

Apolipoprotein nanoparticle platform technology for RNA delivery to immune cells

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Eindhoven University of Technology



Phospholipid Research Center

*Phospholipid Research Center seminar
March 18, 2026*

Team

Leadership



Roy



Ewelina



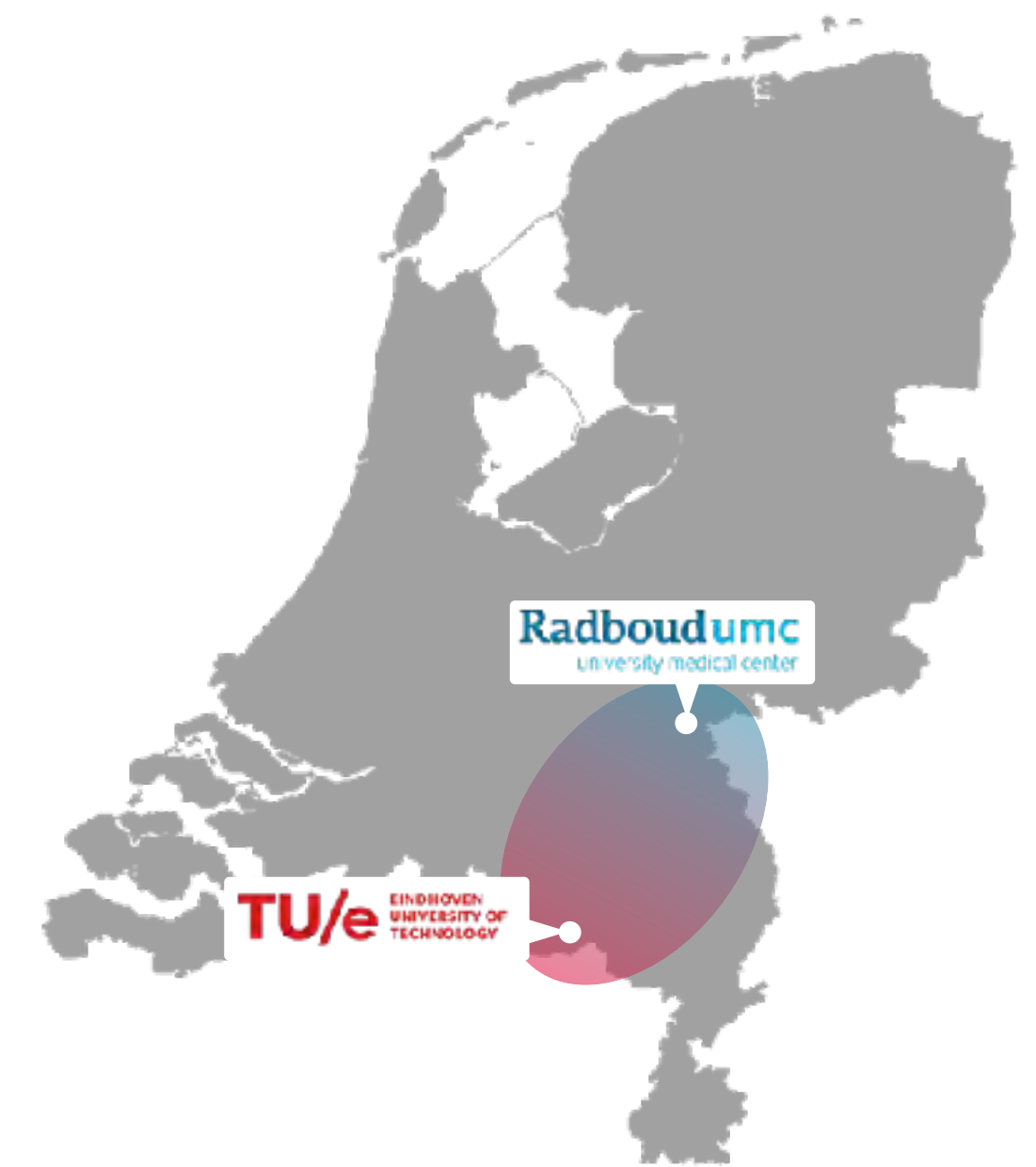
Willem



