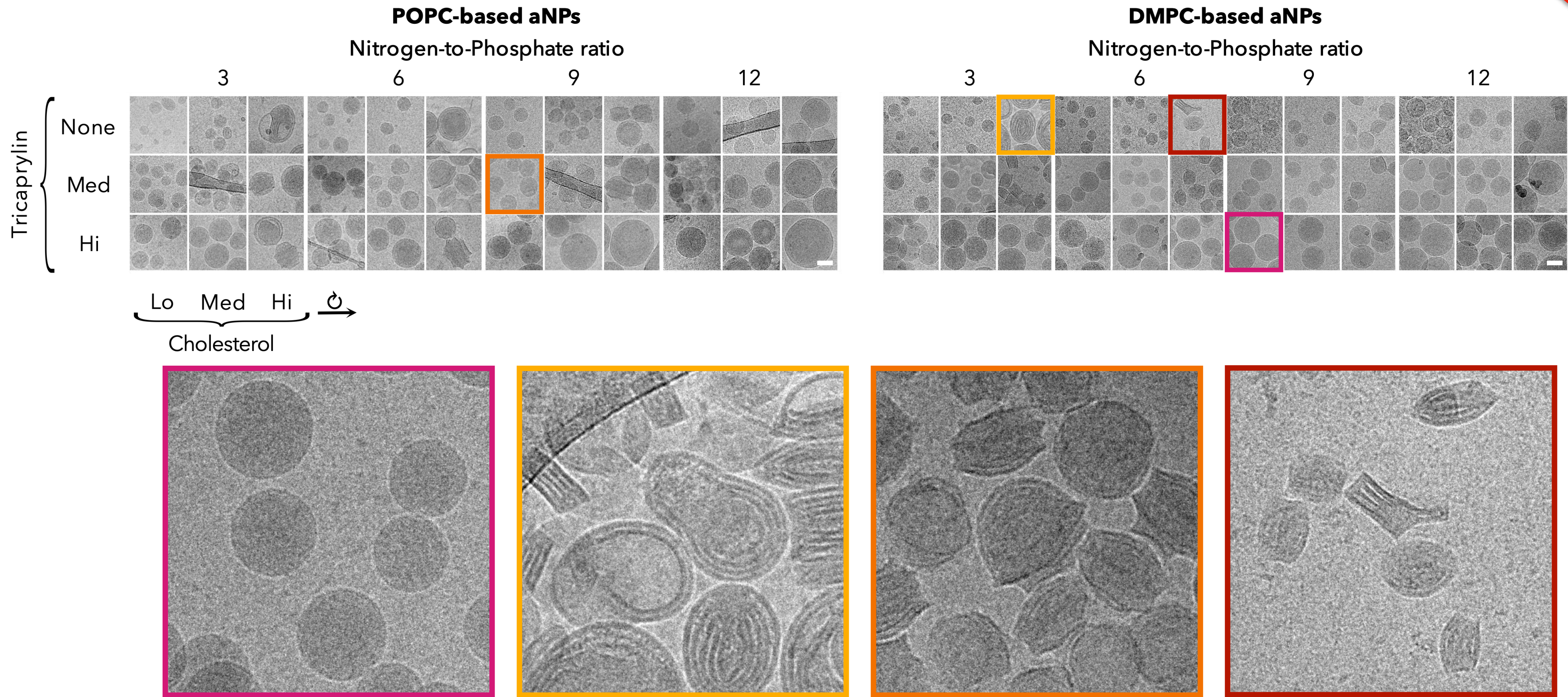


DLIIn-MC3-DMA

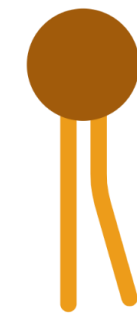
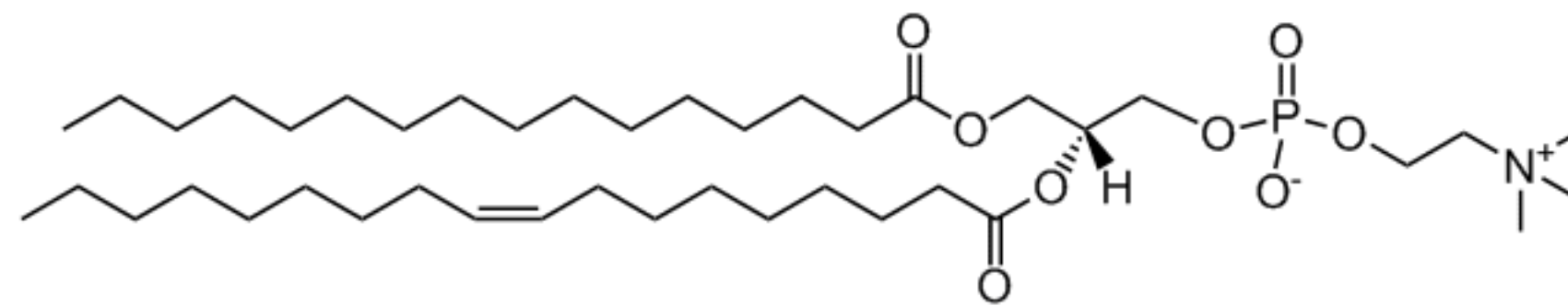
aNP-siRNA library characterization



Ewelina



aNP-siRNA library establishment



POPC-based aNPs

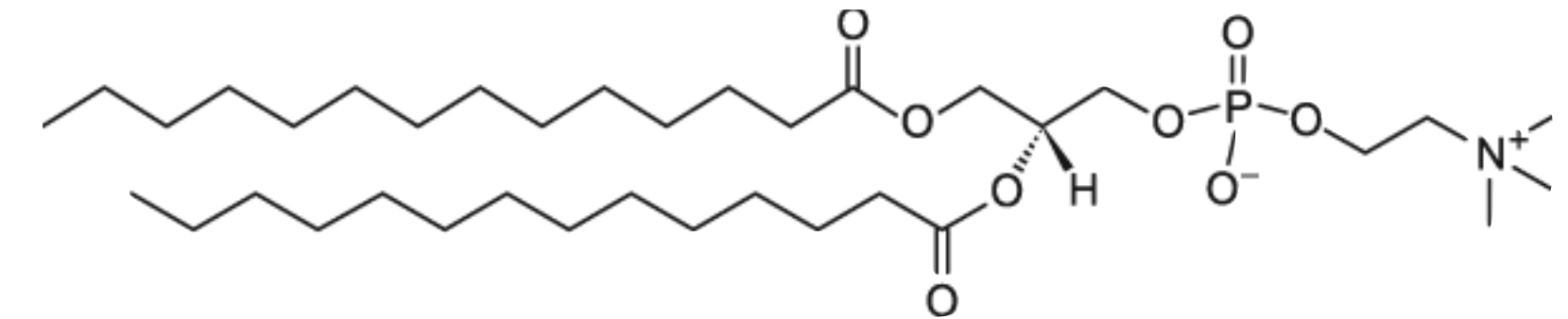
Nitrogen-to-Phosphate ratio

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Lo Med Hi →

Cholesterol

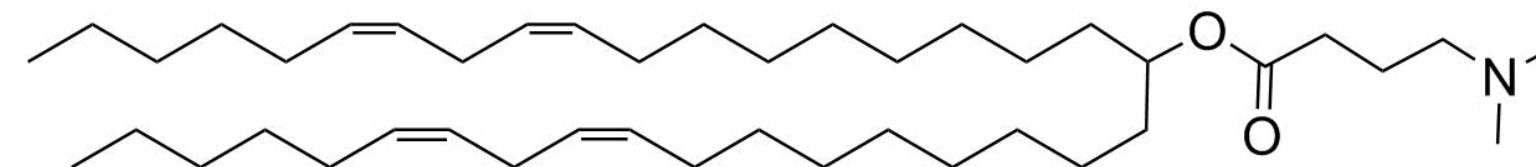


DMPC-based aNPs

Nitrogen-to-Phosphate ratio

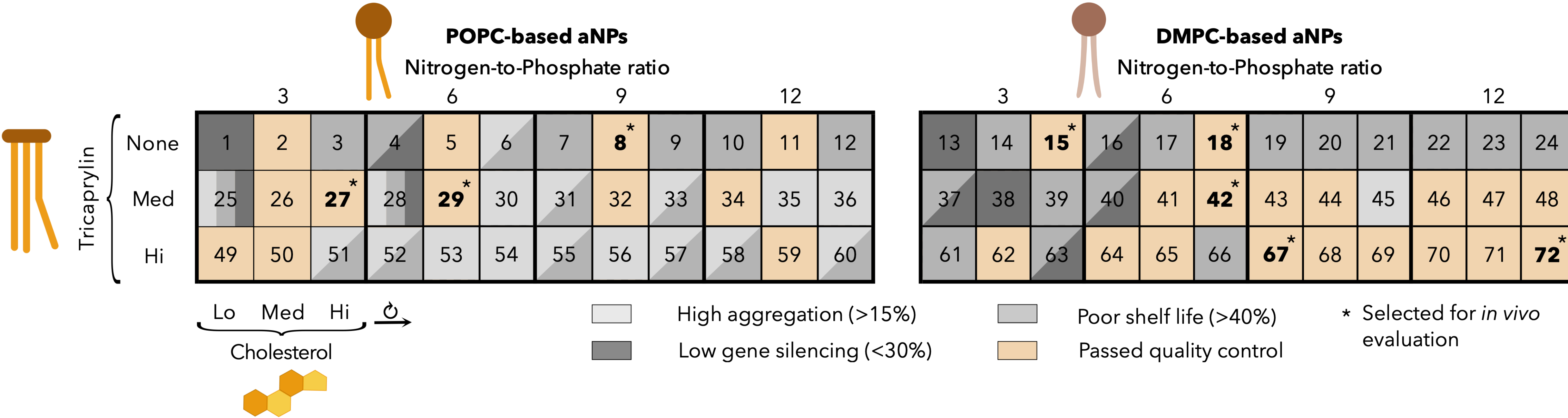
3 6 9 12

13	14	15	16	17	18	19	20	21	22	23	24
37	38	39	40	41	42	43	44	45	46	47	48
61	62	63	64	65	66	67	68	69	70	71	72



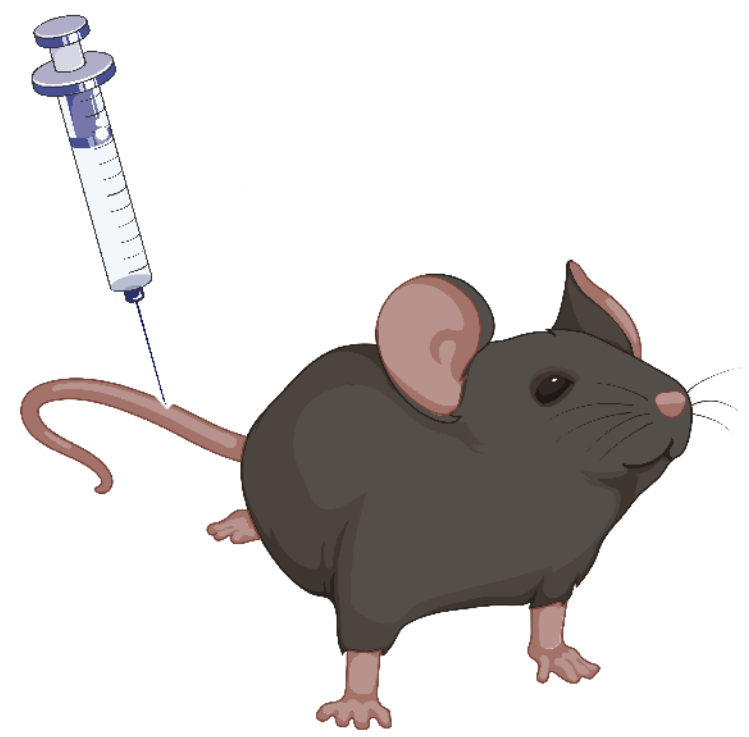
DLIn-MC3-DMA

aNP-siRNA selection for *in vivo* evaluation



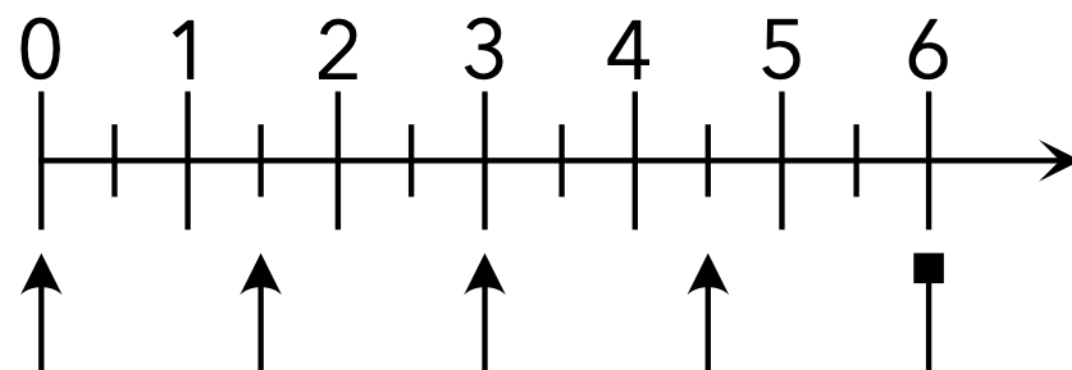
LAMP-1 silencing in mice with aNP-siRNA

LAMP1 - Lysosomal associated membrane protein 1



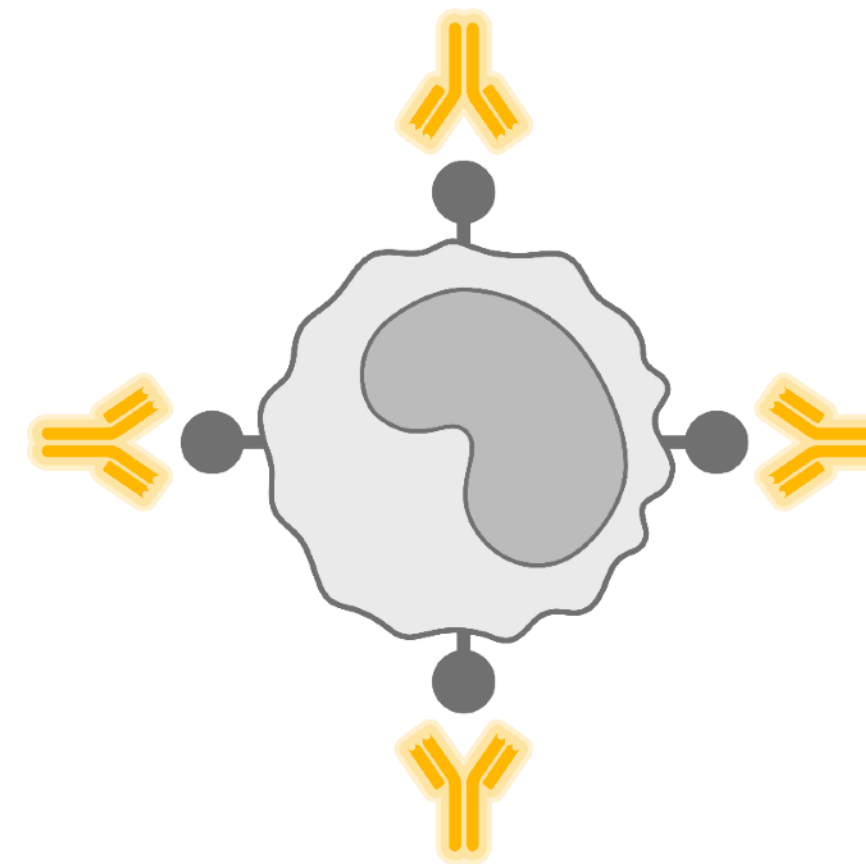
Wildtype C57/BL6 mice

Days



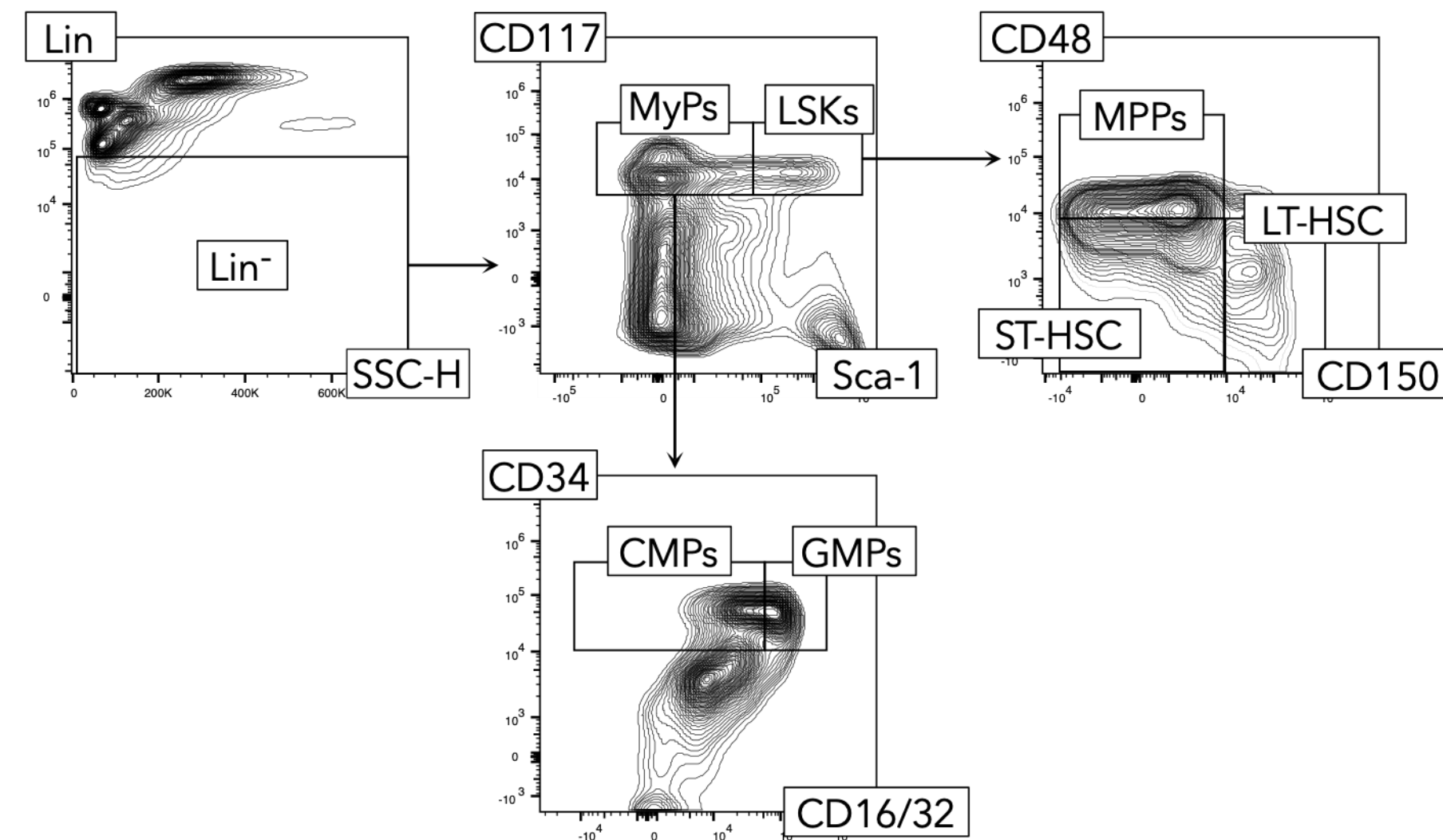
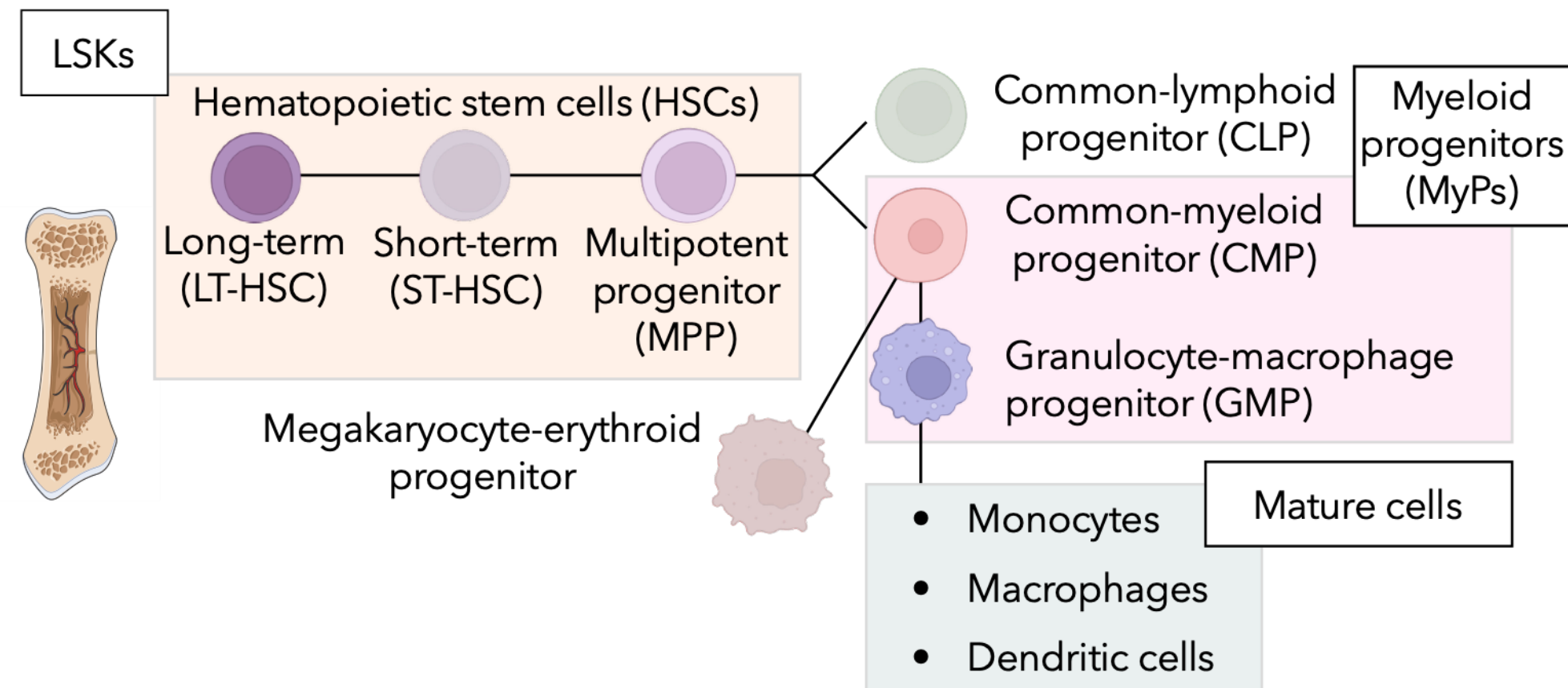
↑ 0.5 mg/kg LAMP1 siRNA