Yohana



Thijs



Postdocs



Matt



Chiara

Ph.D. students



Ayla



Koen



Jari



Rianne



Jeroen



Tom



Mirre



Daniek



Merel



Senna



Yuri

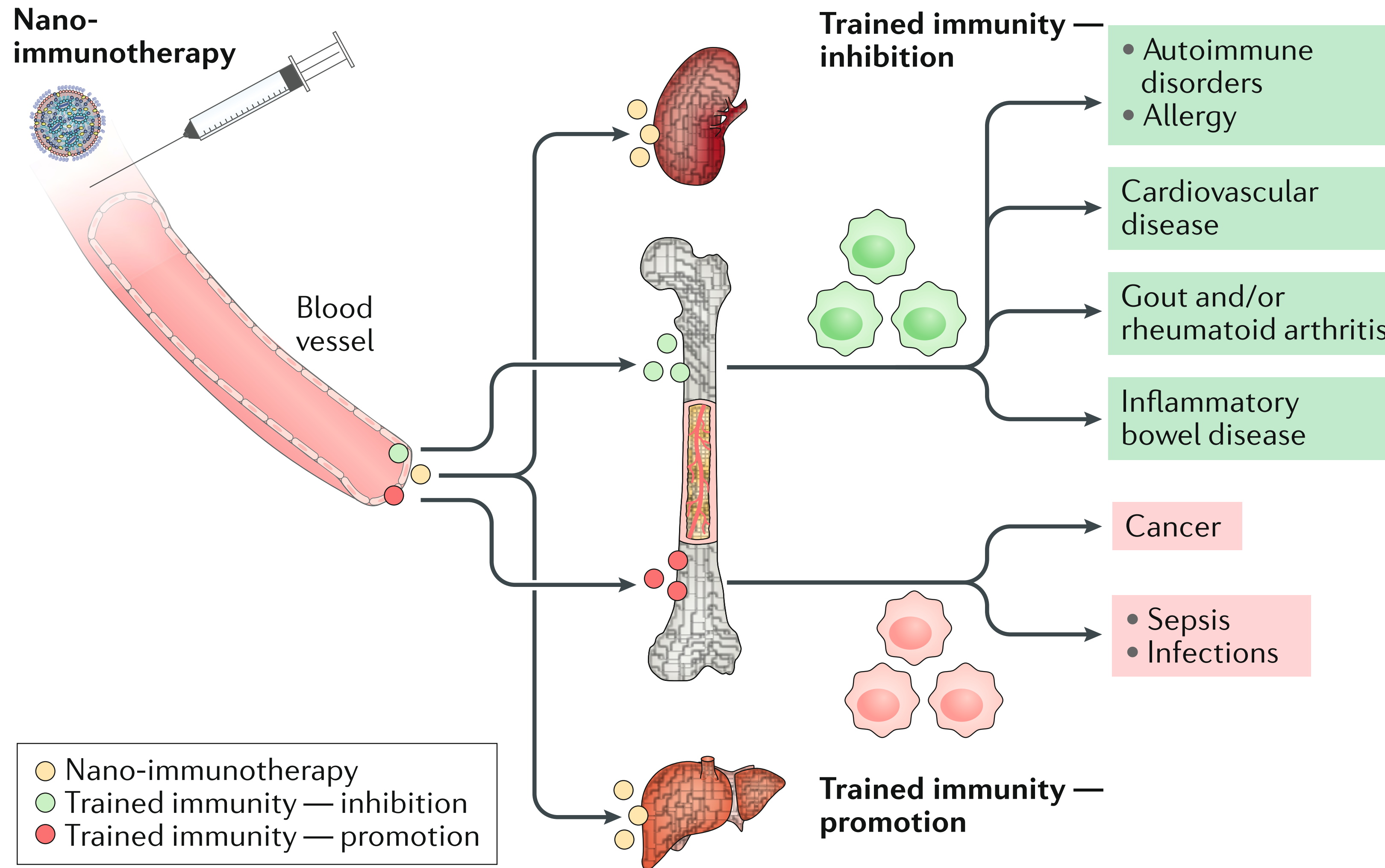


Iris

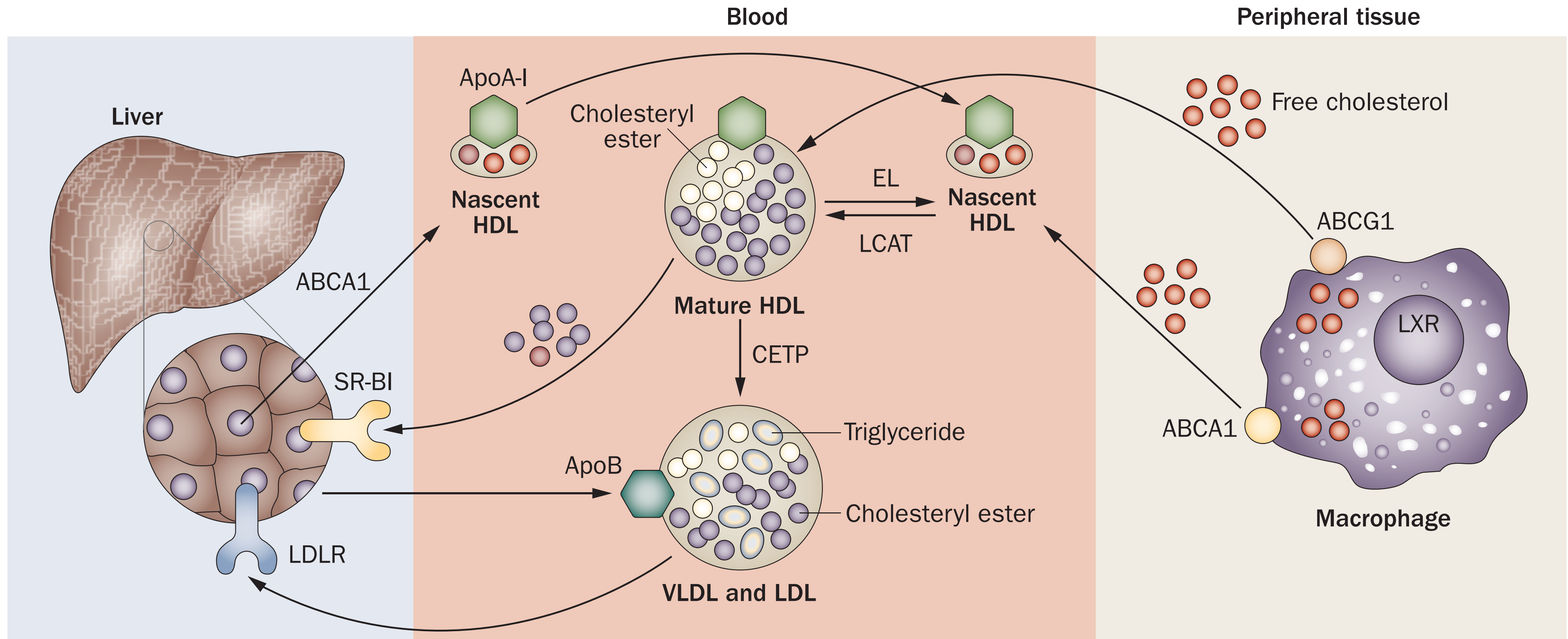
Engaging hematopoietic organs



Mihai Netea
Radboudumc



What does our body offer naturally?