■ Euthanasia and analysis

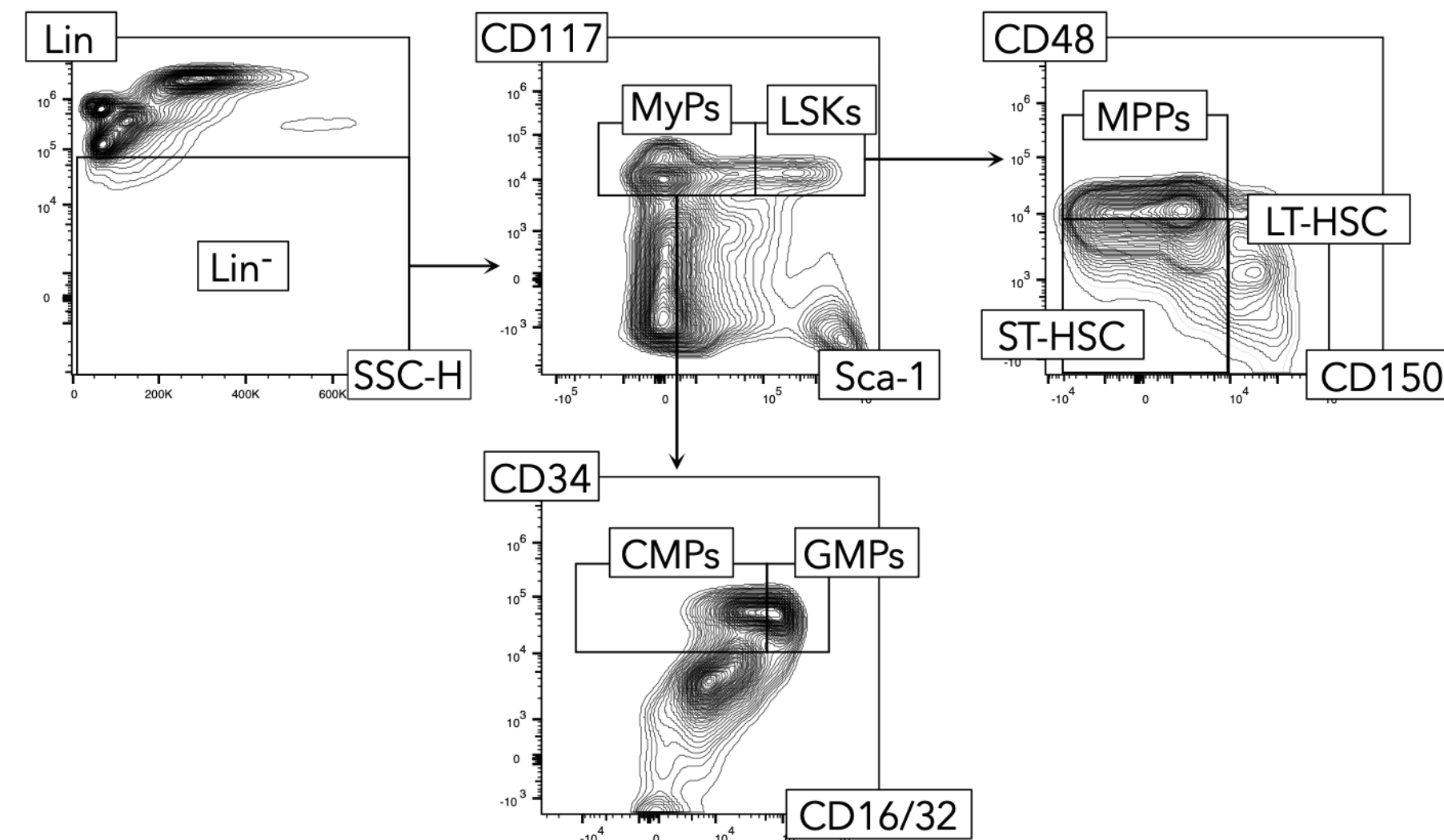
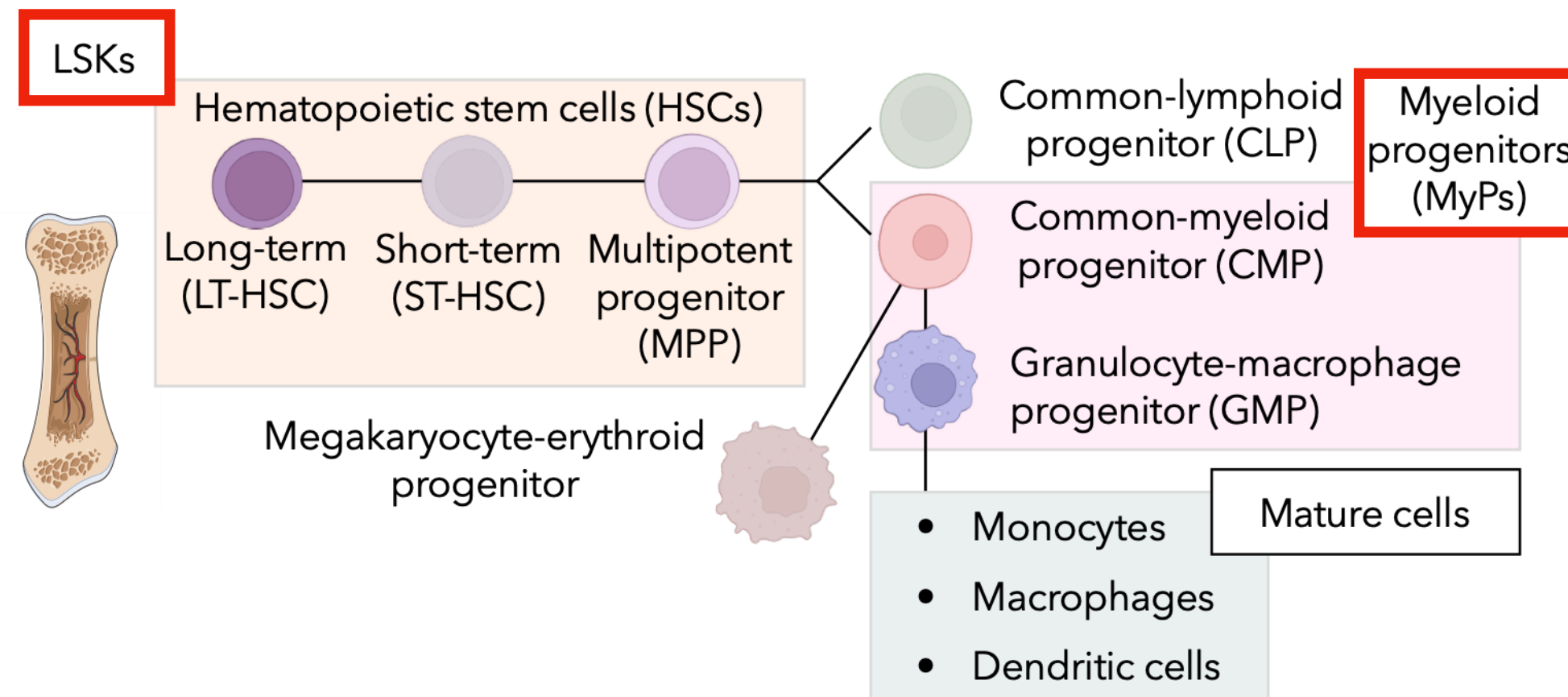


- Membrane bound protein
- Widely expressed
- Function taken over by LAMP2

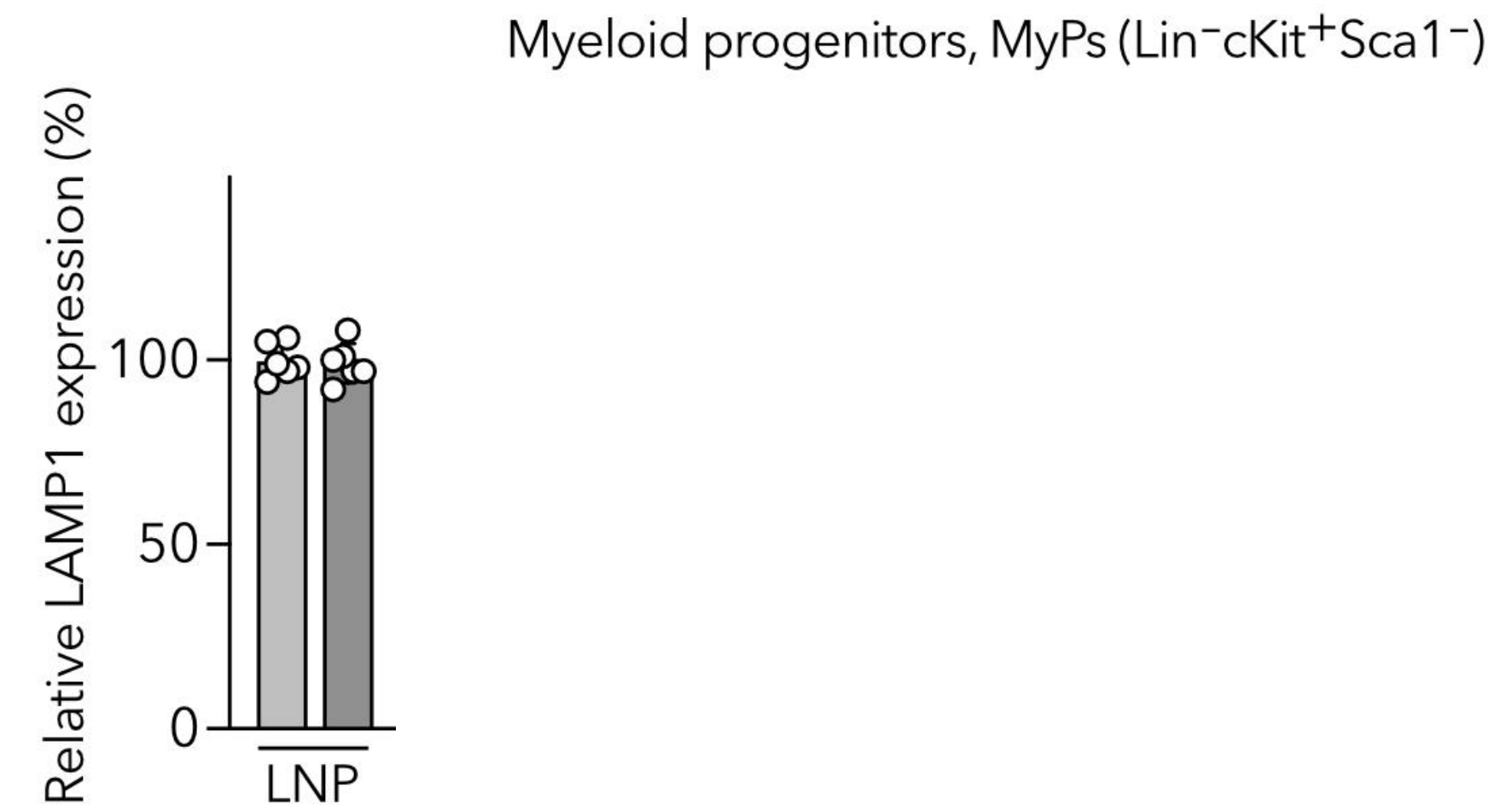
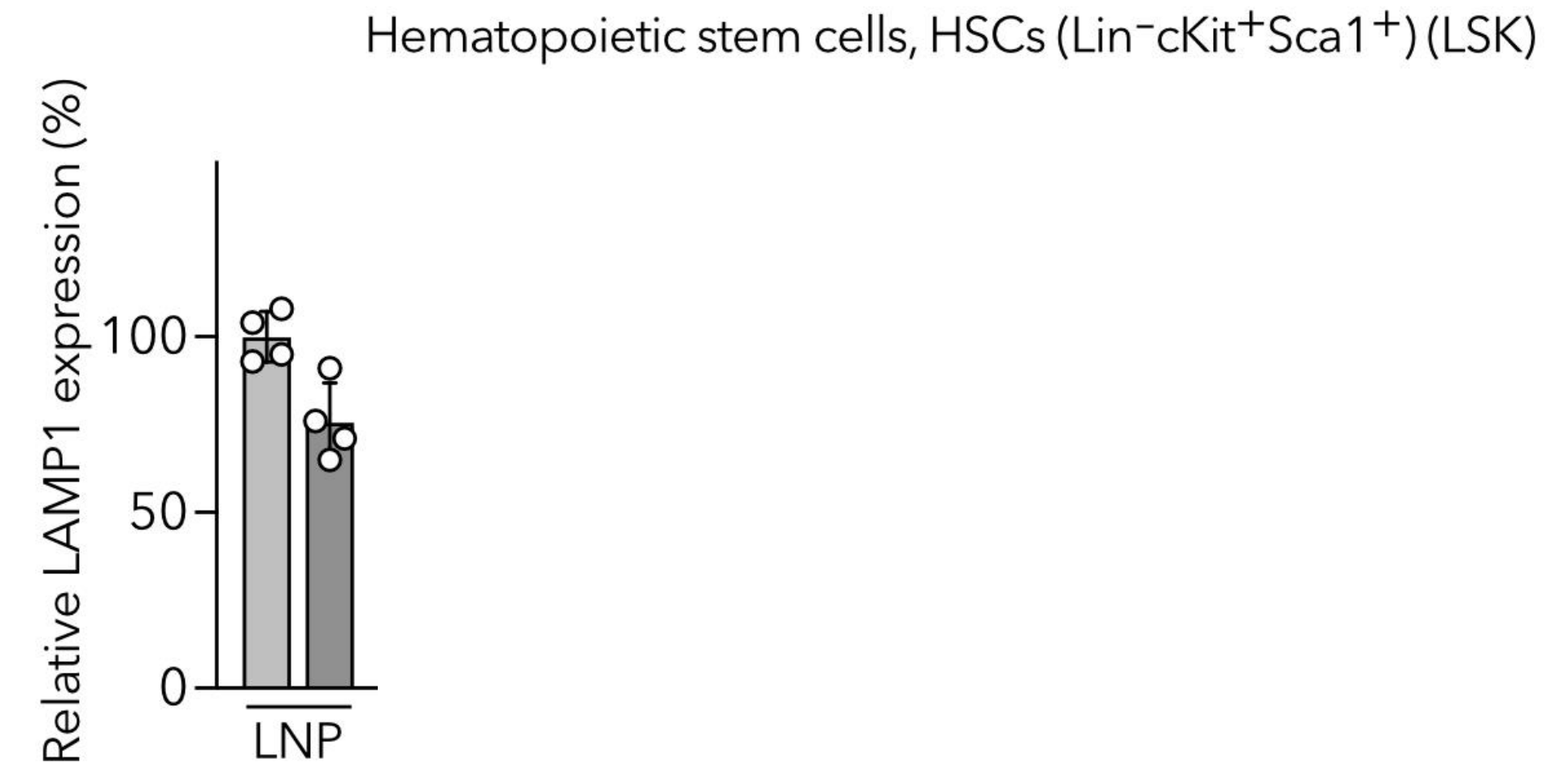
Gene silencing in (myeloid) progenitor cells



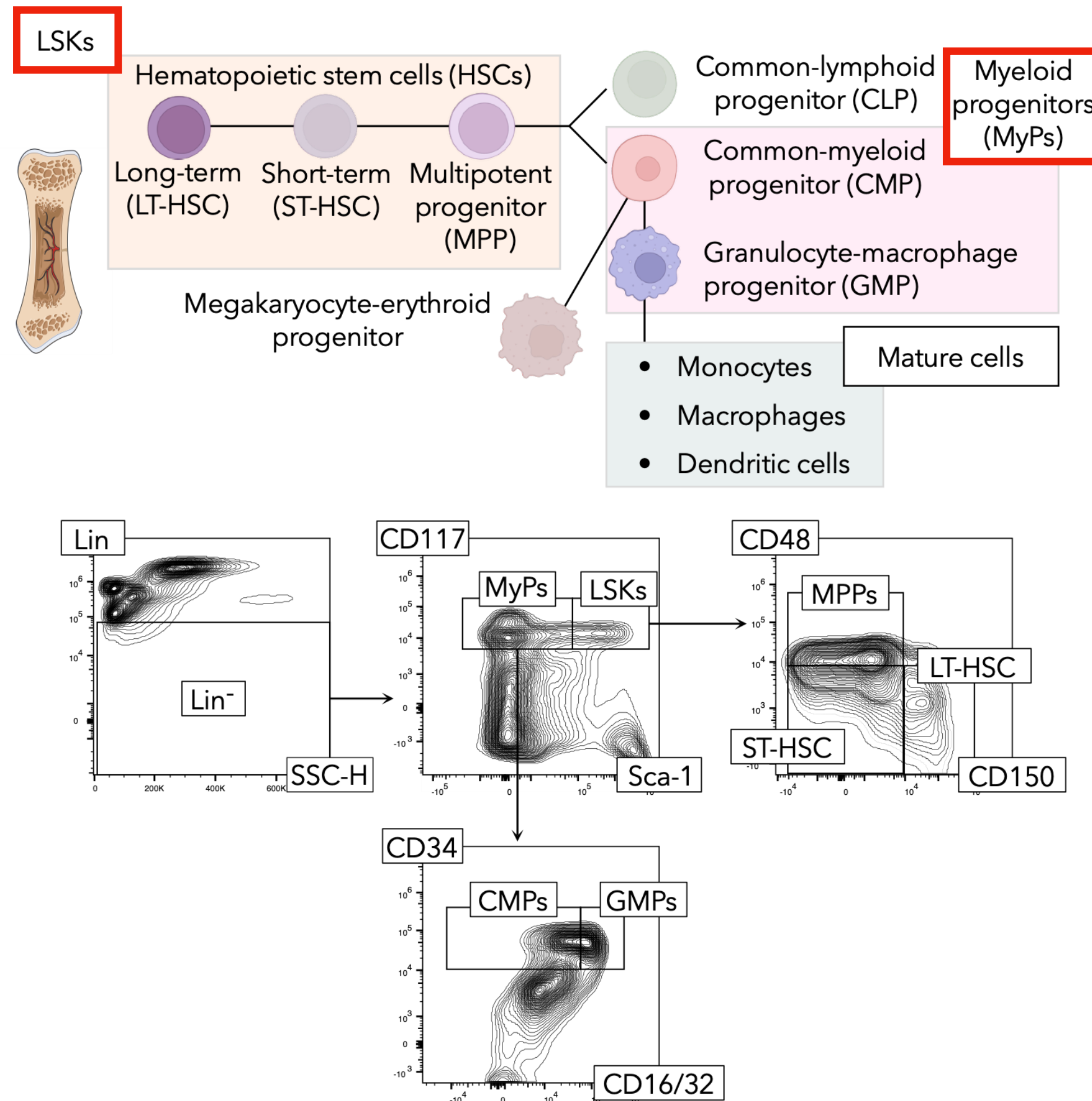
Gene silencing in (myeloid) progenitor cells



□ LNP-siCtrl ■ LNP-siLAMP1

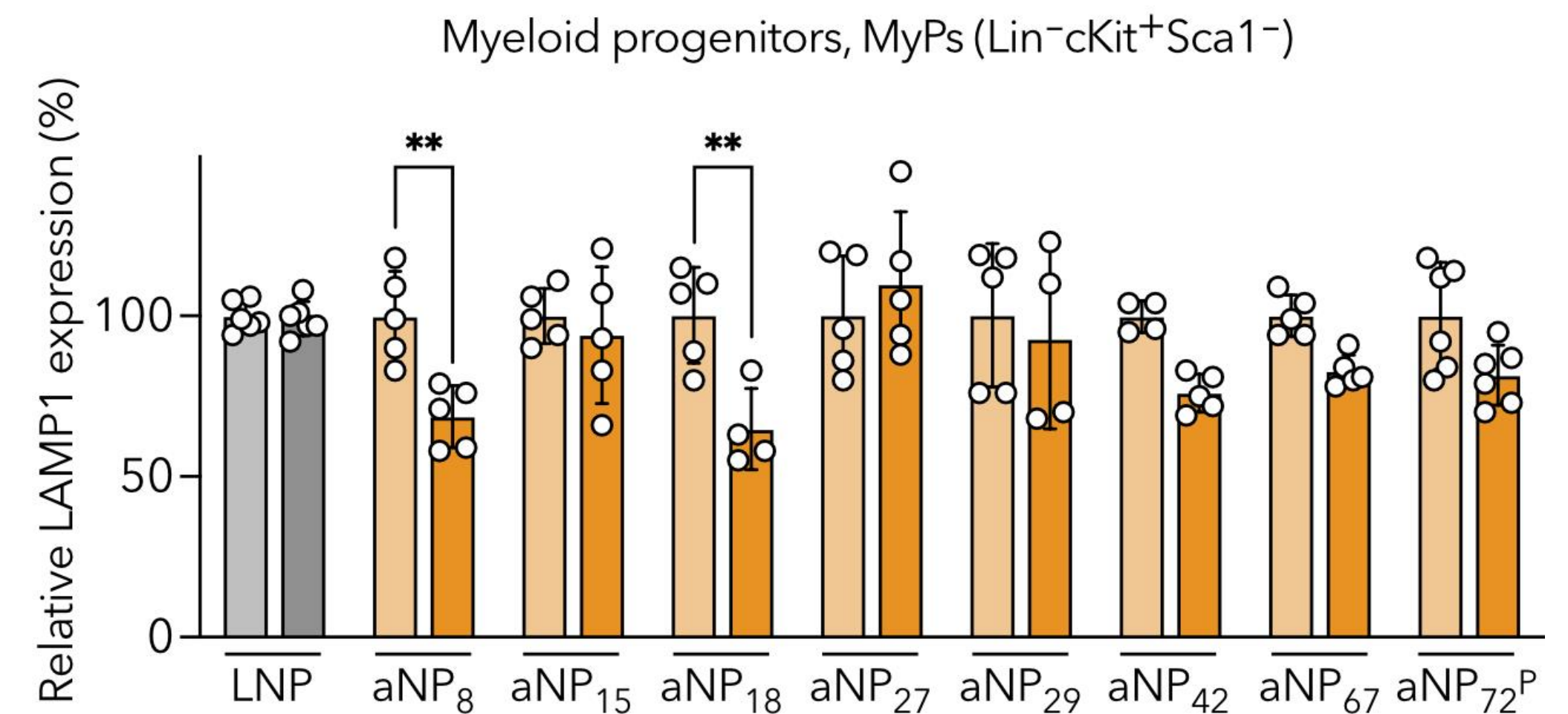
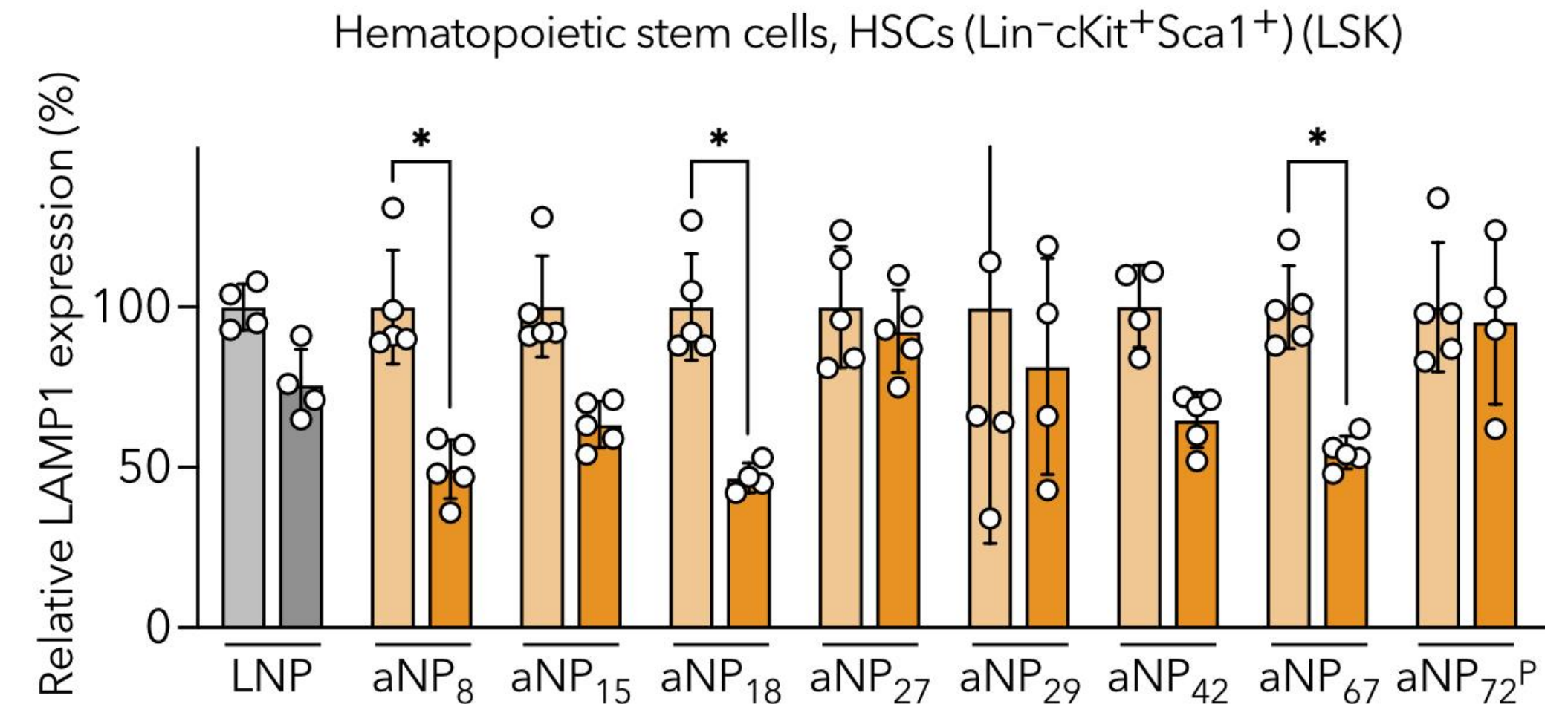


Gene silencing in (myeloid) progenitor cells

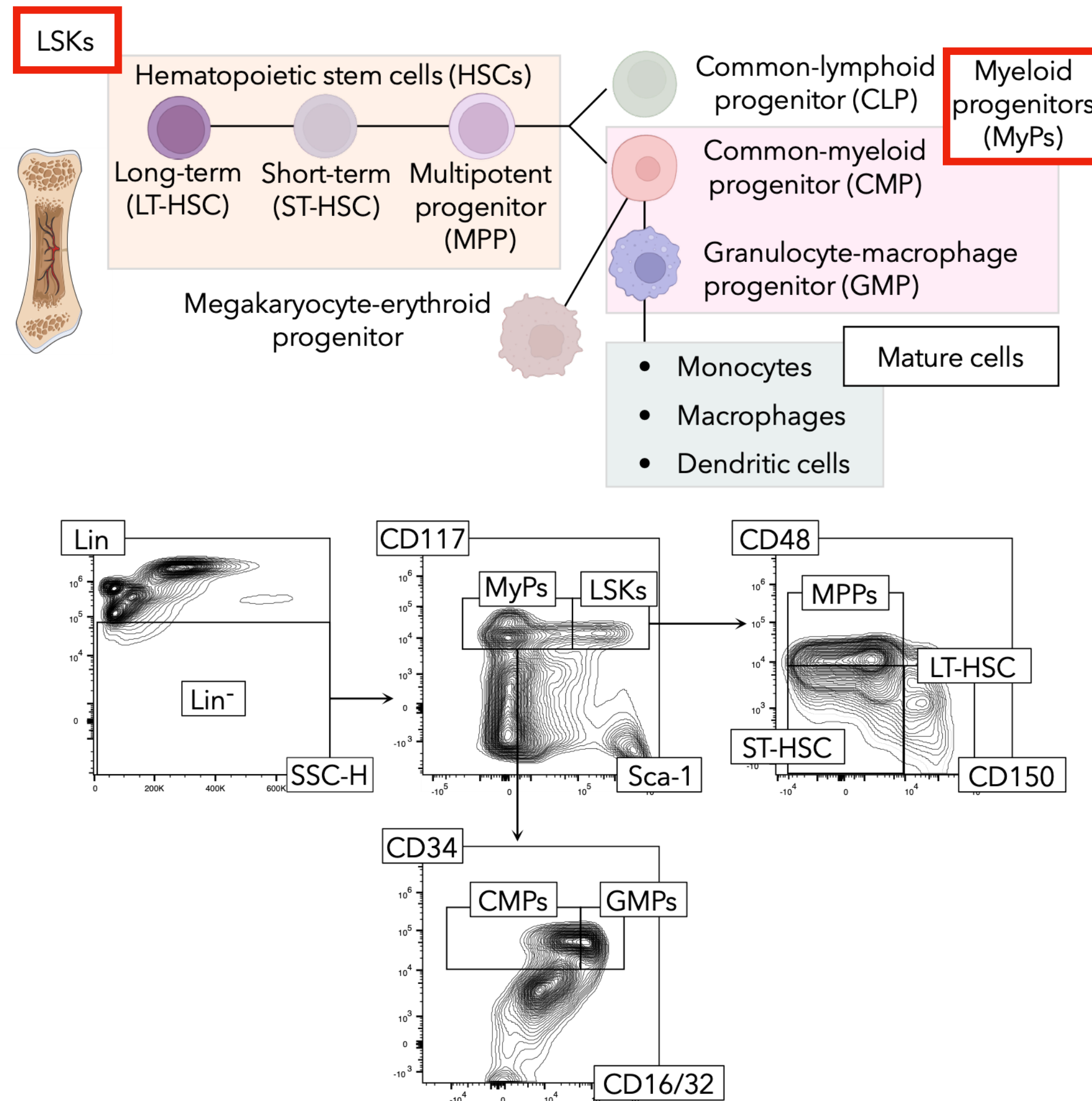


Legend: LNP-siCtrl (light grey), LNP-siLAMP1 (dark grey), aNP-siCtrl (light orange), aNP-siLAMP1 (dark orange)

P: Prototype aNP

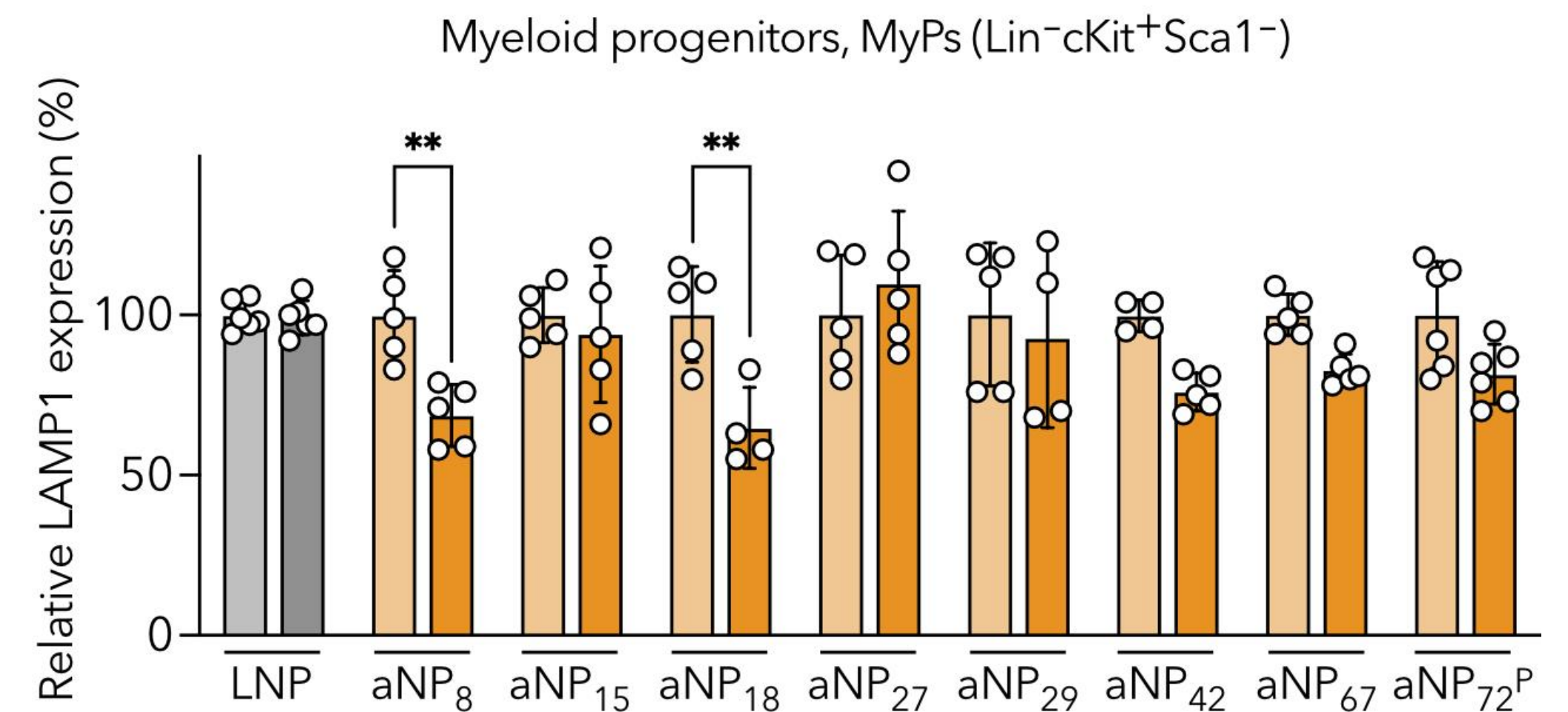
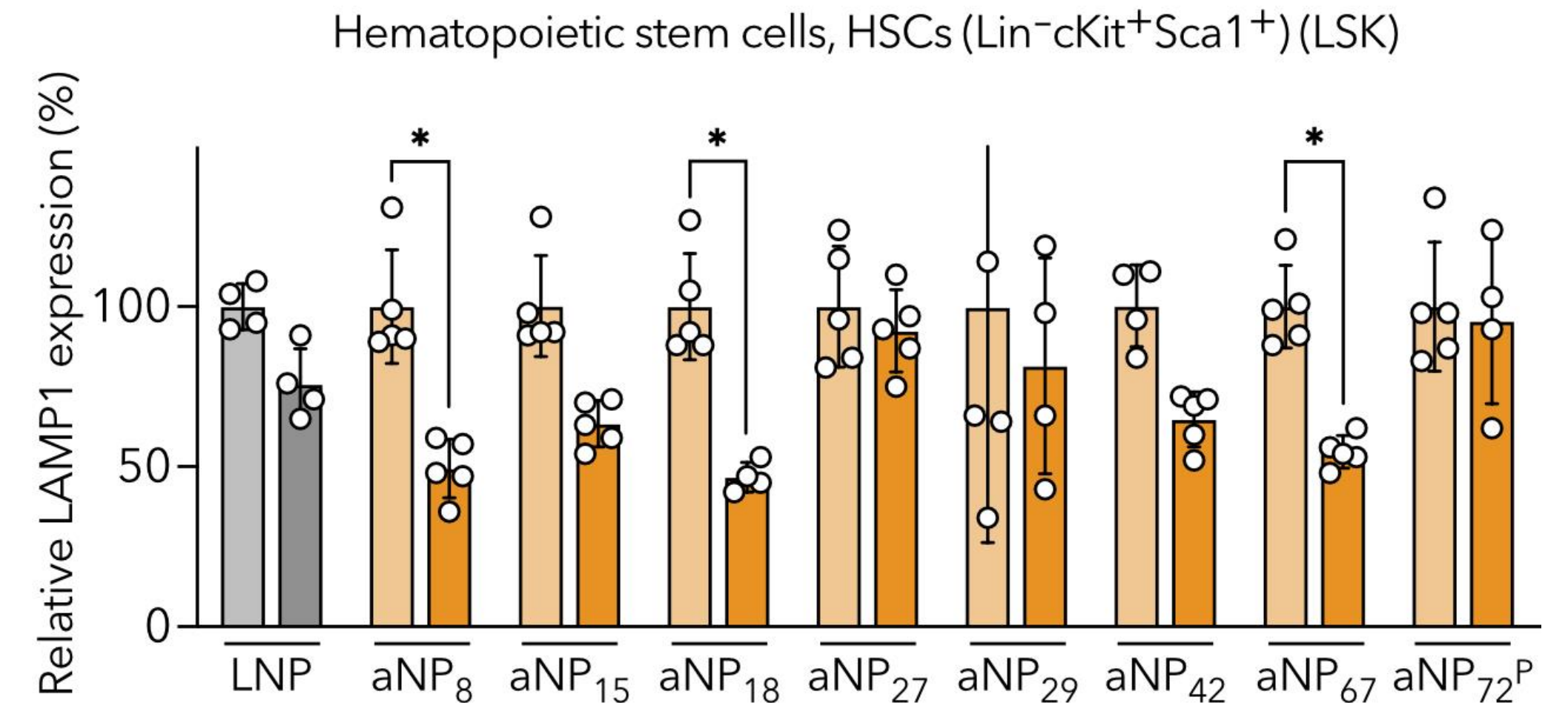


Gene silencing in (myeloid) progenitor cells

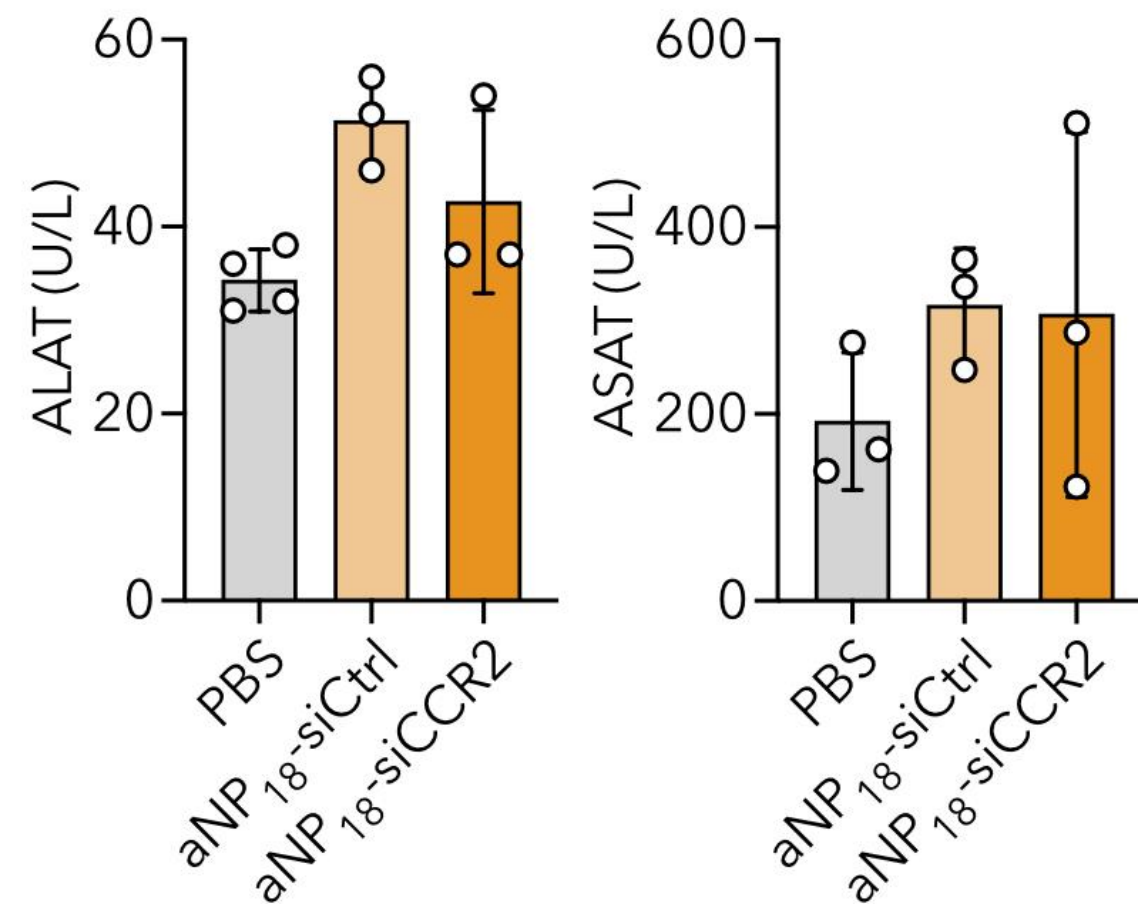
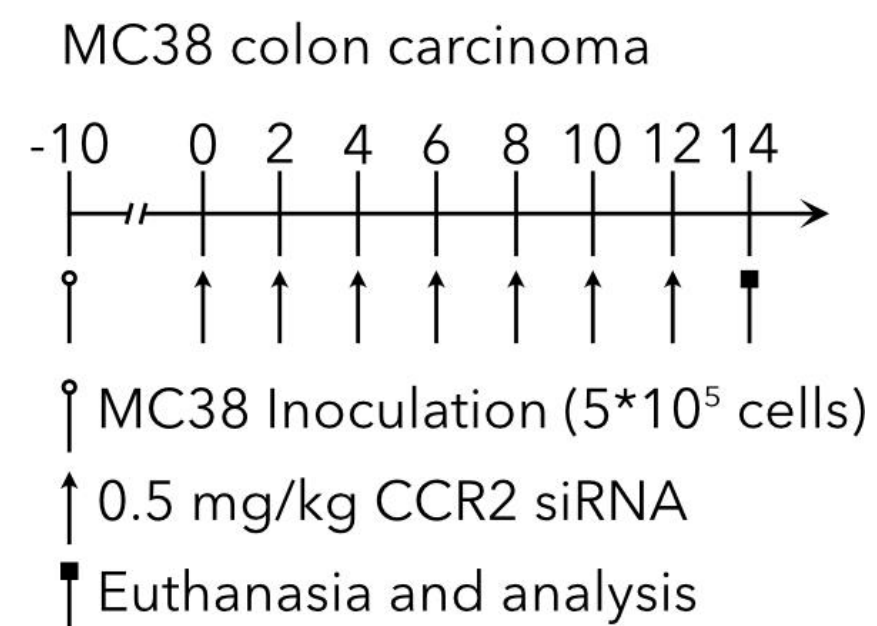
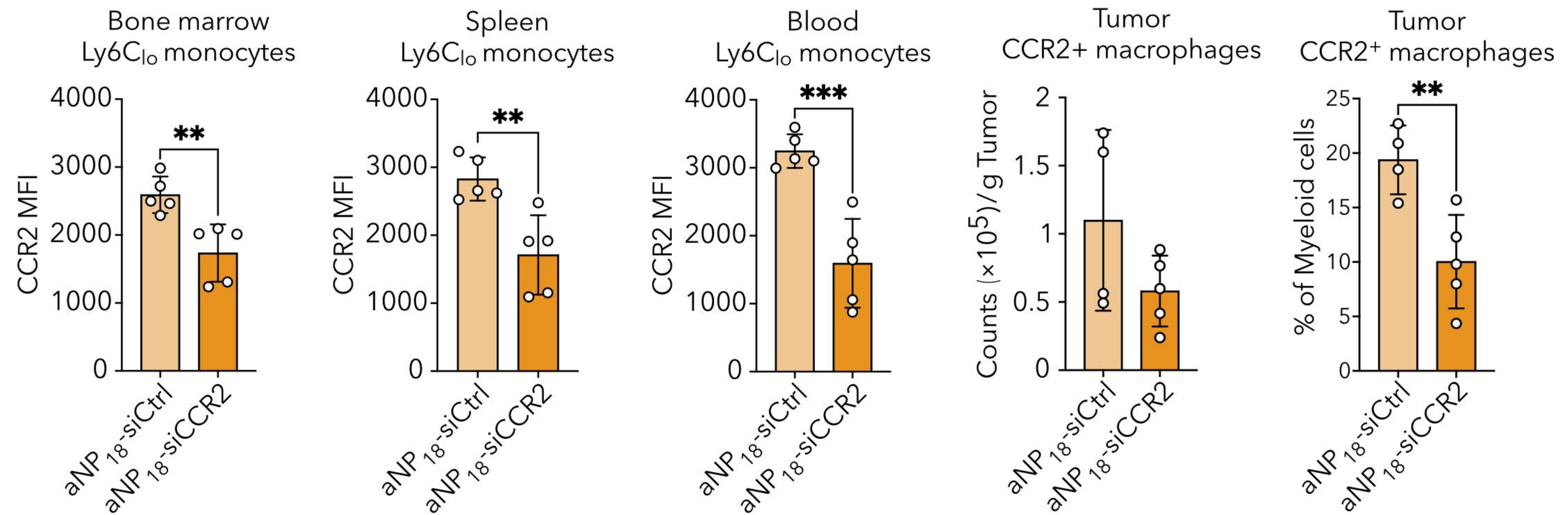
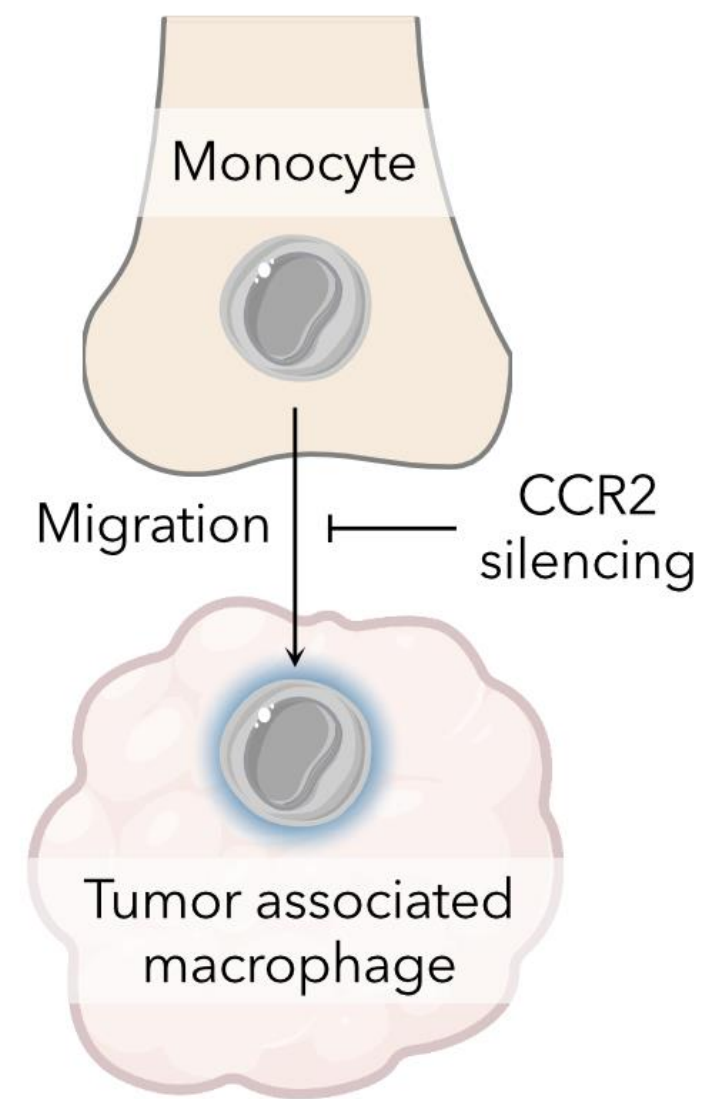


Legend: LNP-siCtrl (light grey), LNP-siLAMP1 (dark grey), aNP-siCtrl (light orange), aNP-siLAMP1 (dark orange)

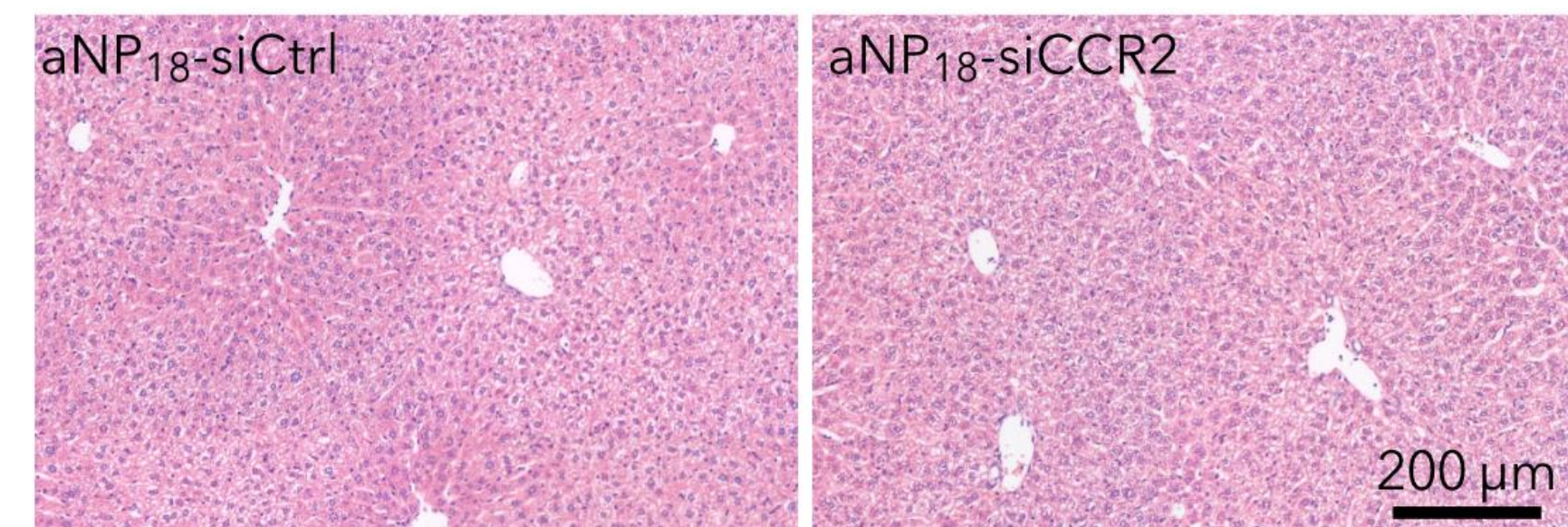
P: Prototype aNP



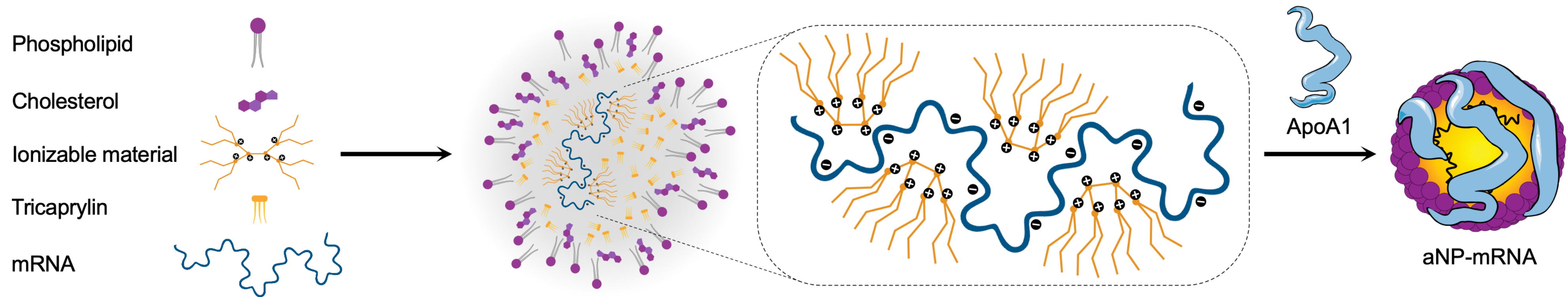
Inhibiting immunosuppressive monocyte migration