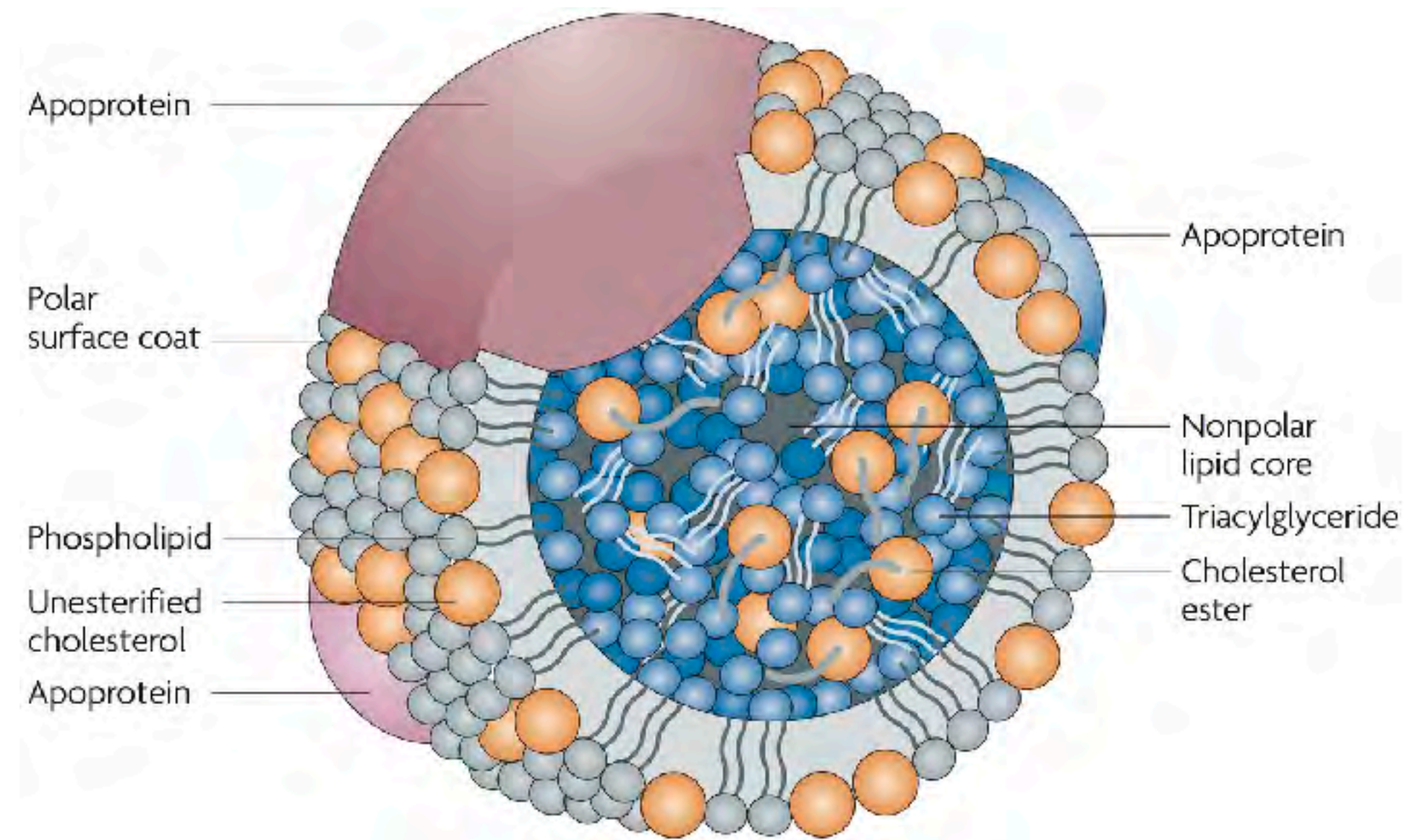
What does our body offer naturally?