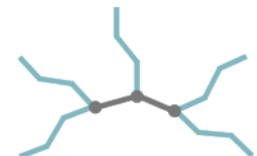
Liver H&E staining



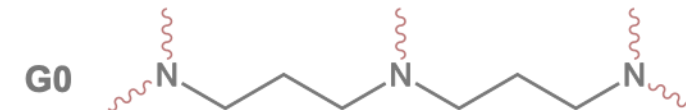
aNPs with polyvalent materials for mRNA delivery



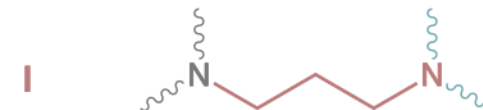
Generation 0
(G0)



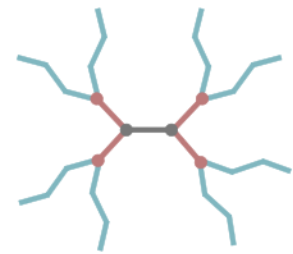
Core unit



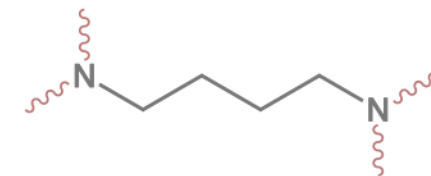
Branching unit



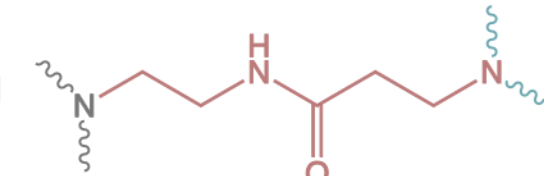
Generation 1
(G1)



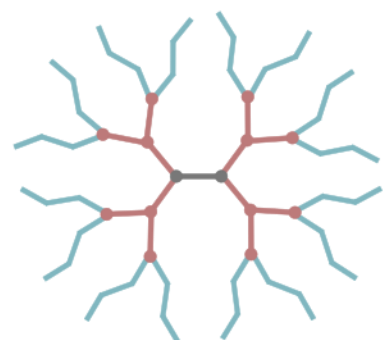
G1 & G2



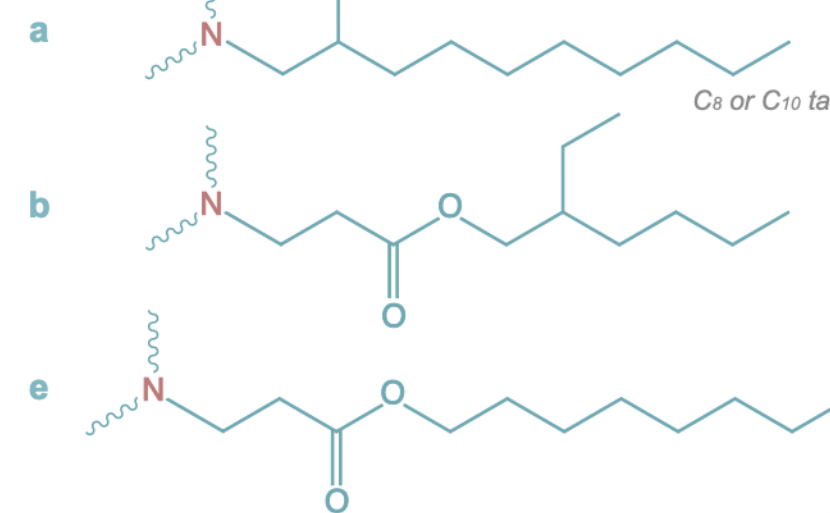
M



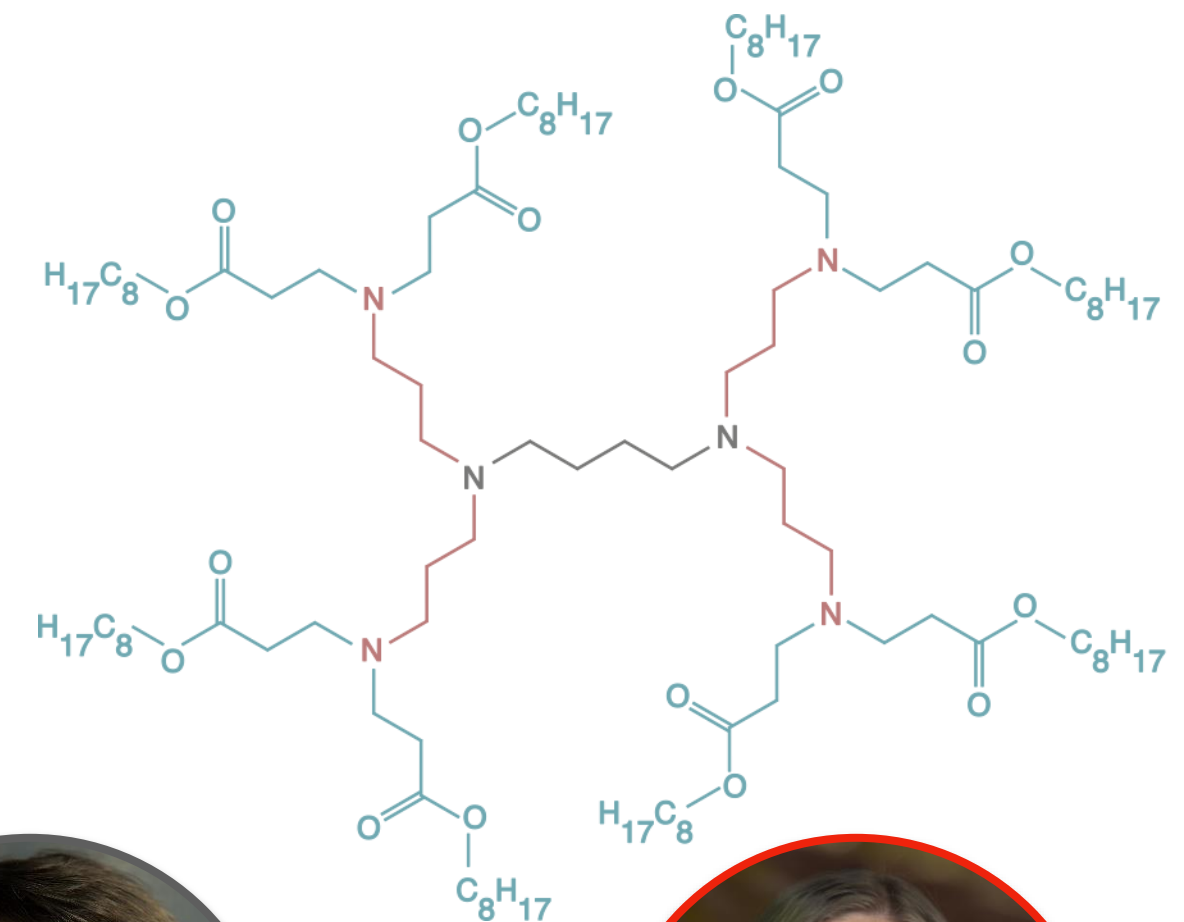
Generation 2
(G2)



Terminal unit



Henk Janssen *in memoriam*

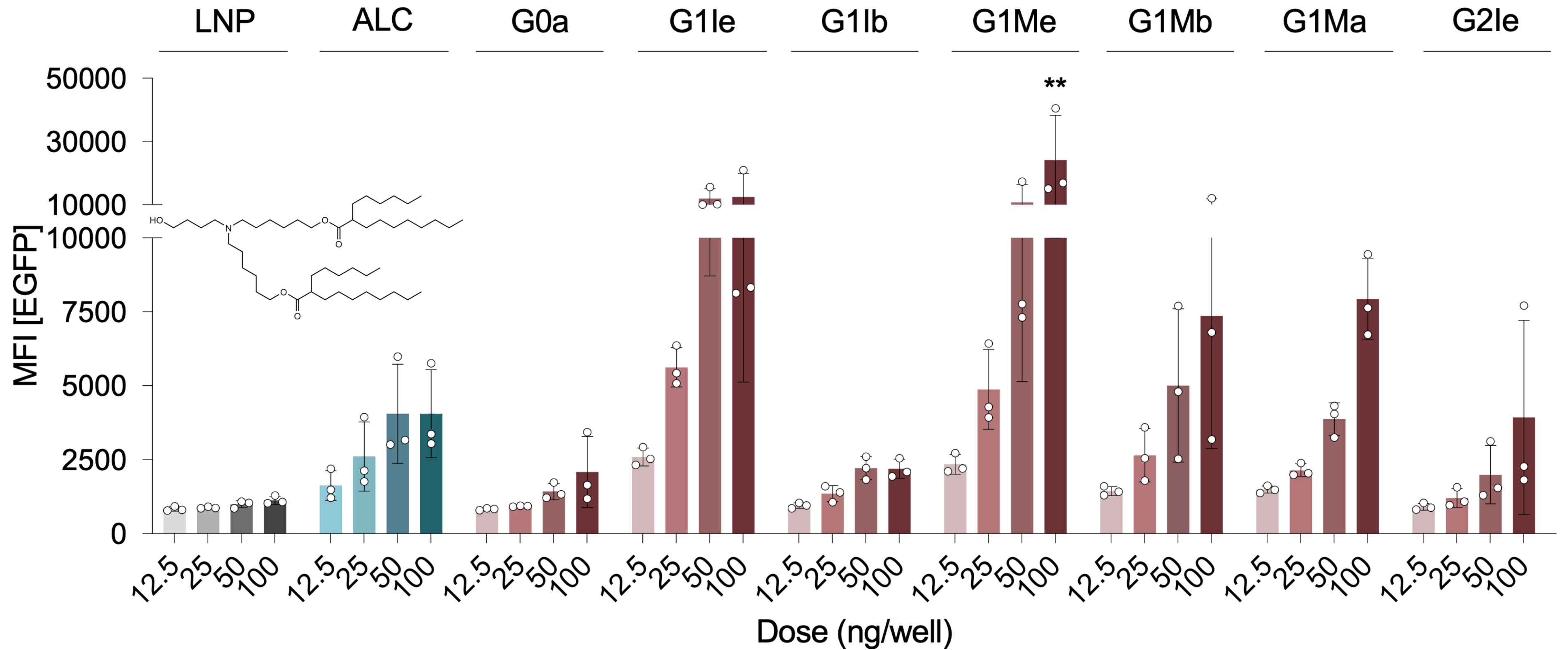
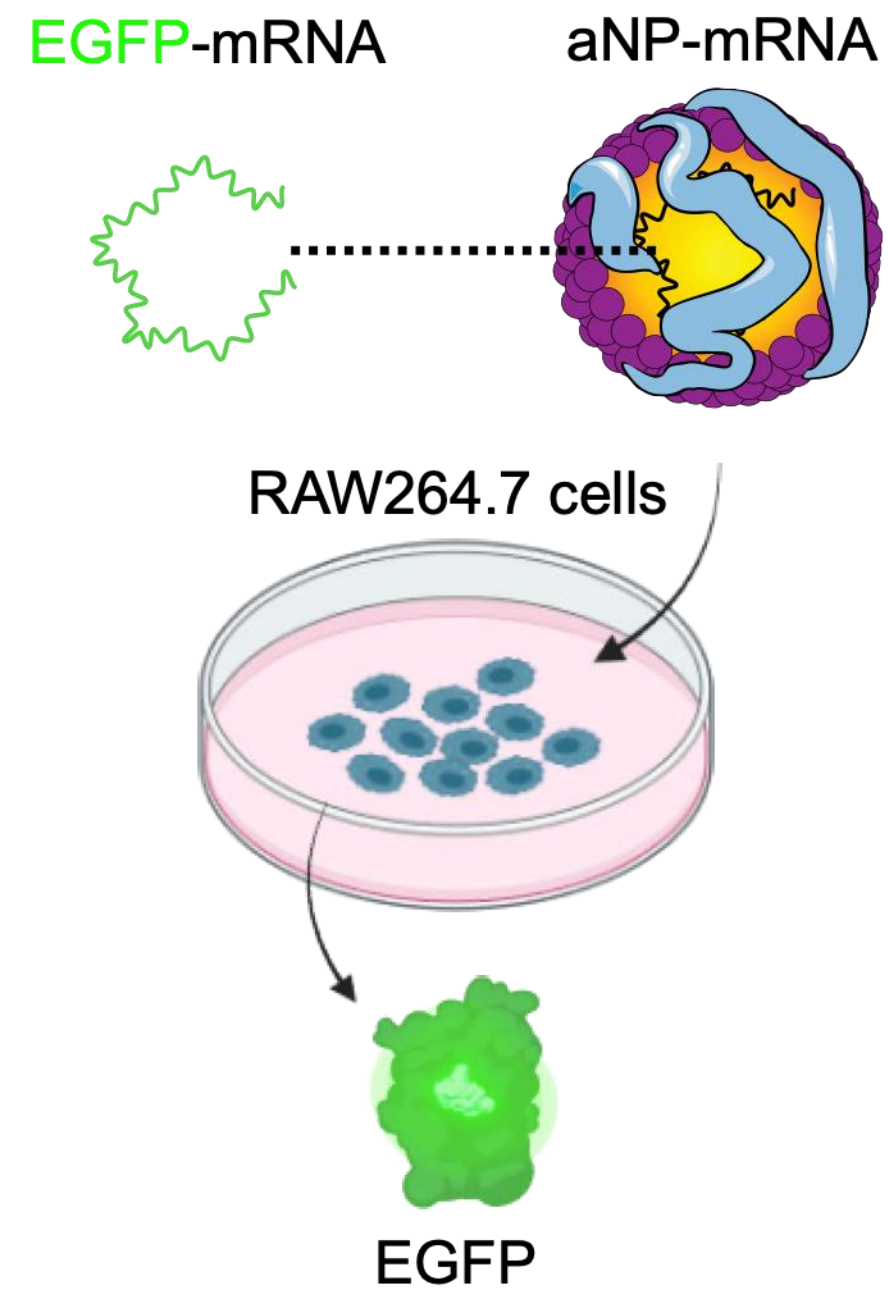
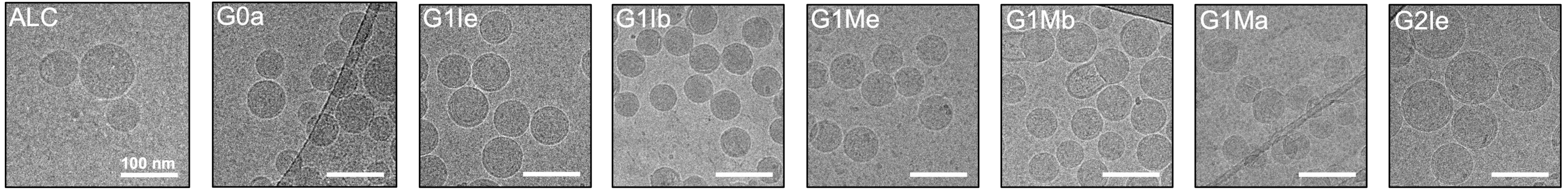


Mirre

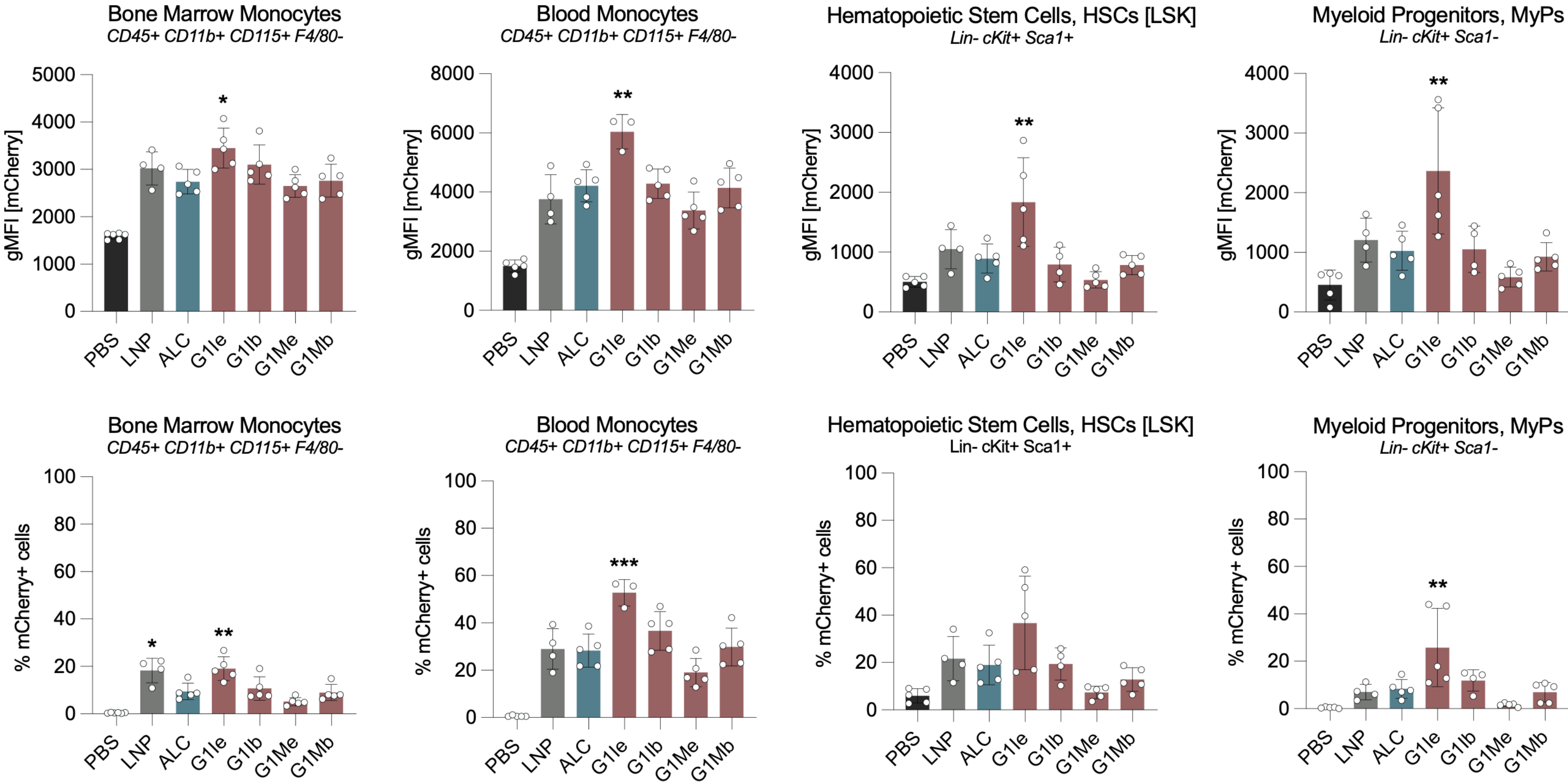
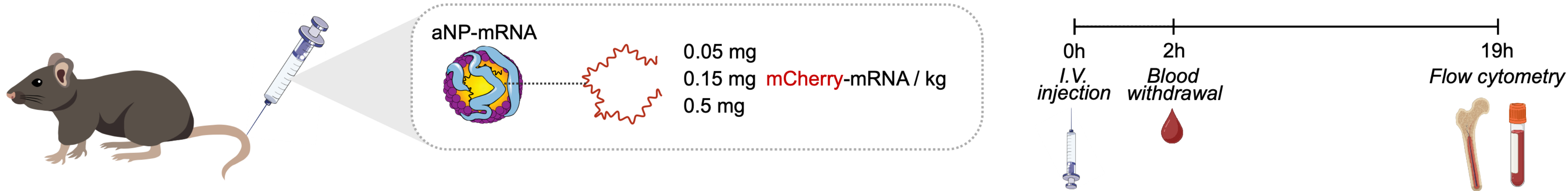