LIPID-POOR Apo A-1



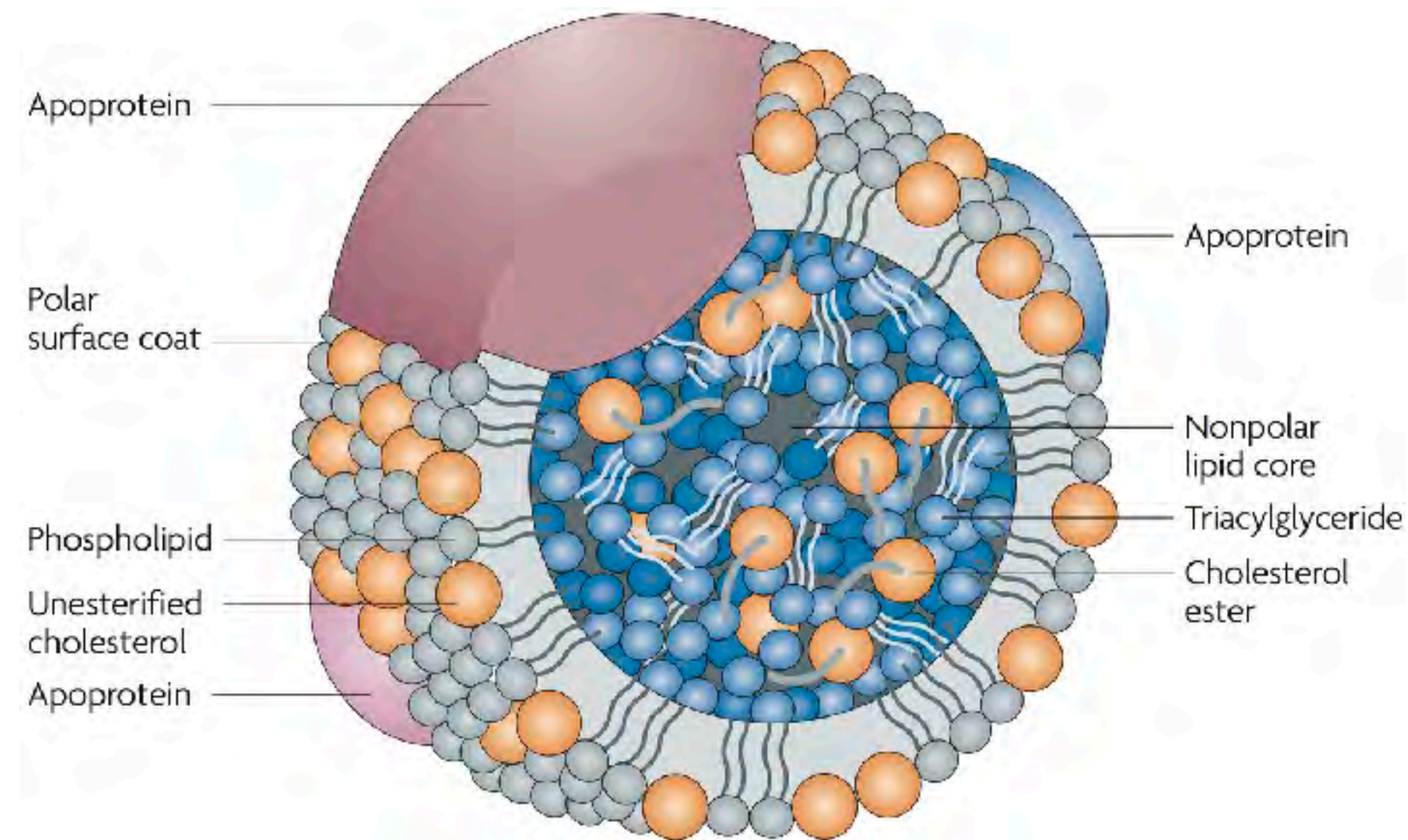
High density lipoprotein architecture

Lipoprotein morphology



High density lipoprotein architecture

Lipoprotein morphology



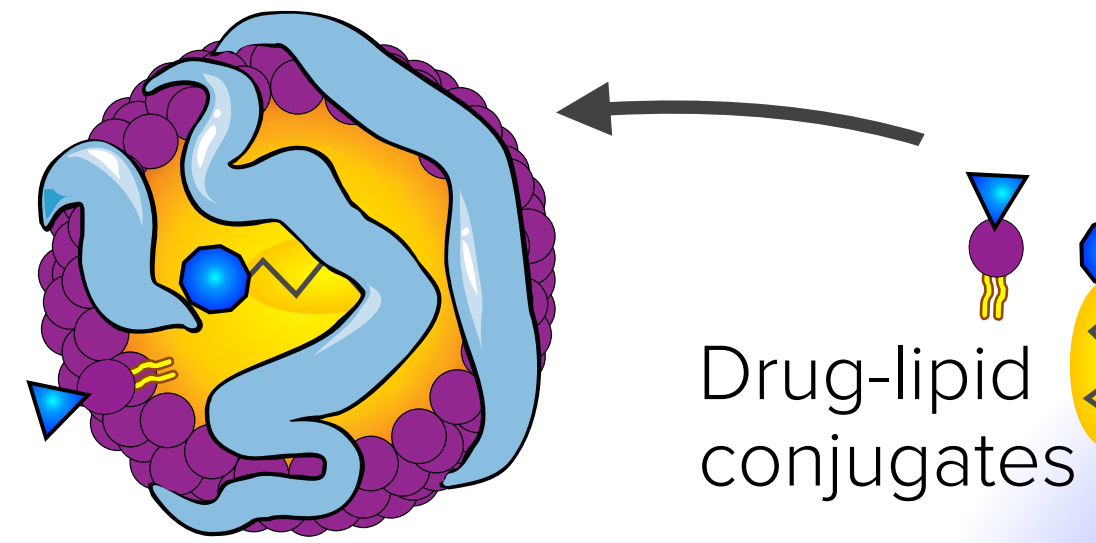
Apolipoprotein A1



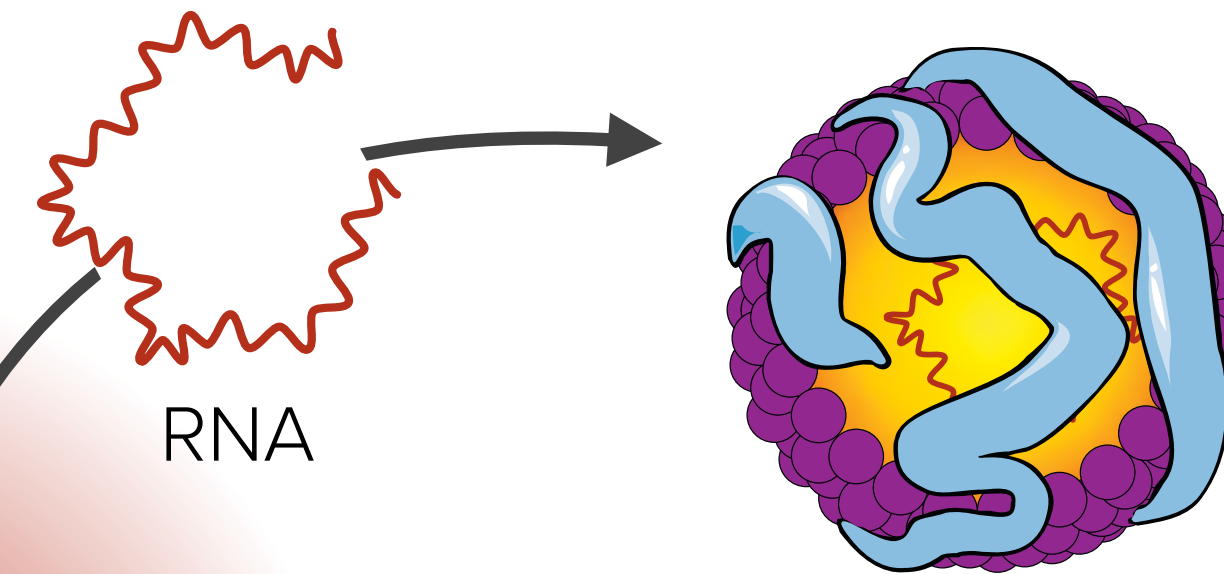
- Structural integrity
- Natural stealth
- Natural affinity for immune cells
 - ABCA1, ABCG1, SRB1

Modular aNP platform for delivery to immune cells

1 Small molecules



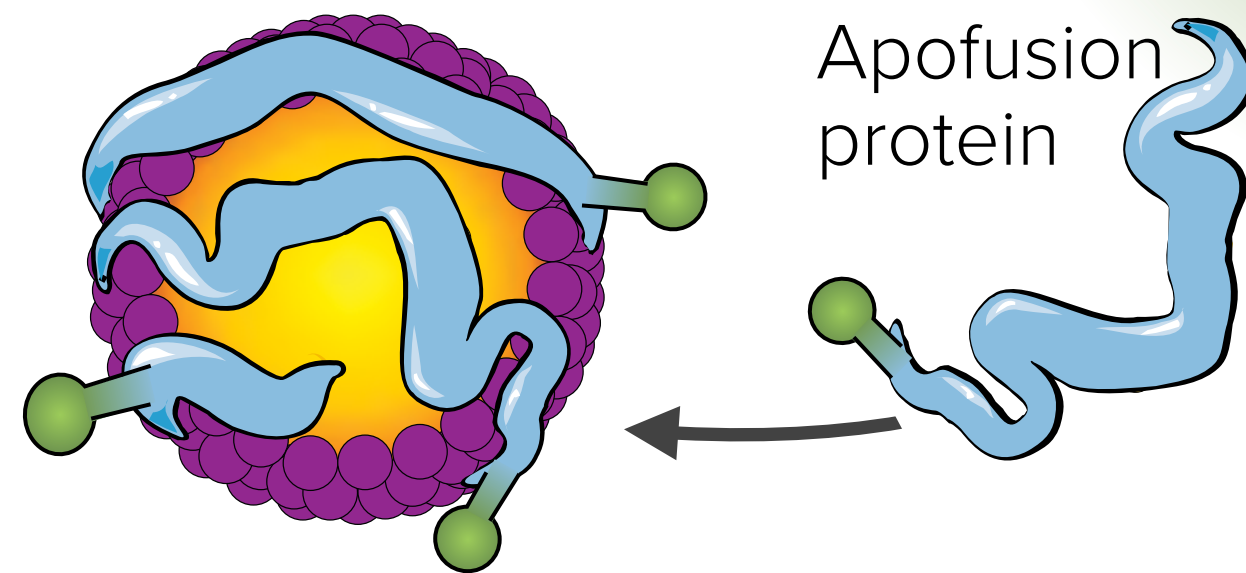
2 RNA



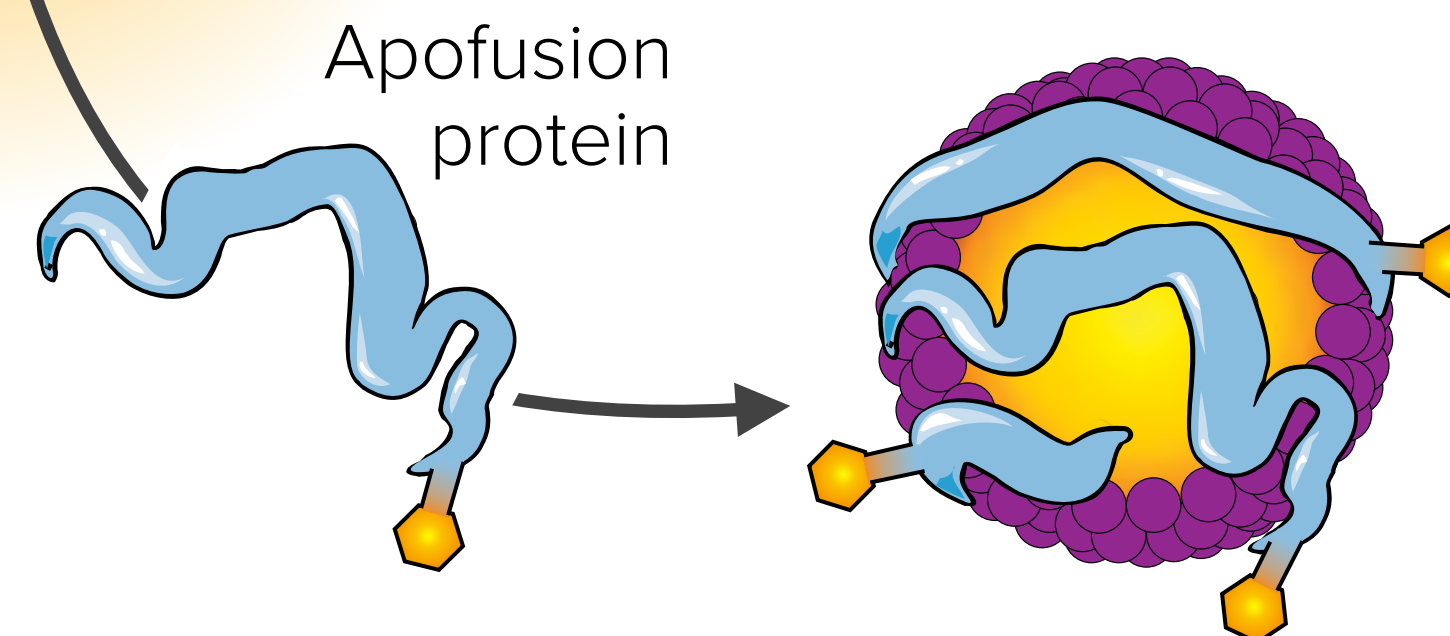
Priem et al., Sci Adv, 2026; Priem et al., Cell, 2020; Braza et al., Immunity, 2018; Van Leent et al., Sci Adv, 2021; Lameijer et al., Nat Biomed Eng, 2018; Binderup et al., Sci Transl Med, 2019