Daniek

aNPs with polyvalent materials for mRNA delivery

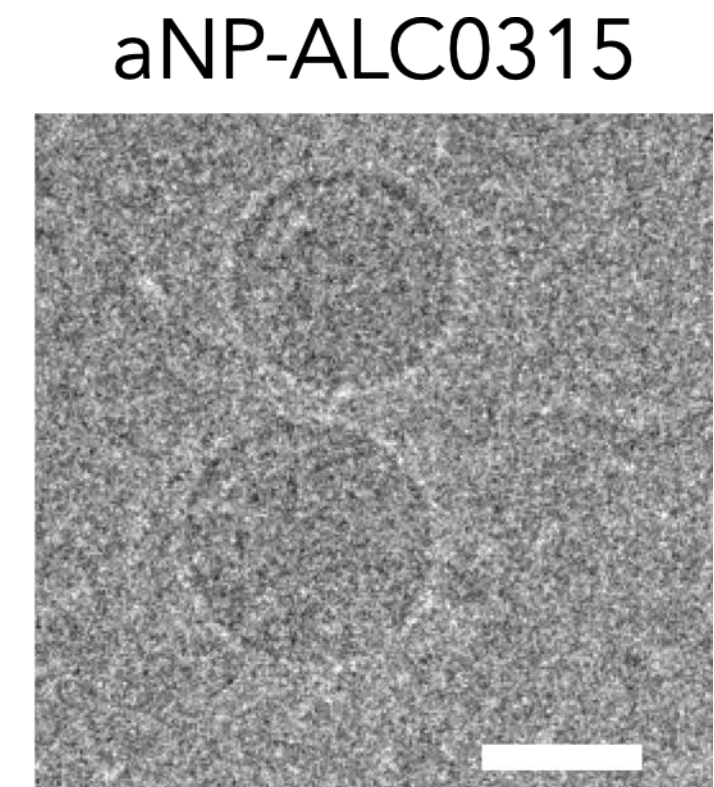
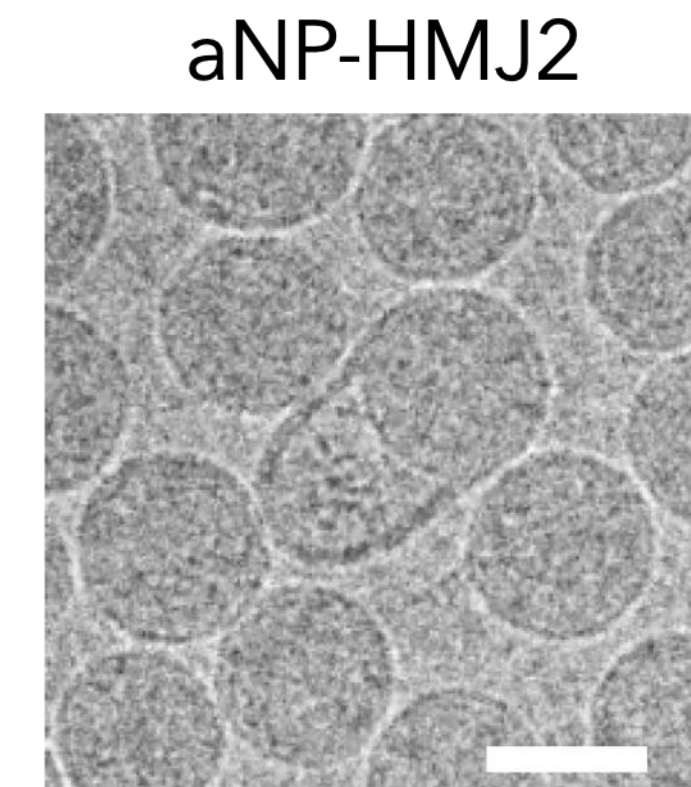
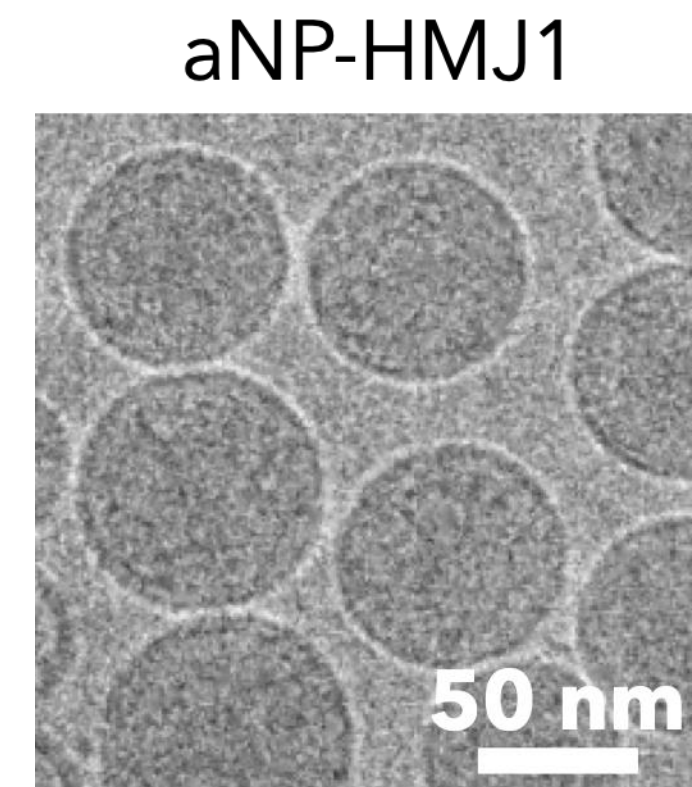
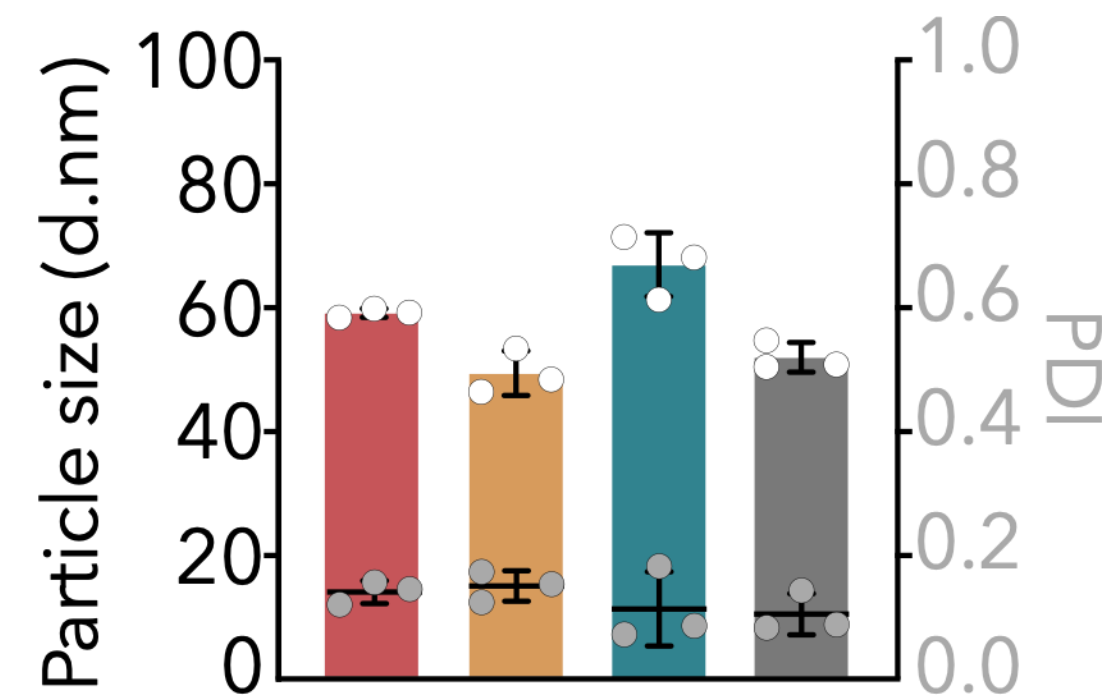
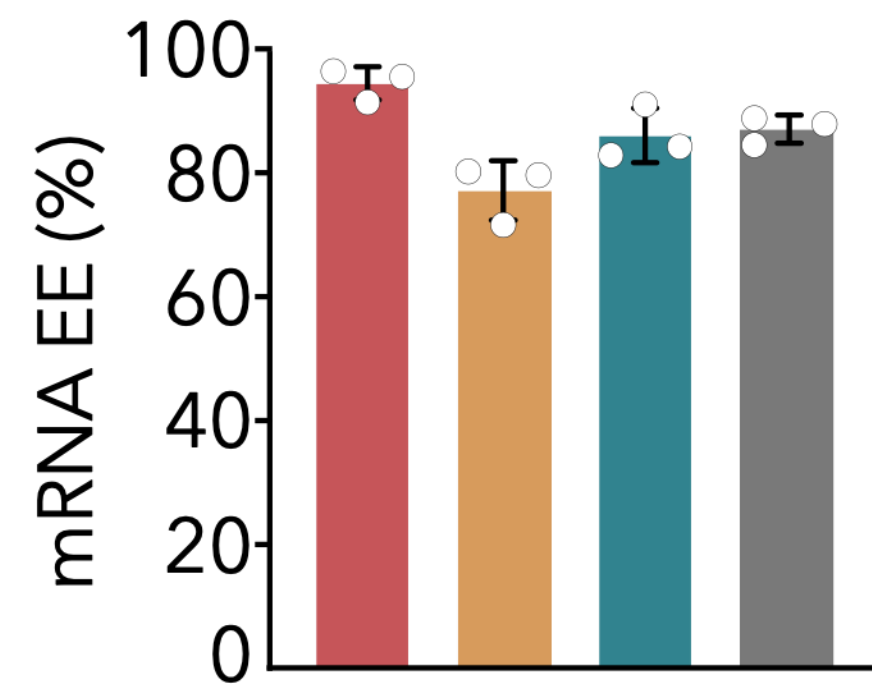


aNPs with polyvalent materials for mRNA delivery



aNPs deliver reporter mRNA to monocytes

- aNP-HMJ1
- aNP-HMJ2
- aNP-ALC0315
- LNP-ALC0315



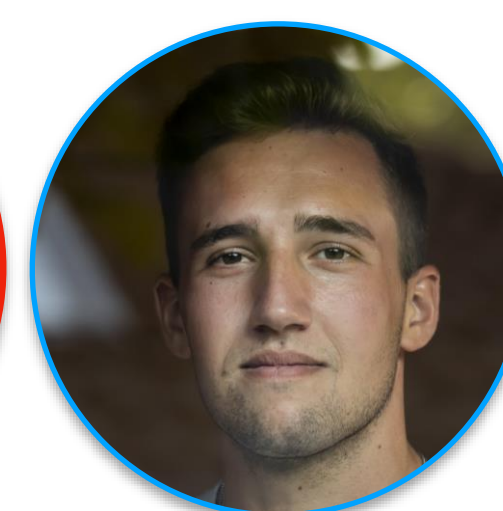
Stijn



Tom



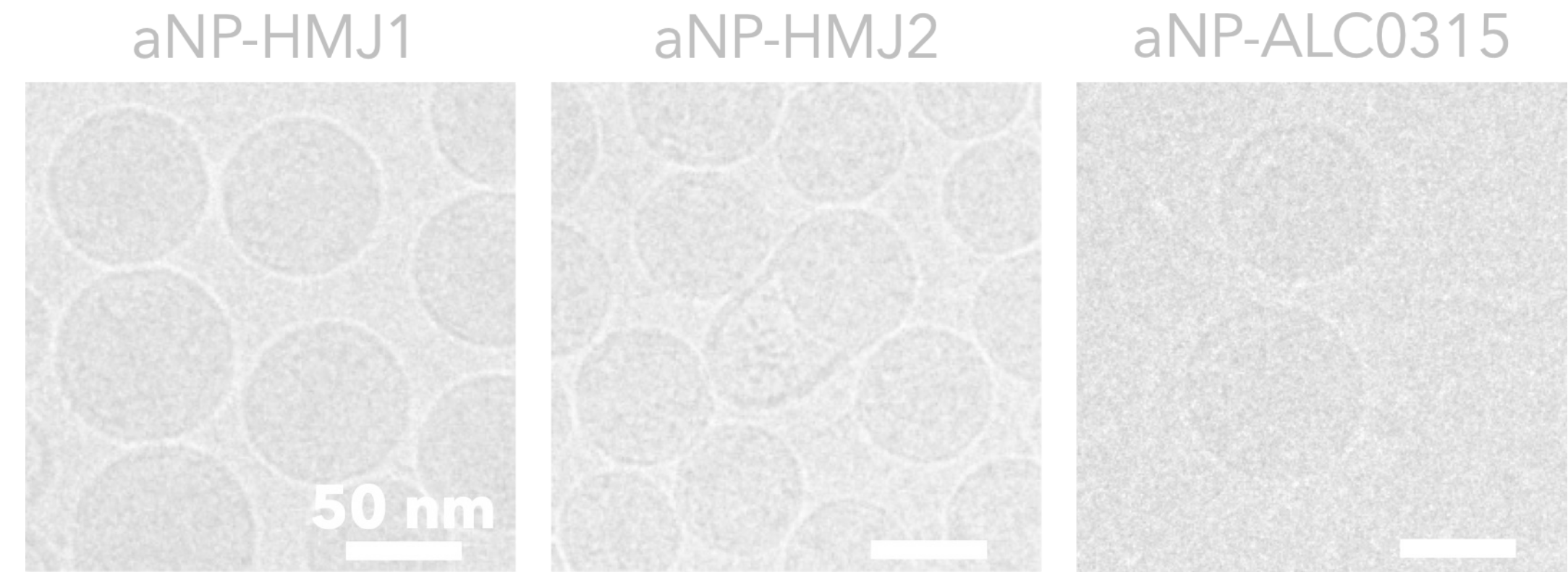
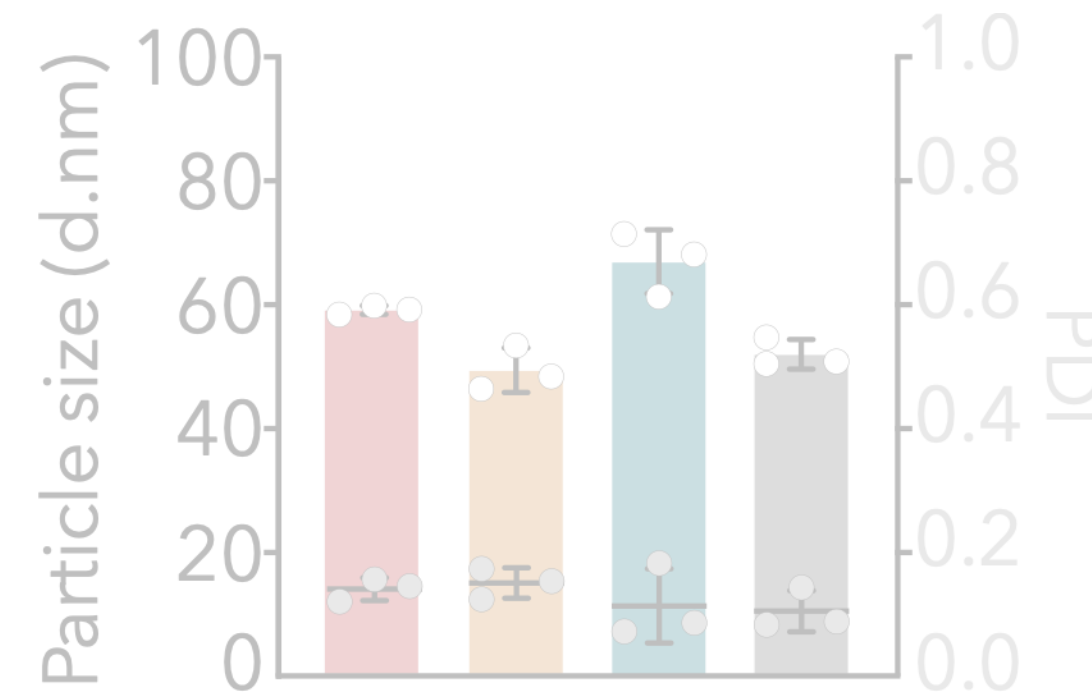
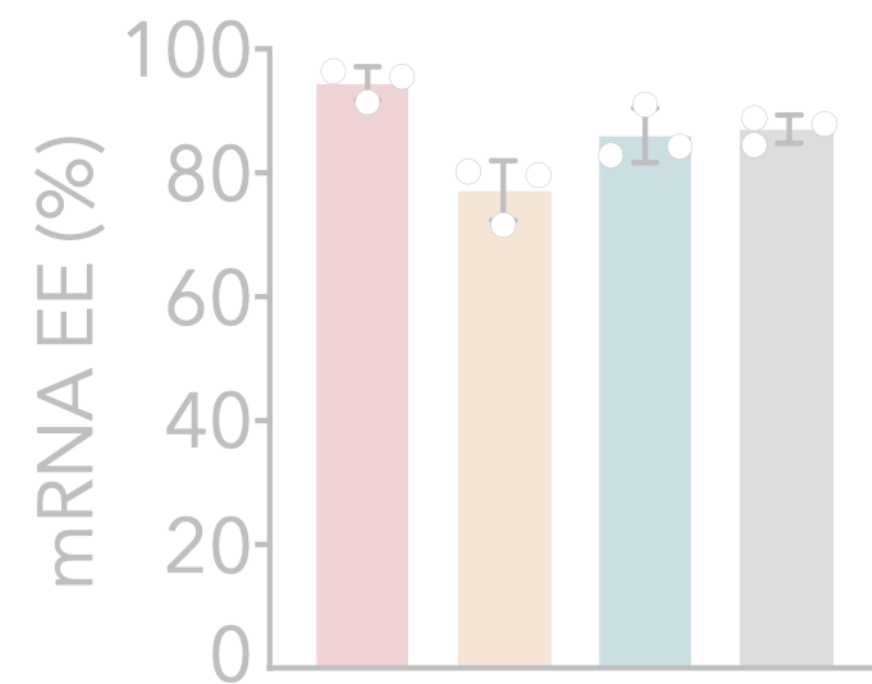
Merel



Yuri

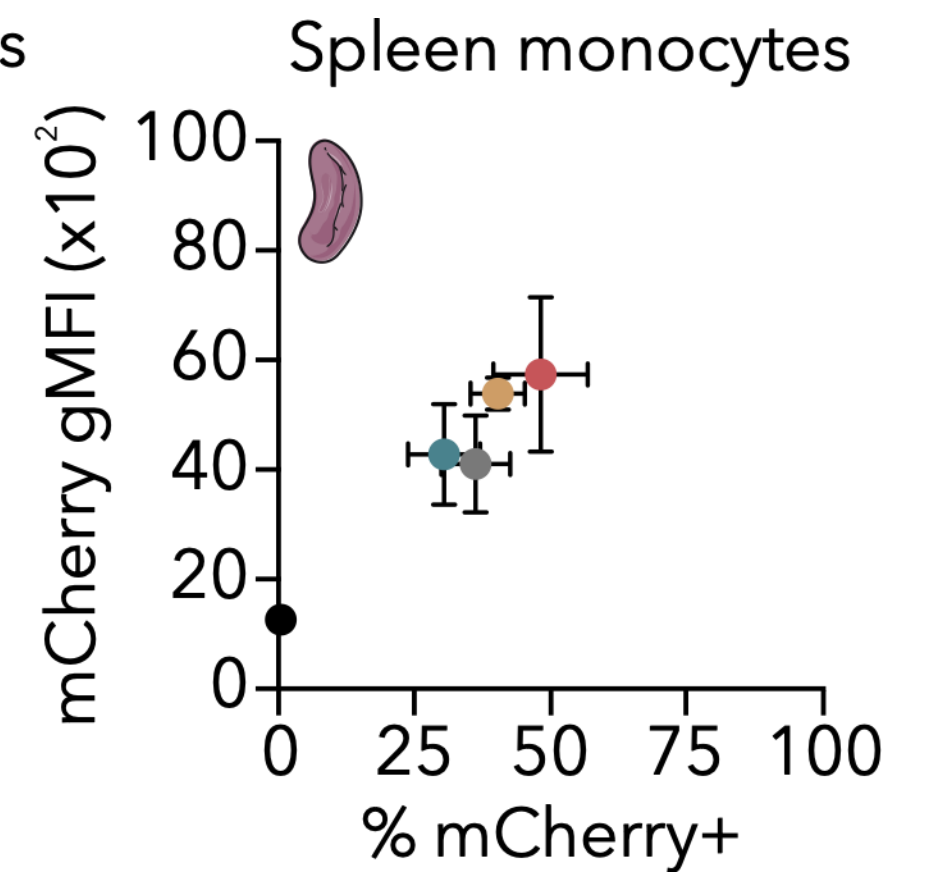
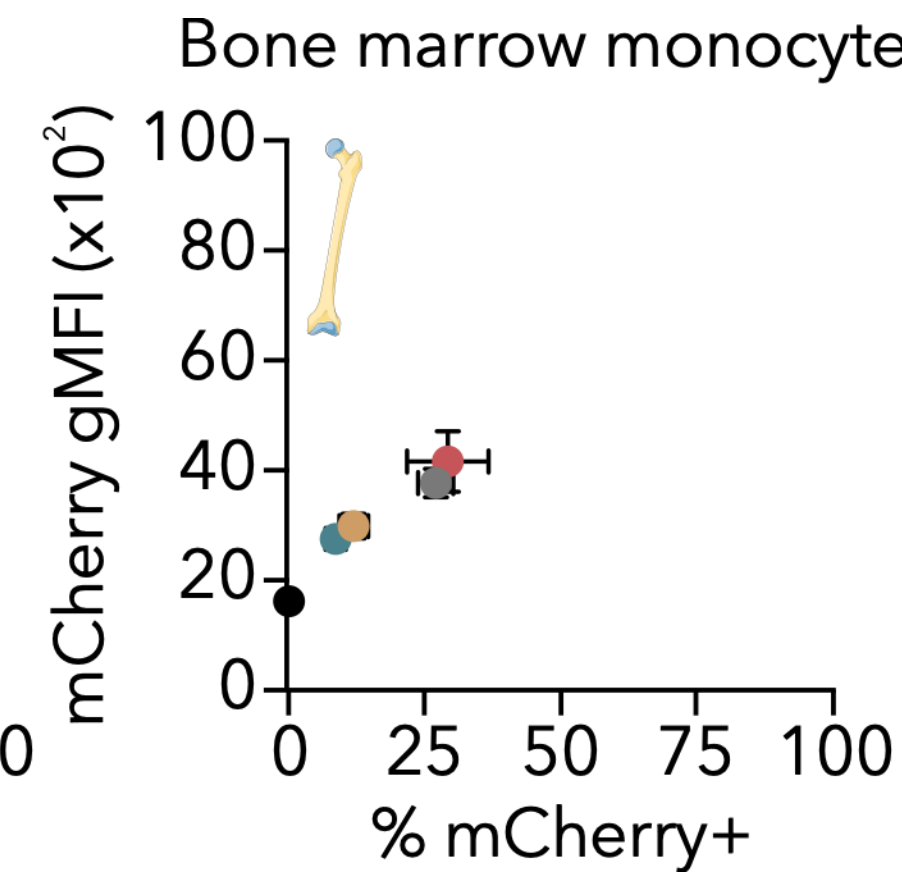
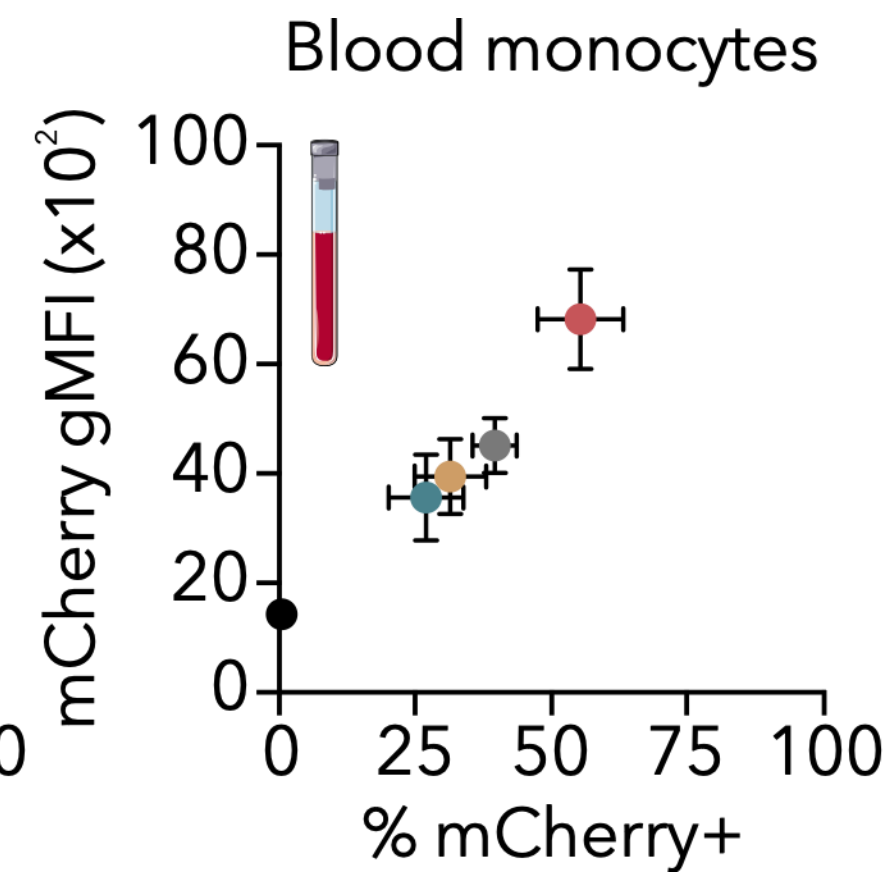
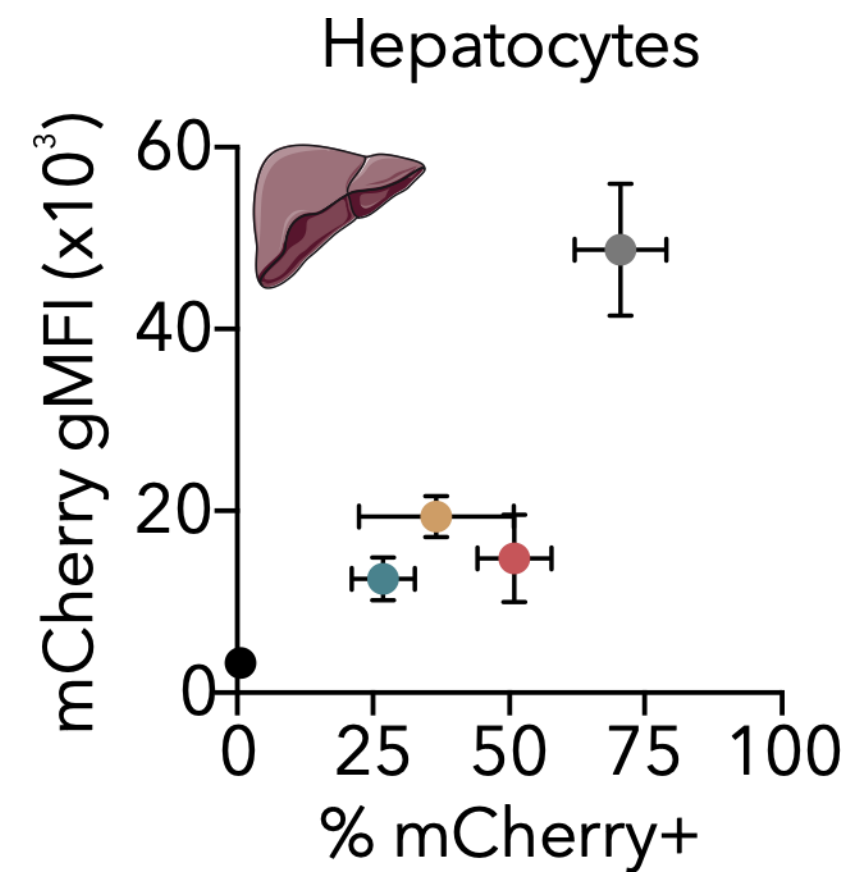
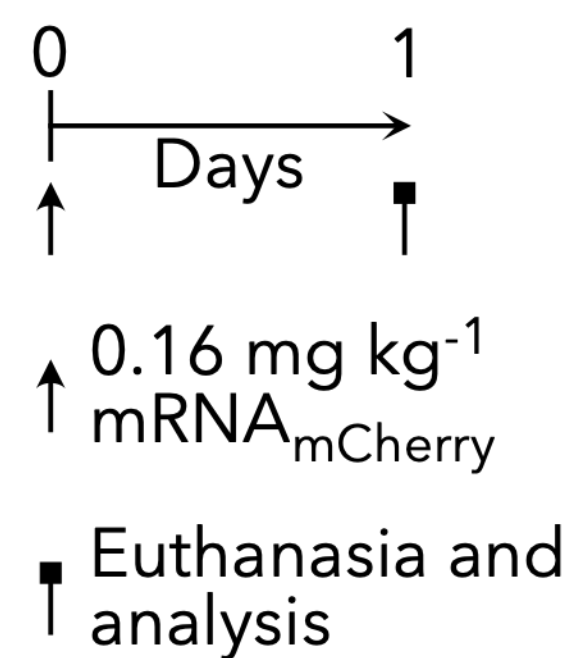
aNPs deliver reporter mRNA to monocytes