Hofstraat et al., Nat Nanotechnol, 2025; Trines et al., Adv Mater, 2025

3 Targeting

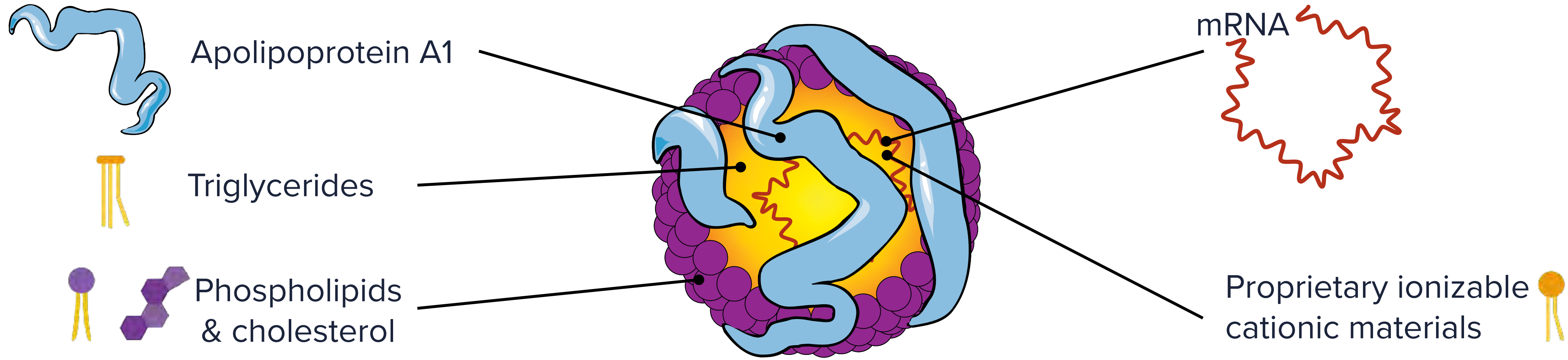


4 Proteins

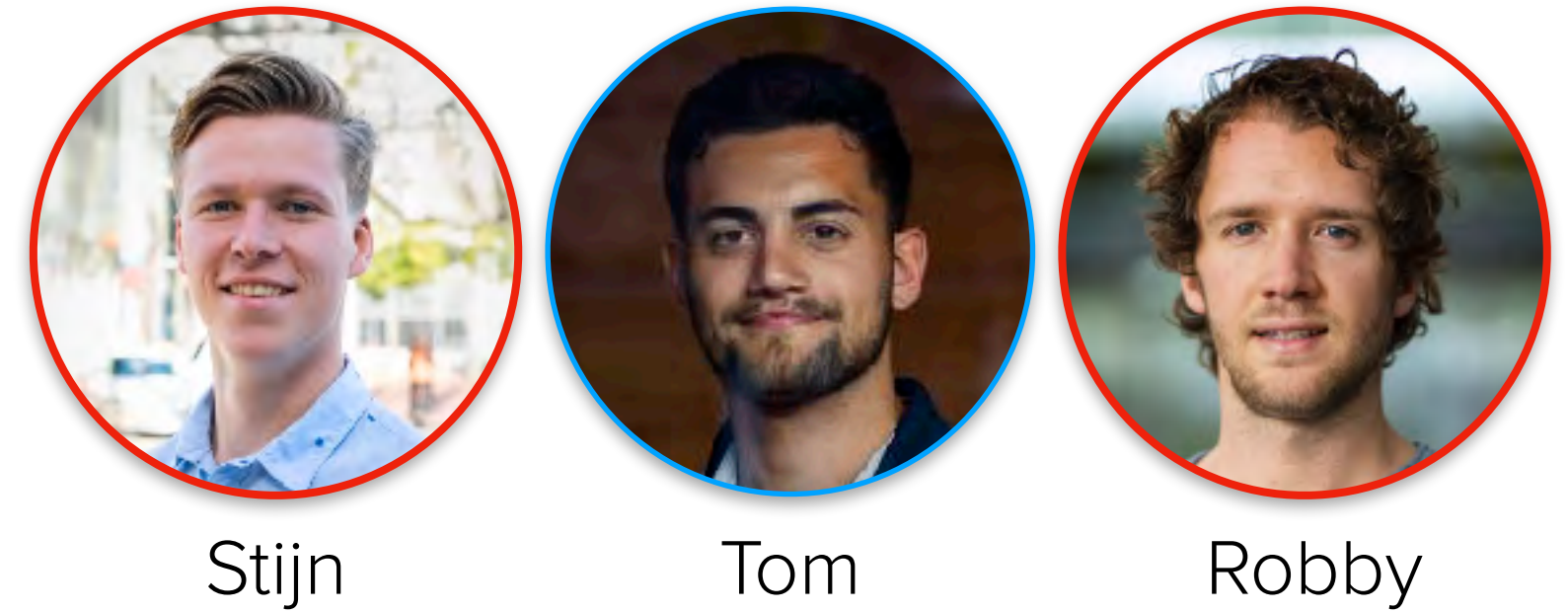
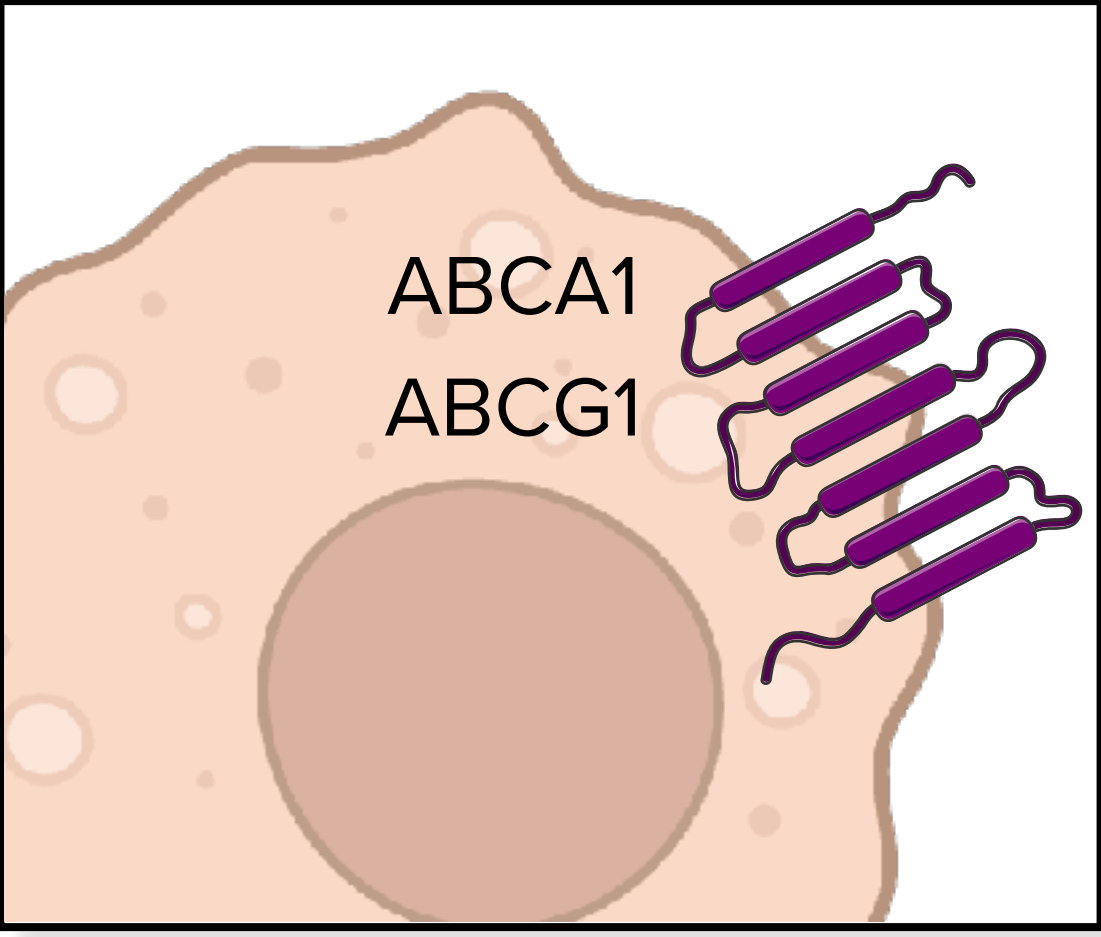