- aNP-HMJ1
- aNP-HMJ2
- aNP-ALC0315
- LNP-ALC0315

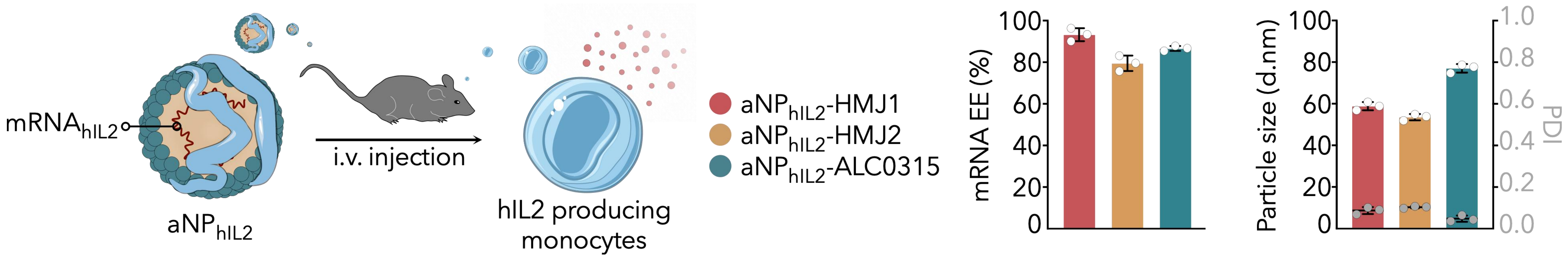


Wildtype C57/BL6 mice

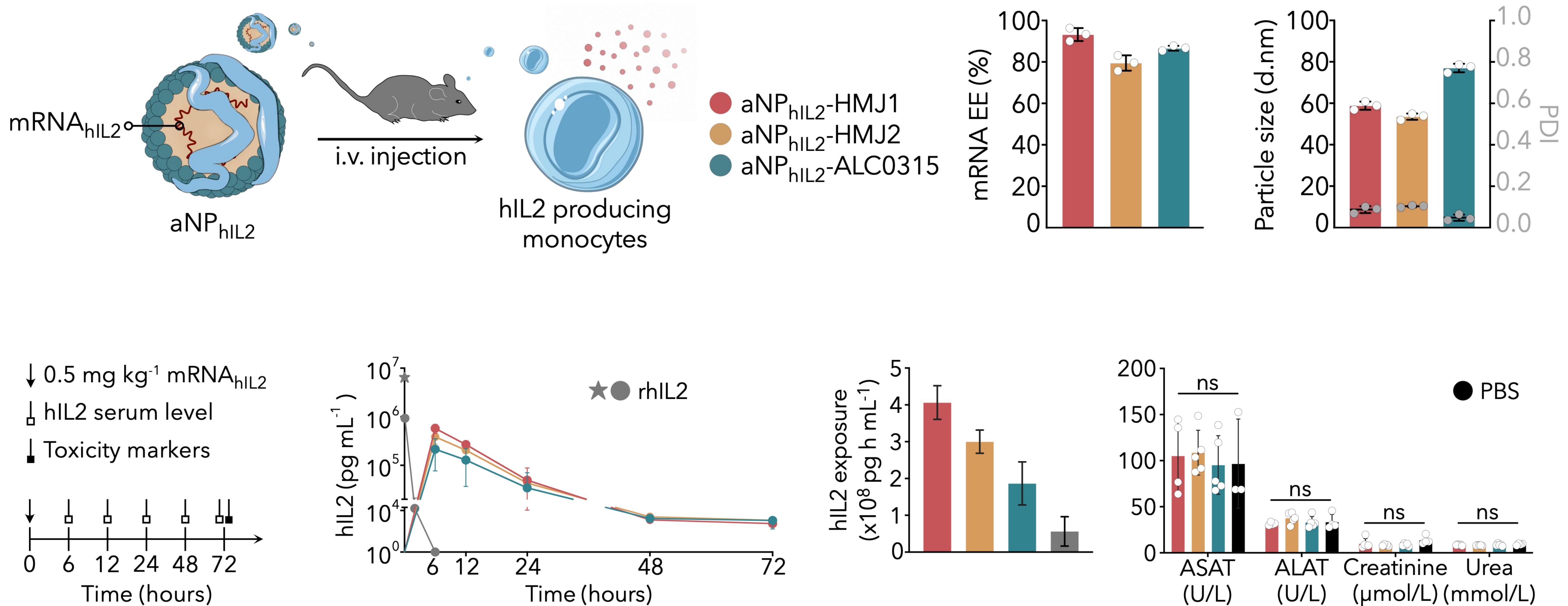
- aNP-HMJ1
- aNP-HMJ2
- aNP-ALC0315
- LNP-ALC0315



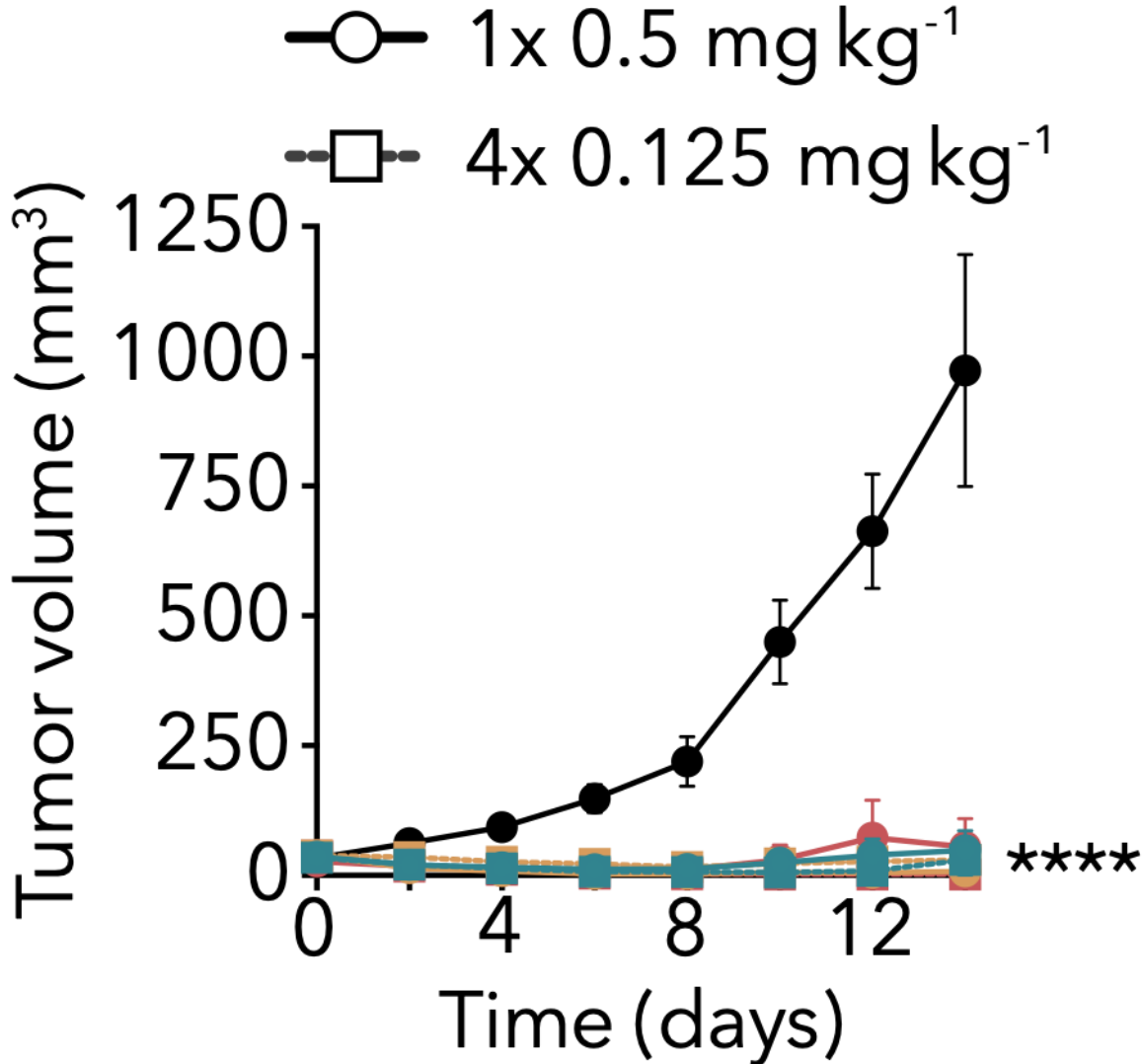
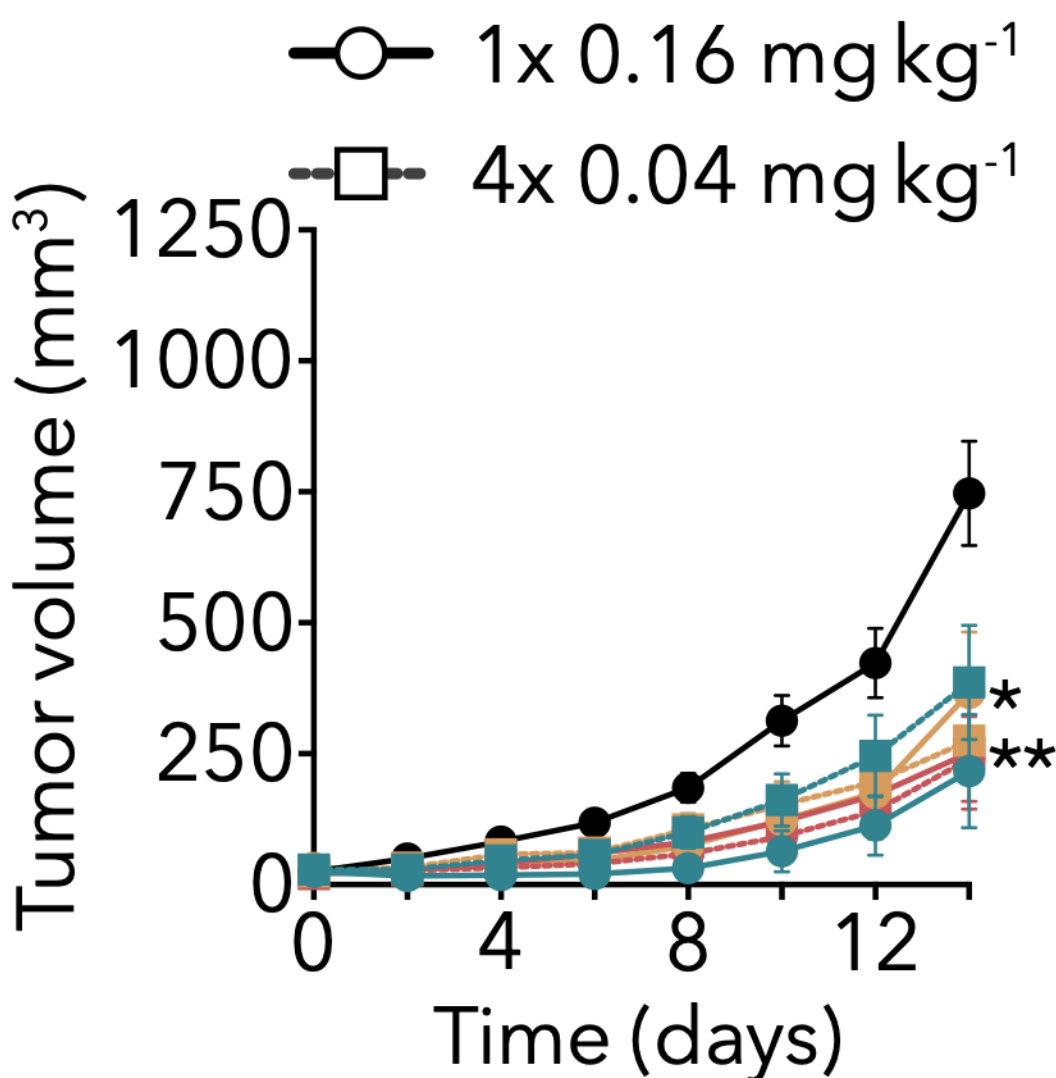
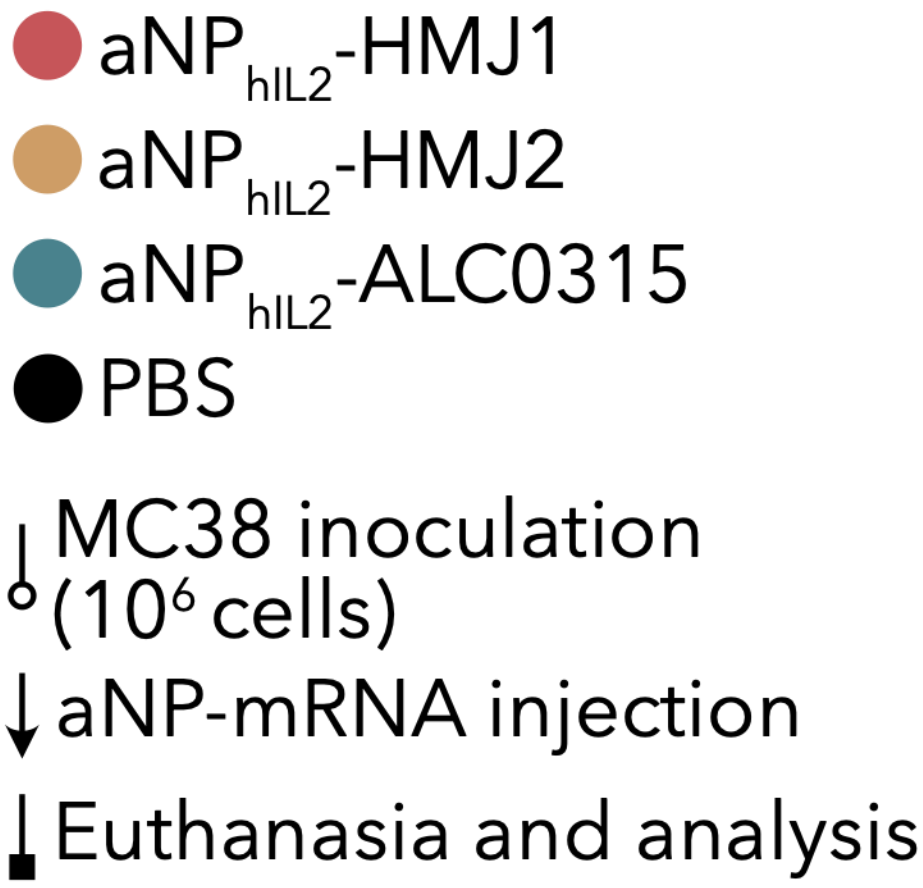
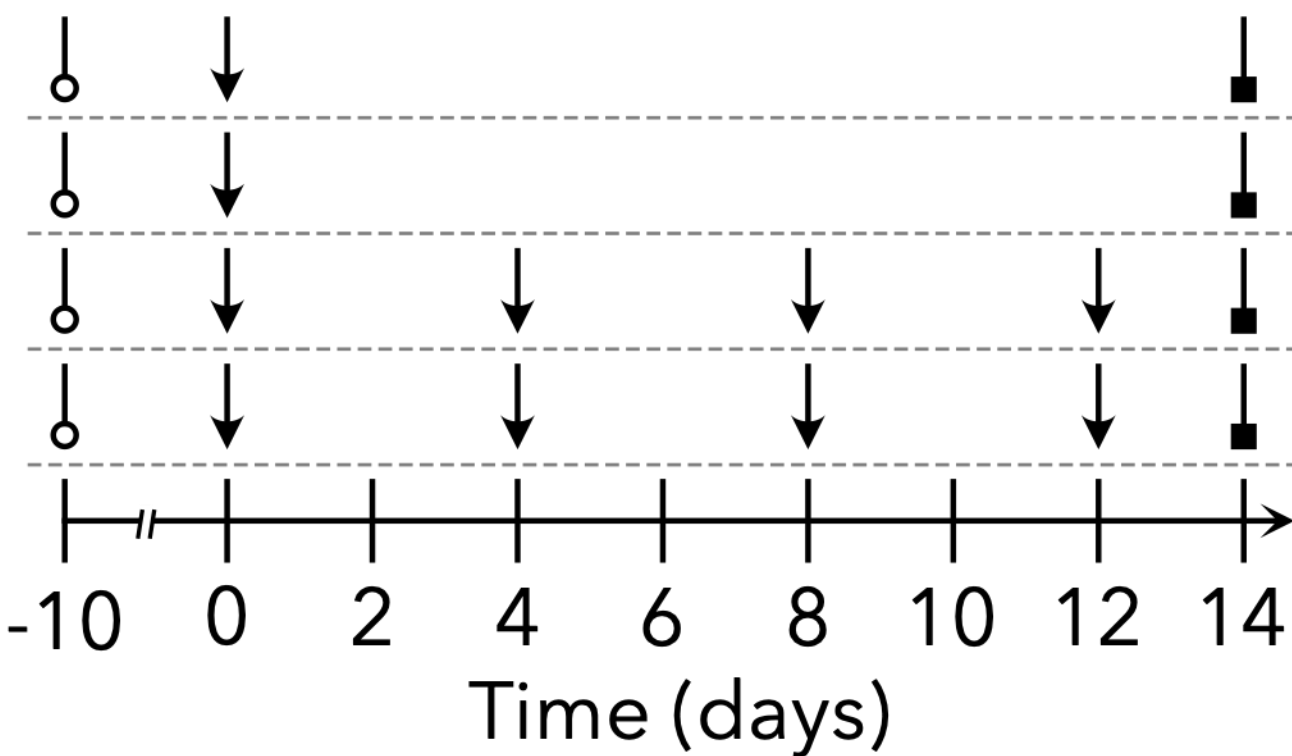
aNP-mRNA induces sustained IL-2 production



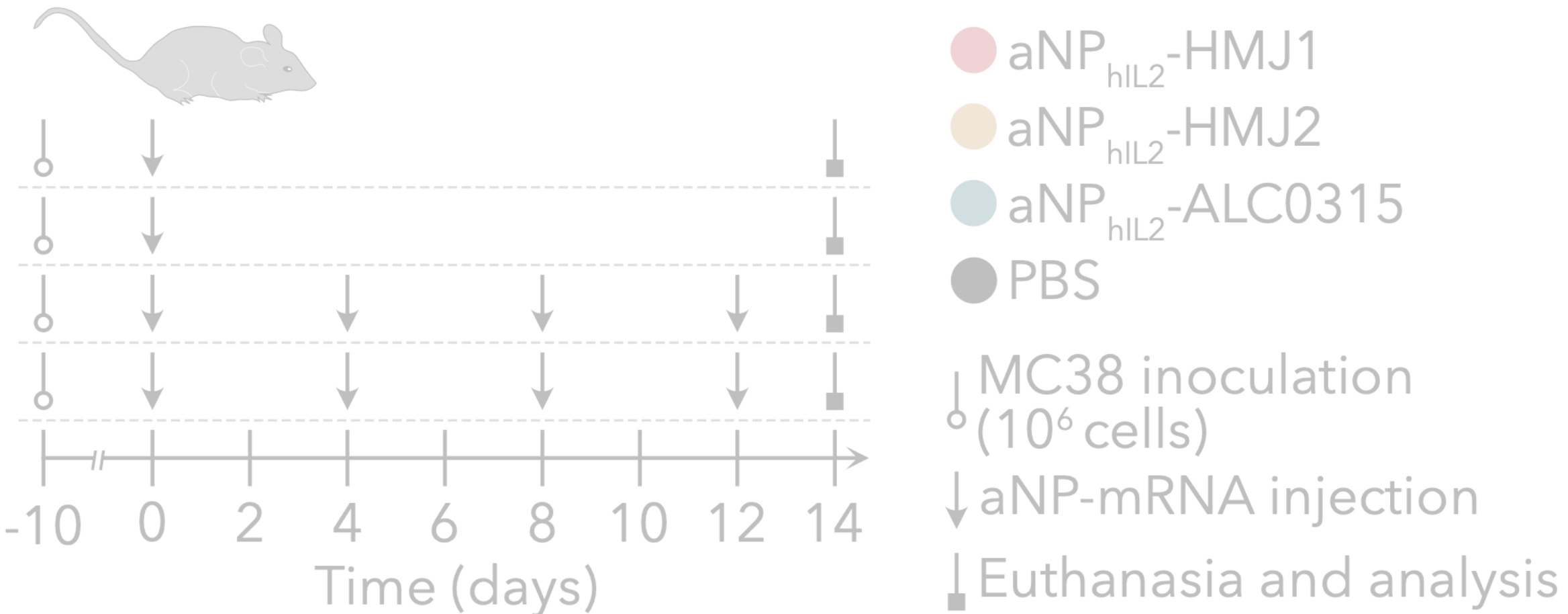
aNP-mRNA induces sustained IL-2 production