Schrijver et al., Nat Biomed Eng, 2023

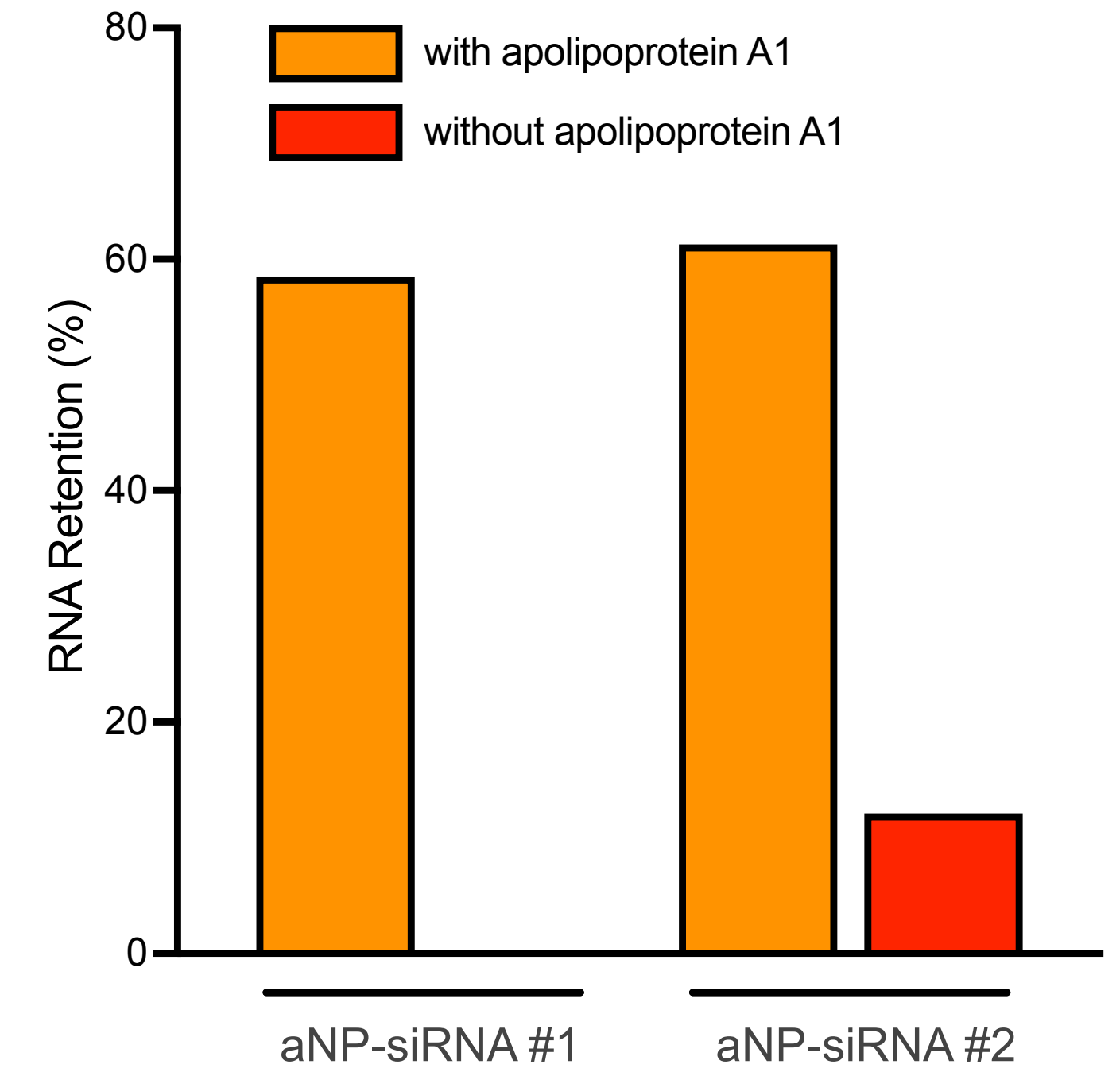
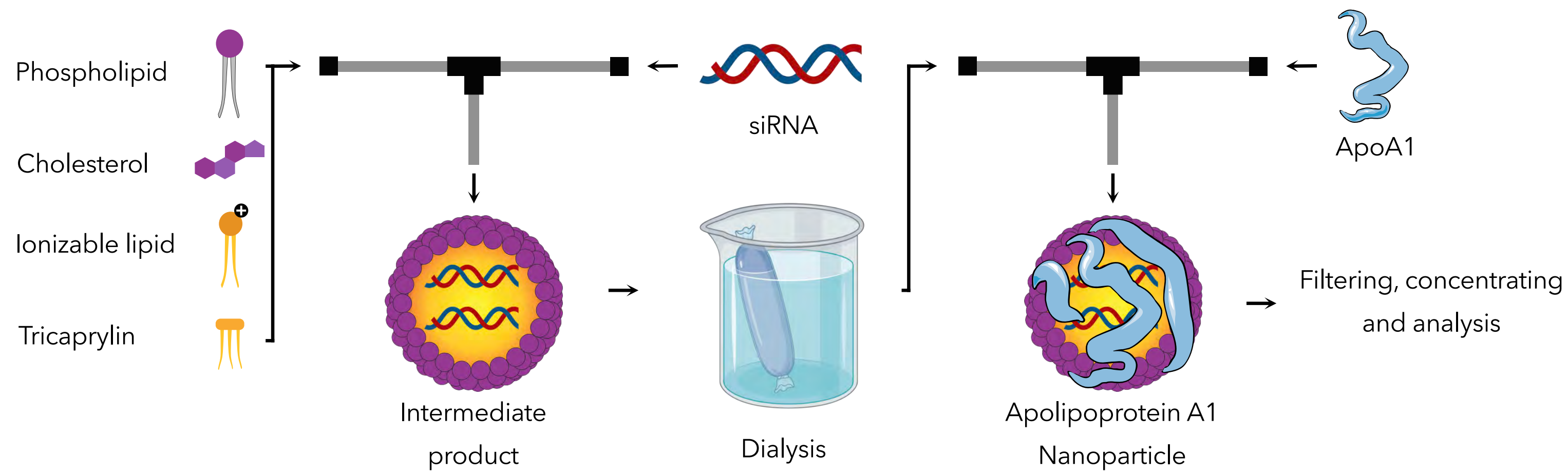
Modular aNP-RNA platform technology