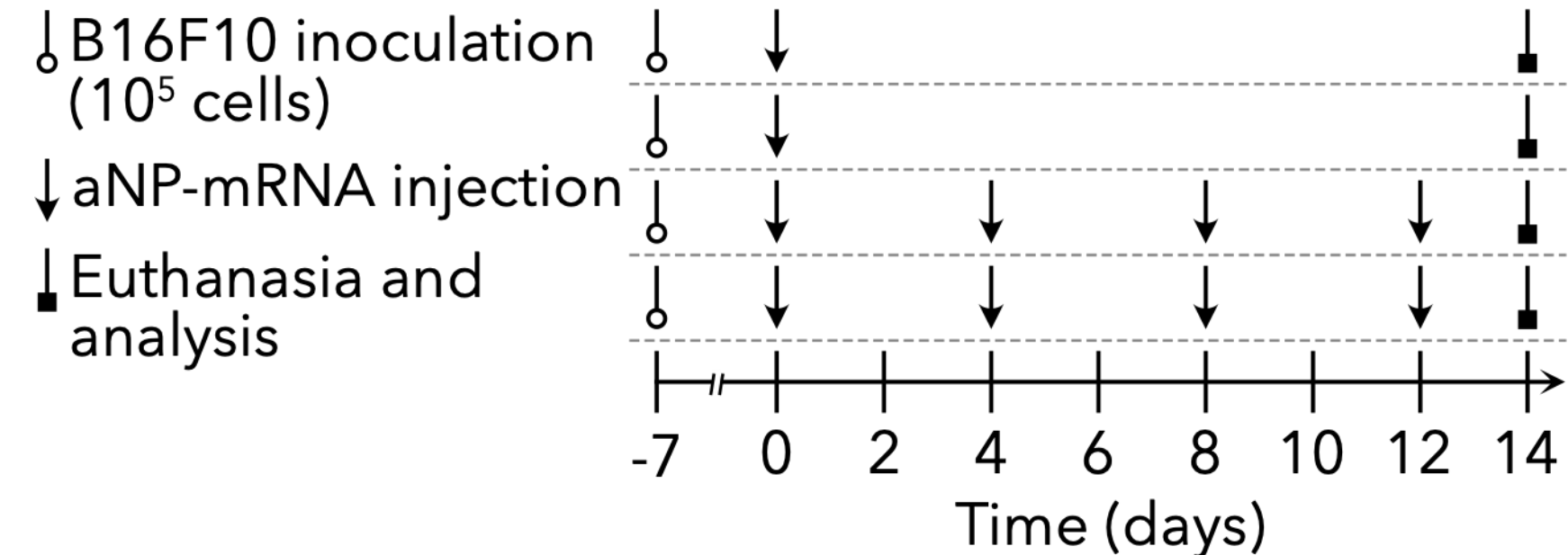
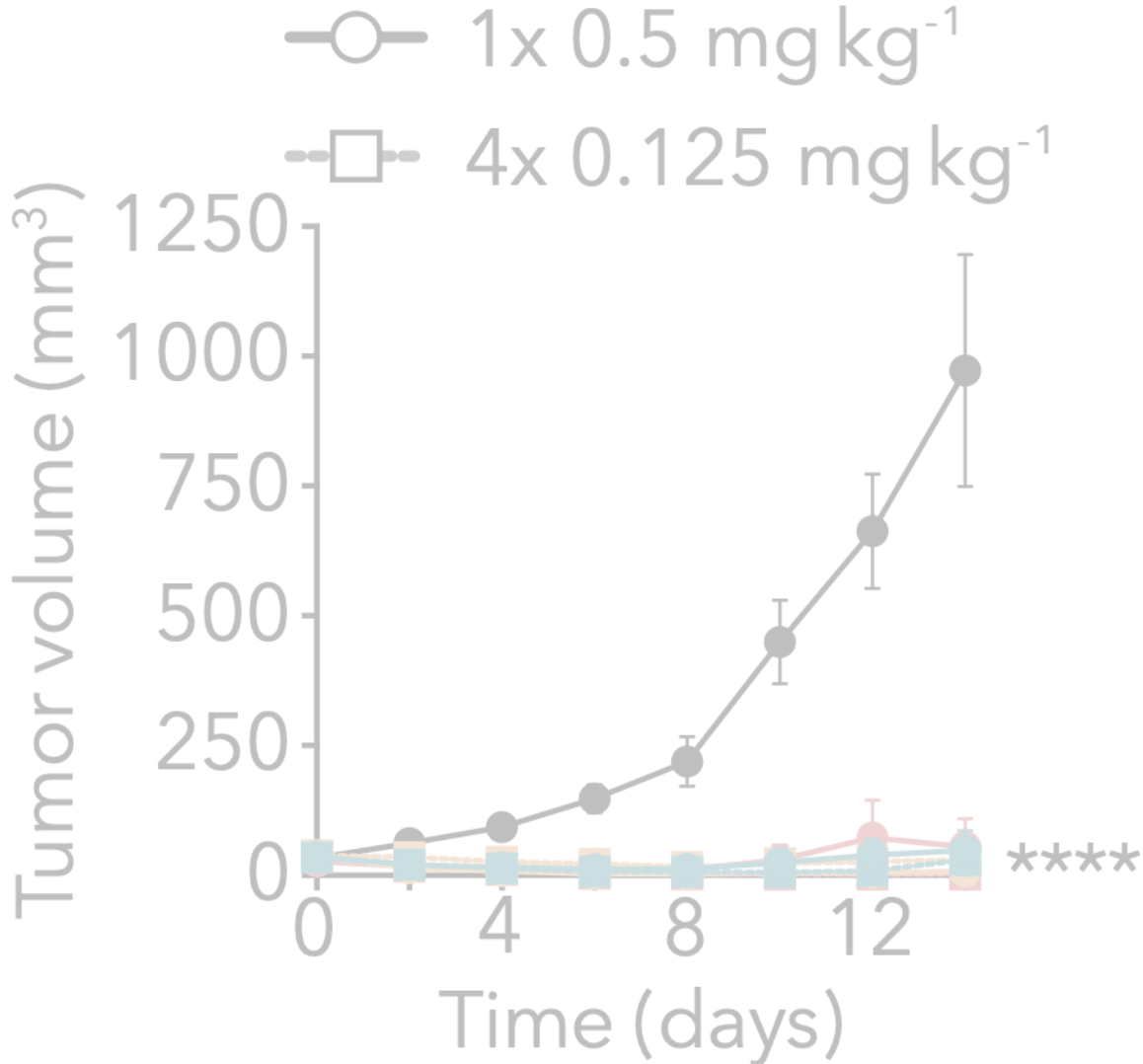
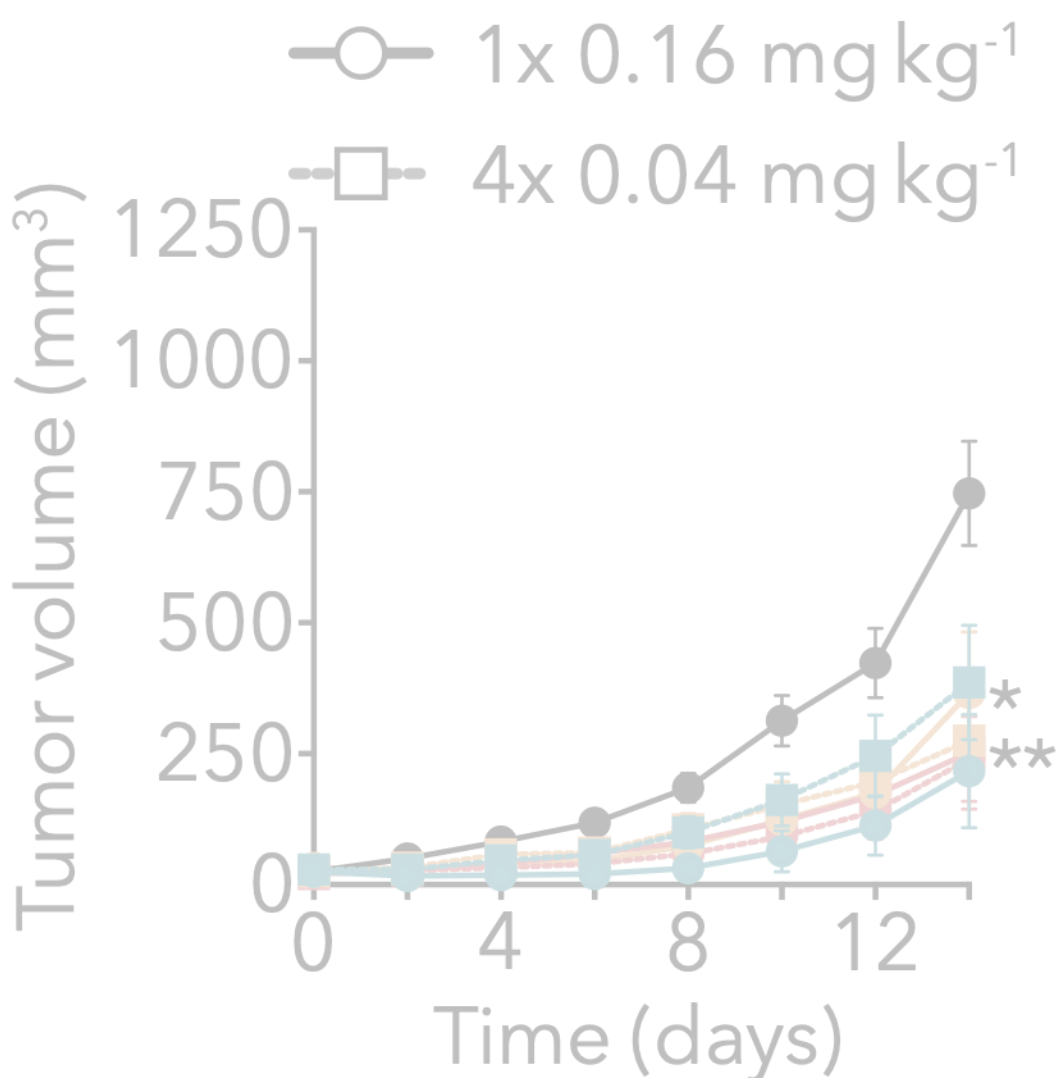
aNP-mRNA IL-2 induces potent anti-tumor effects



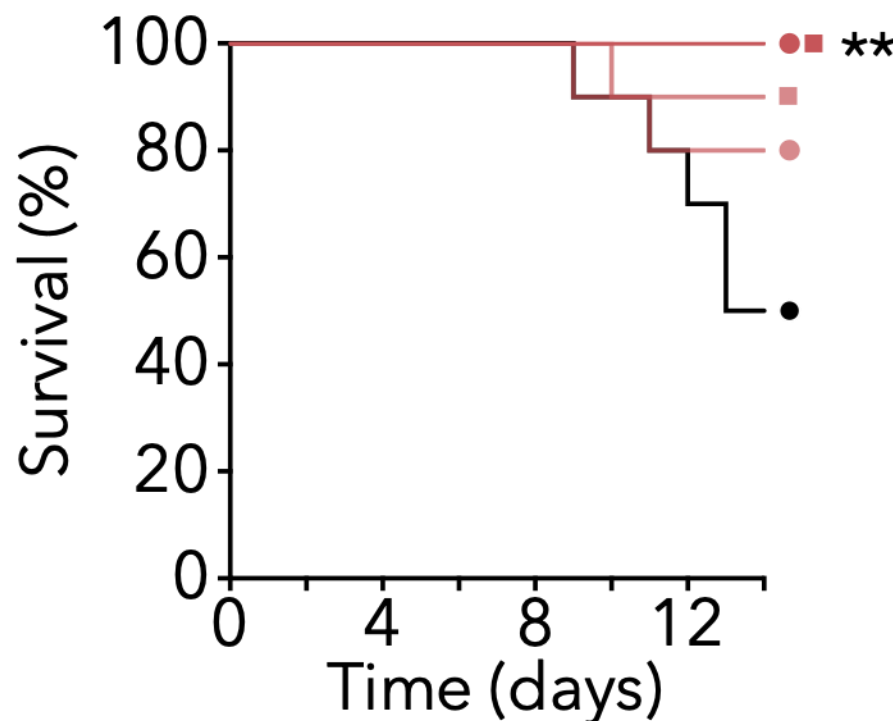
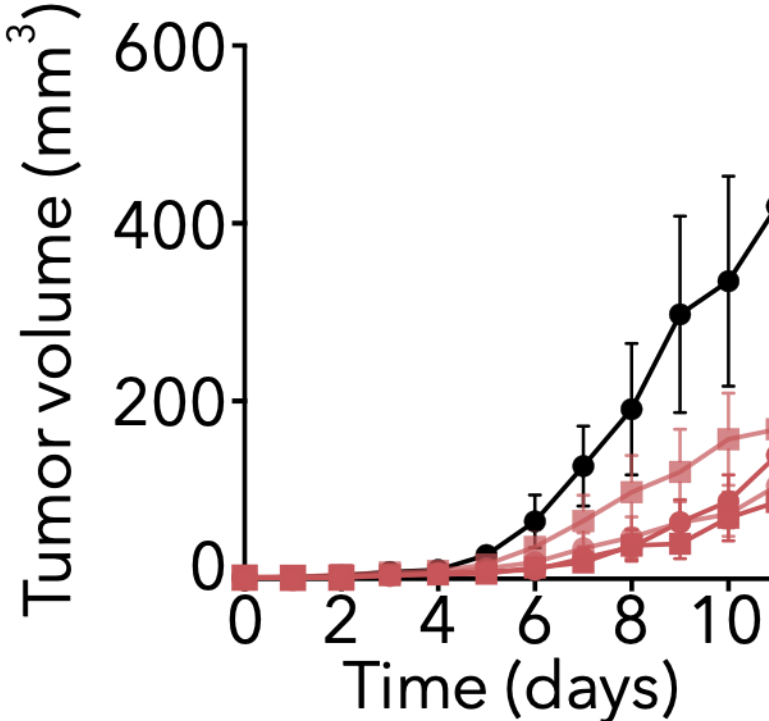
aNP-mRNA IL-2 induces potent anti-tumor effects



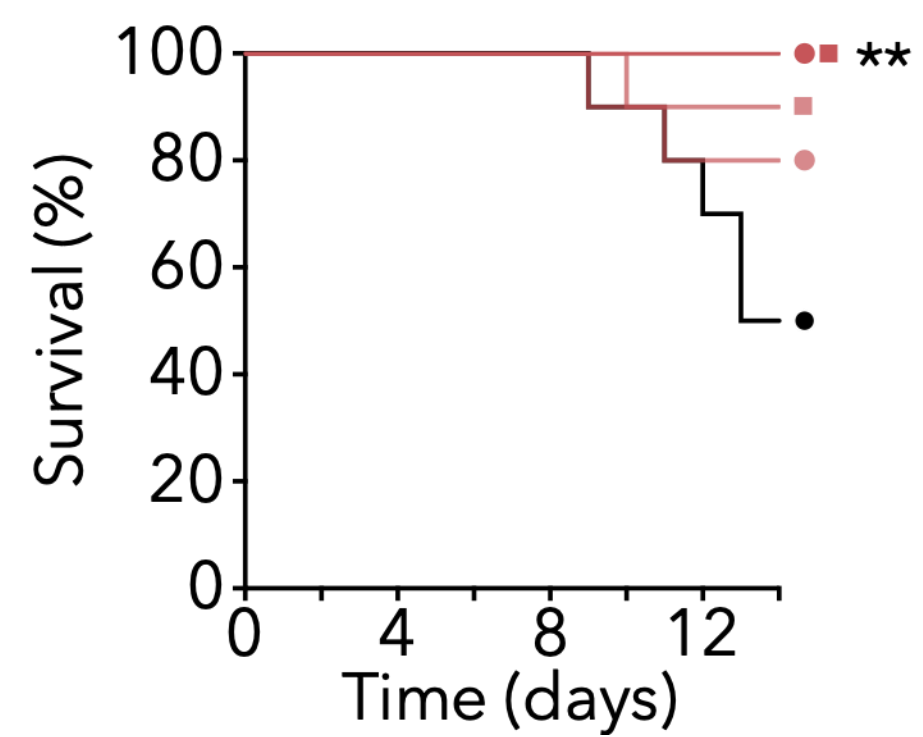
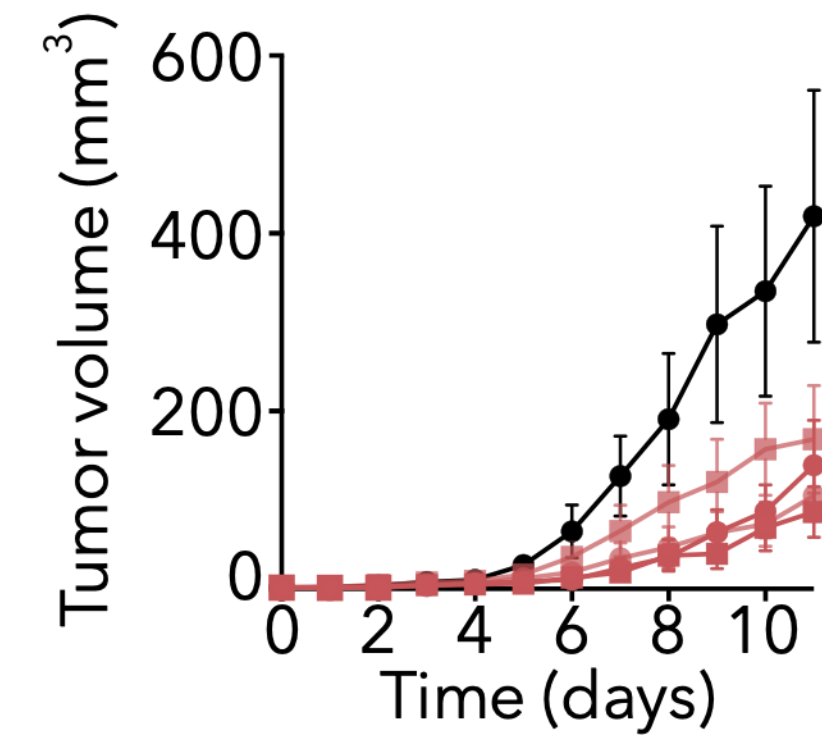
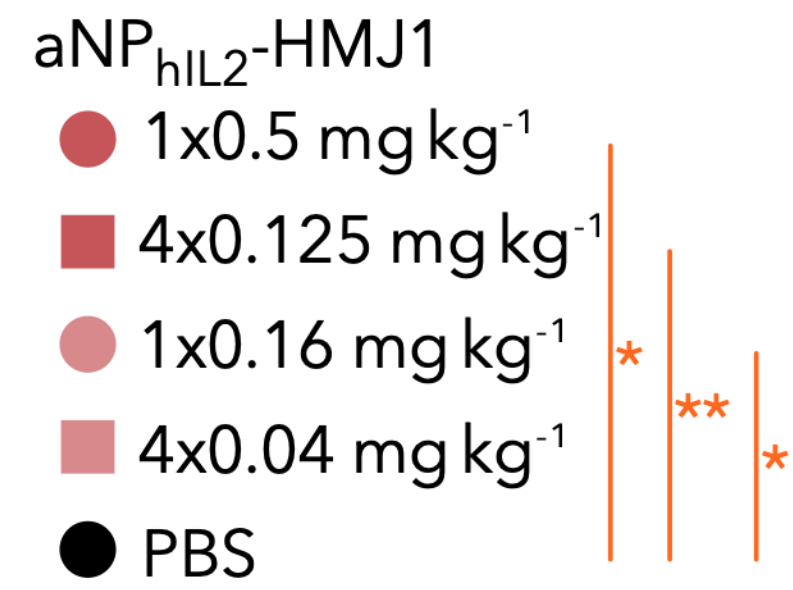
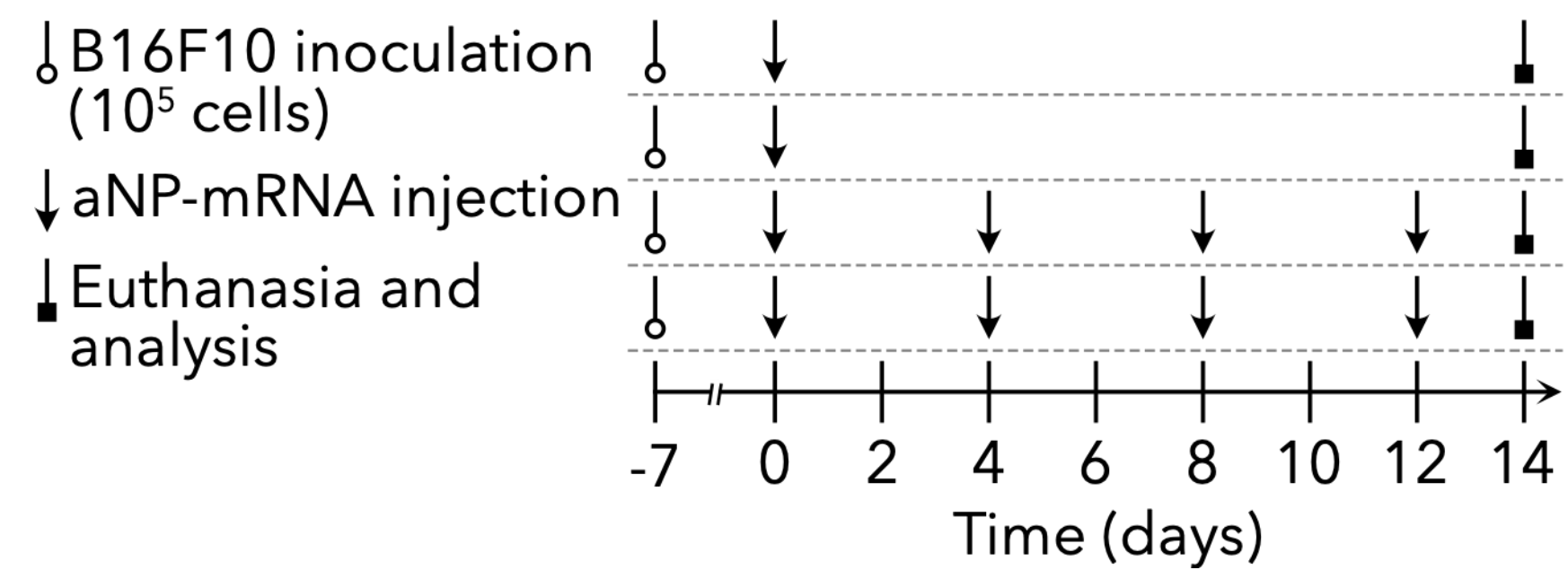
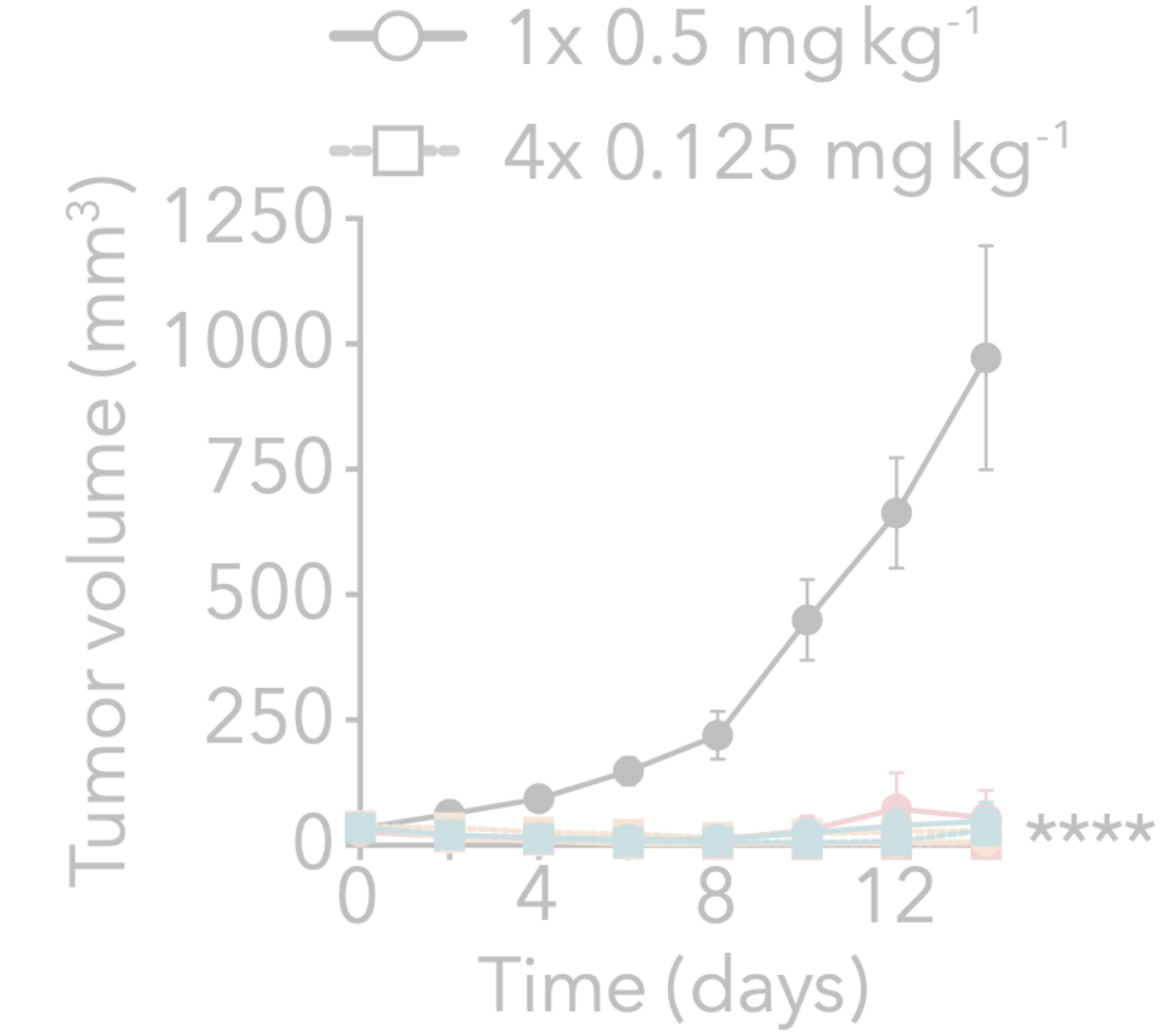
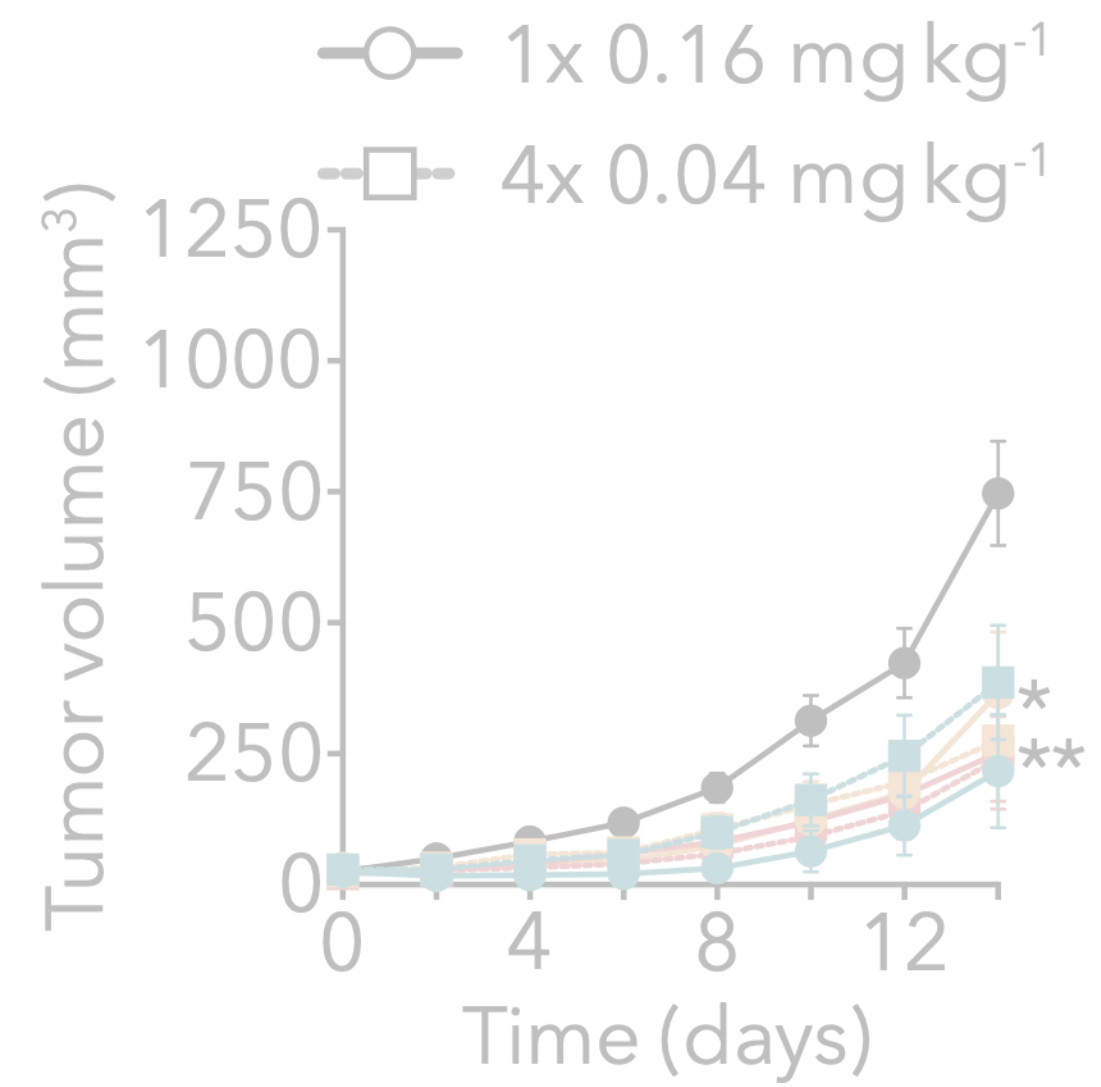
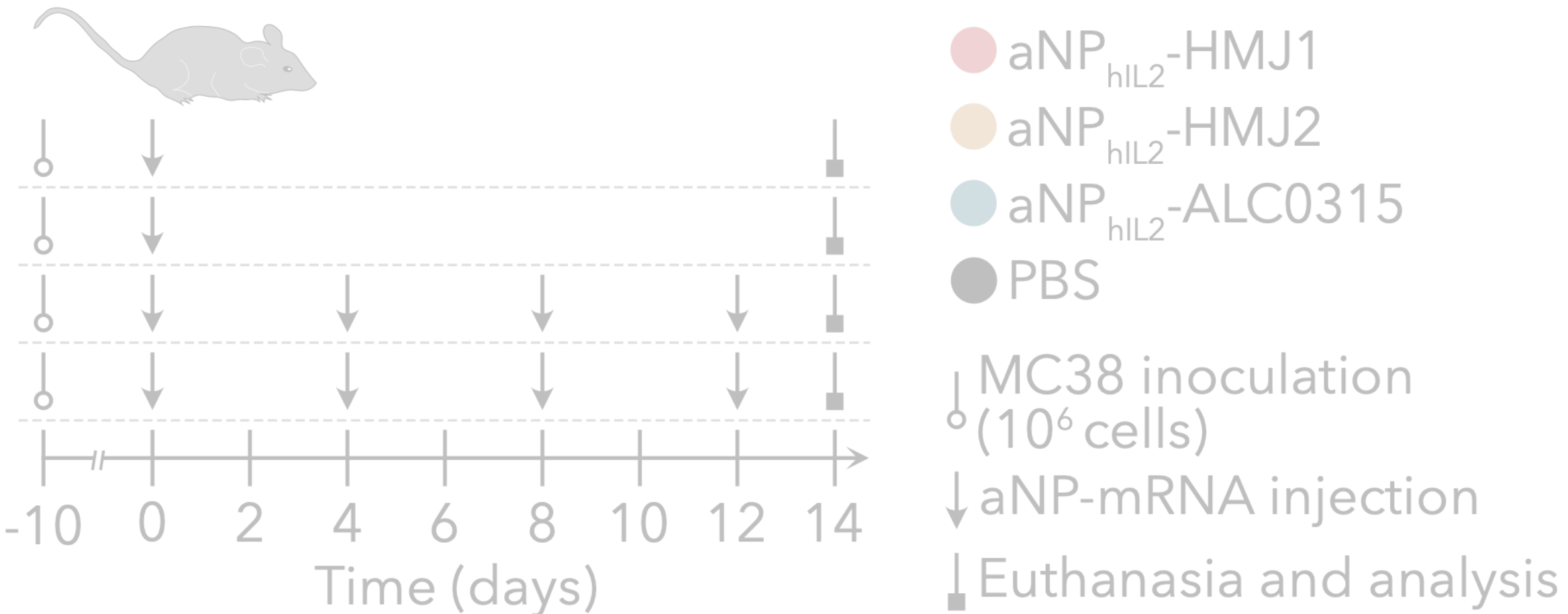
- aNP_{hIL2}-HMJ1
- aNP_{hIL2}-HMJ2
- aNP_{hIL2}-ALC0315
- PBS



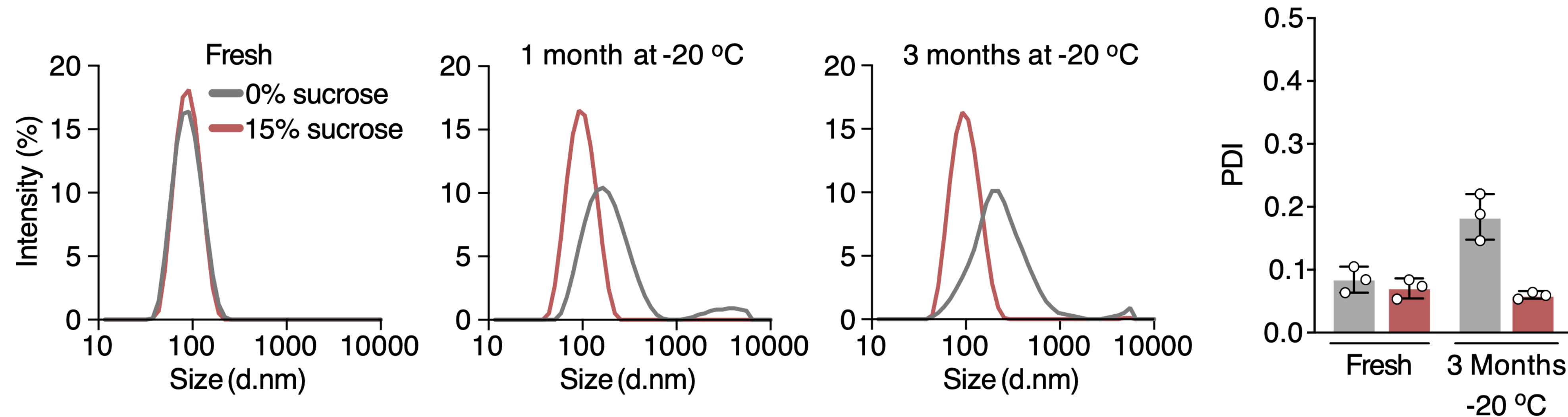
- aNP_{hIL2}-HMJ1
- 1x0.5 mg kg⁻¹
 - 4x0.125 mg kg⁻¹
 - 1x0.16 mg kg⁻¹
 - 4x0.04 mg kg⁻¹
 - PBS
- Significance markers: * (p < 0.05), ** (p < 0.01)



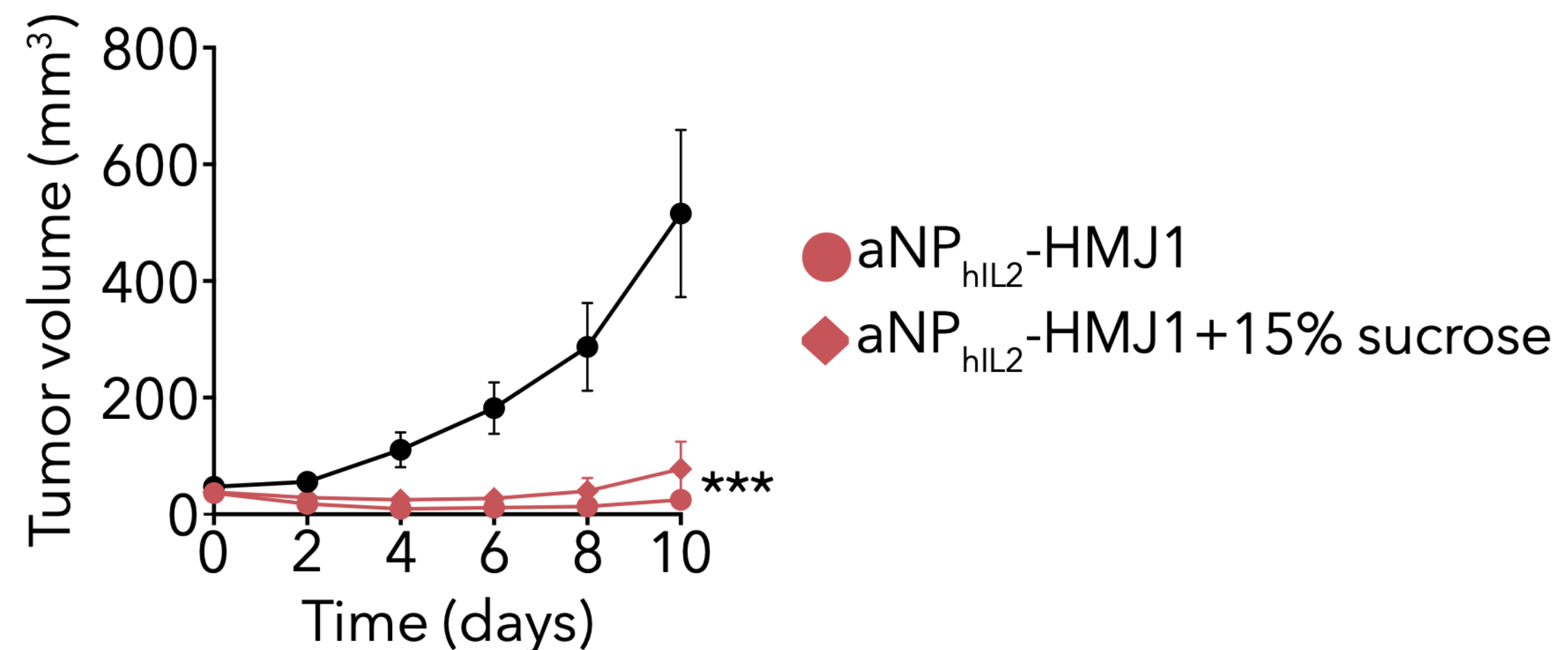
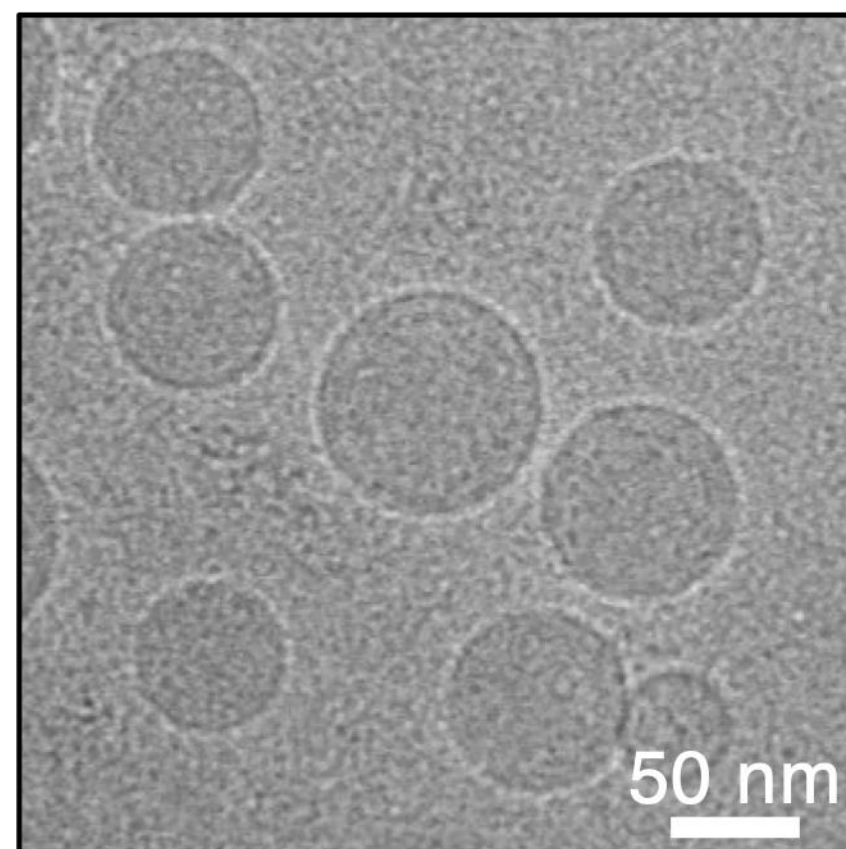
aNP-mRNA IFN γ induces potent anti-tumor effects



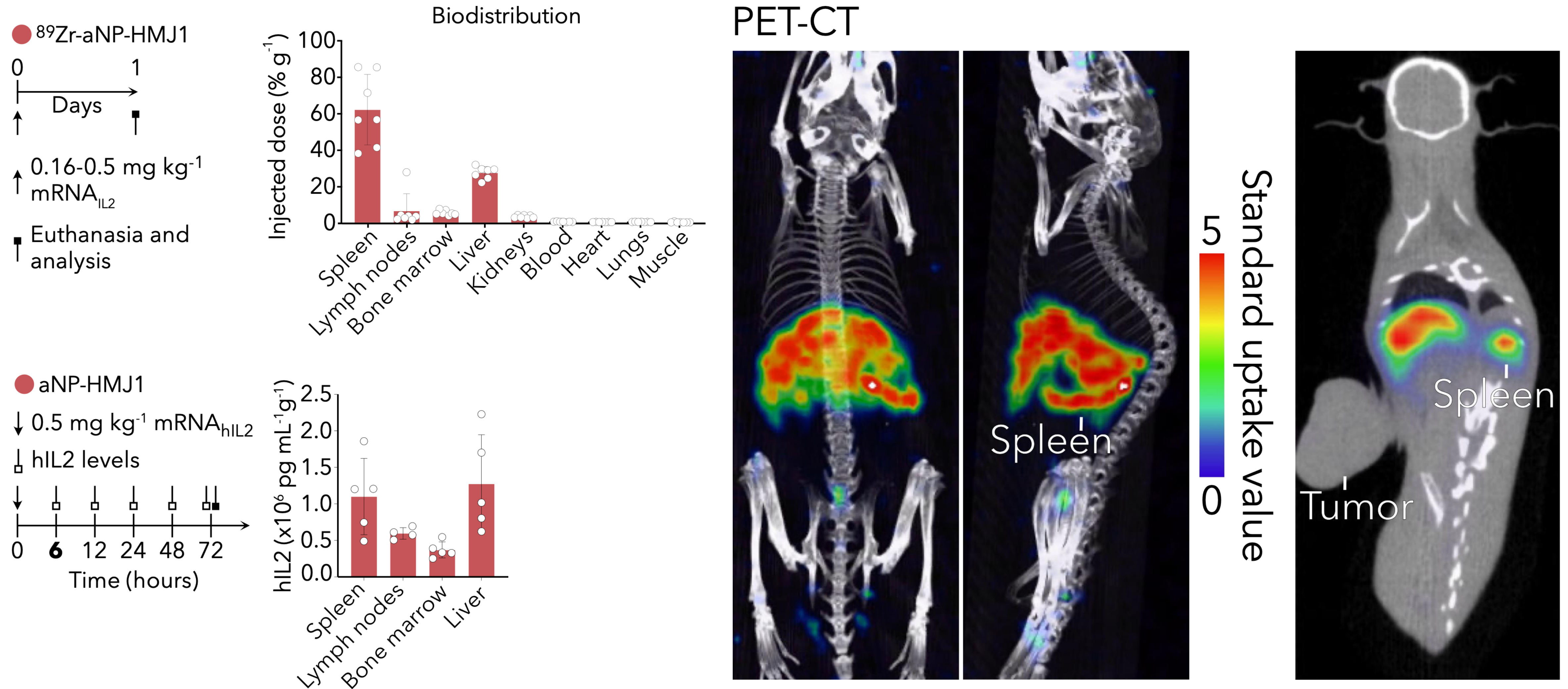
aNP-mRNA maintain functionality after storage



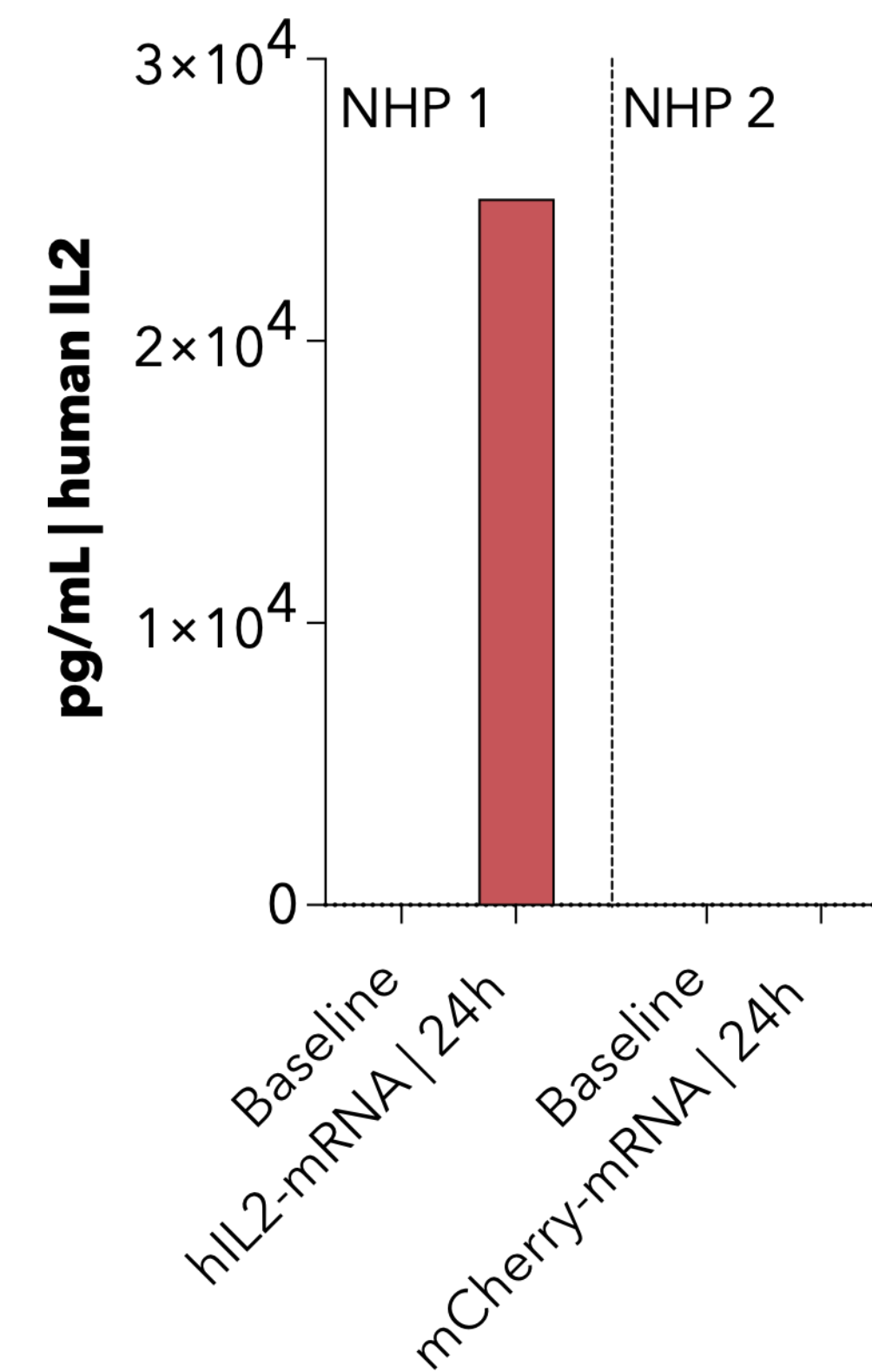
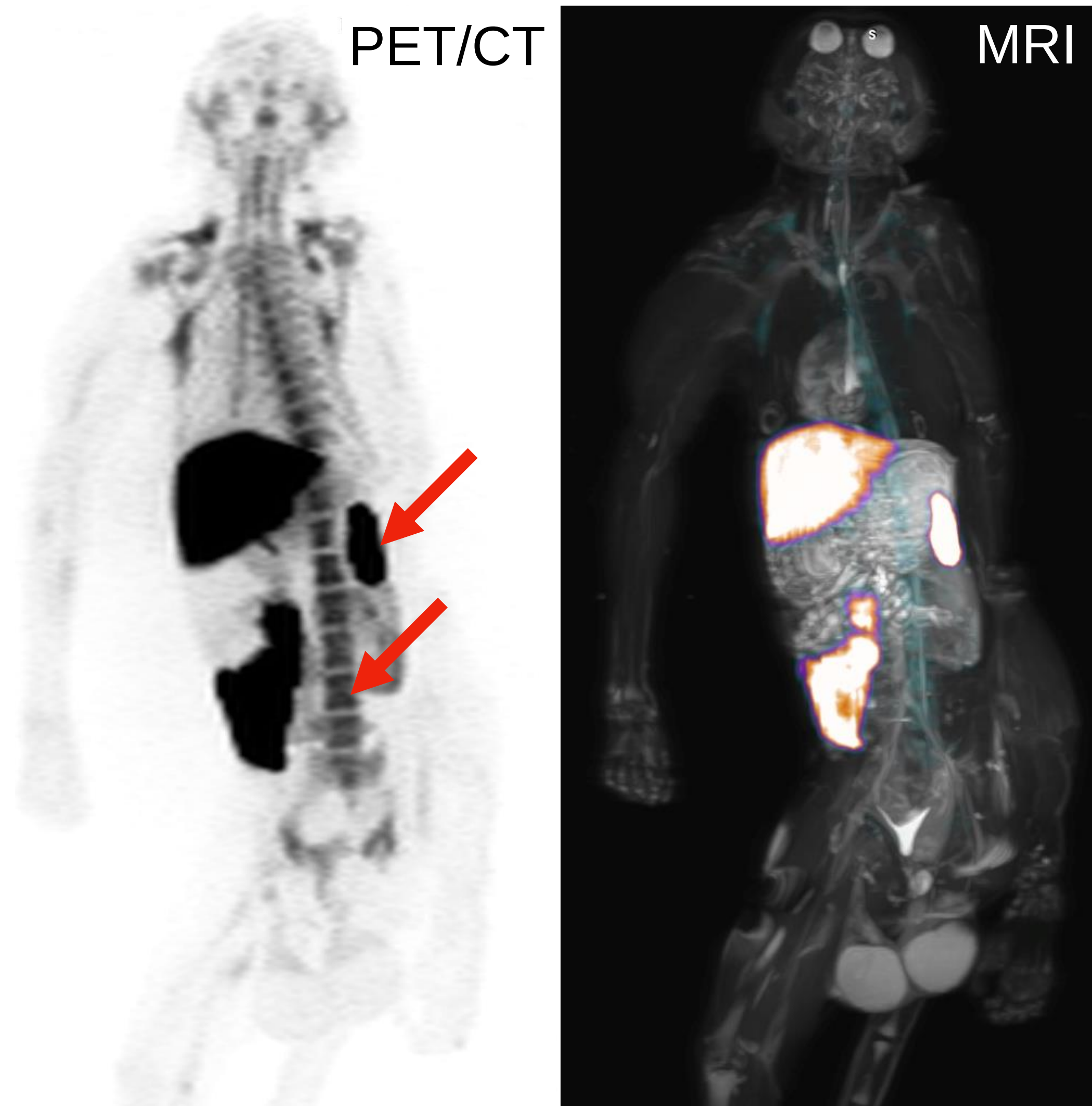
aNP-HMJ1 + 15 w/v% Sucrose
3 months, -20 °C



aNP-mRNA IL-2 biodistribution in mice



aNP-mRNA IL-2 biodistribution in non-human primates





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