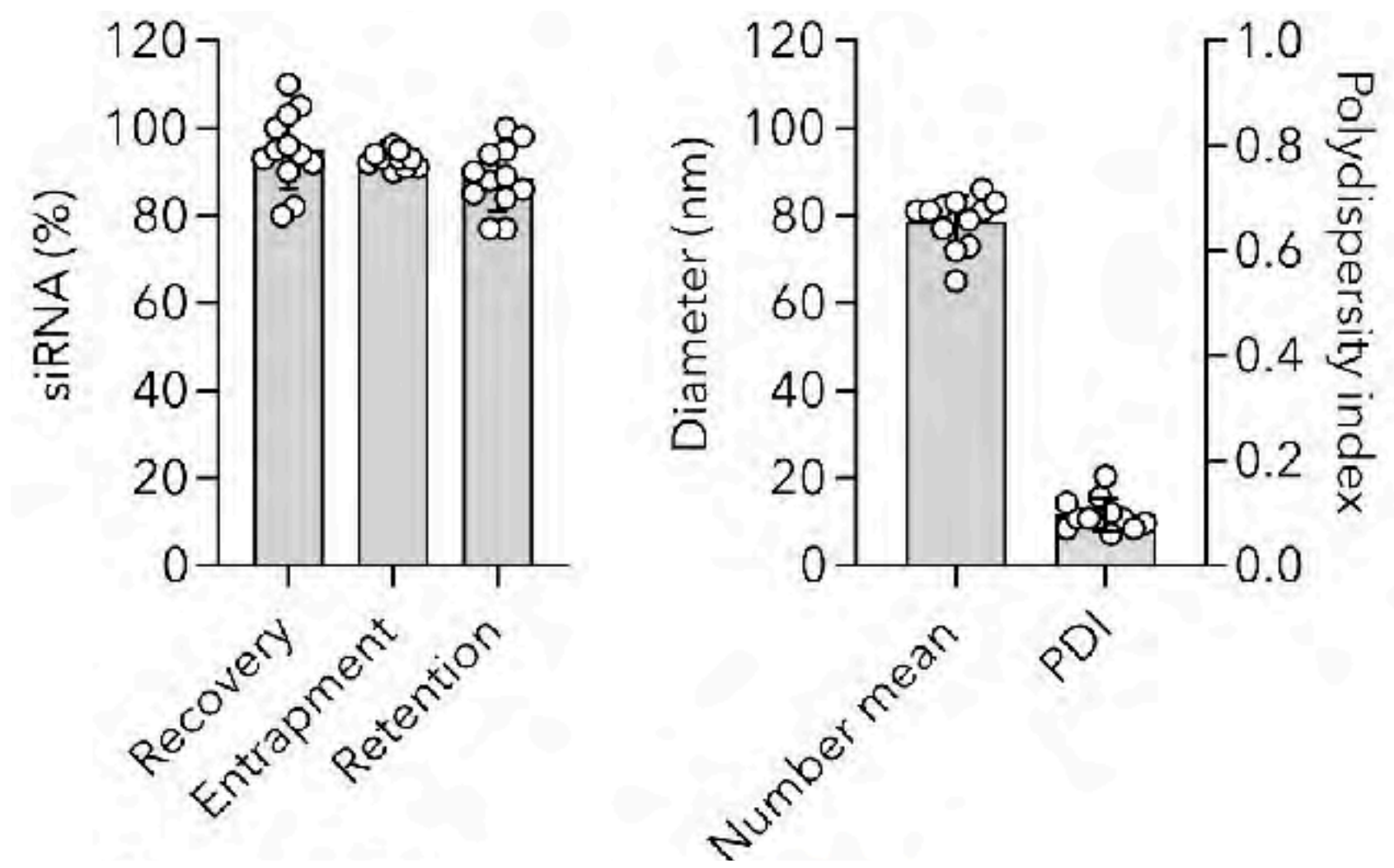
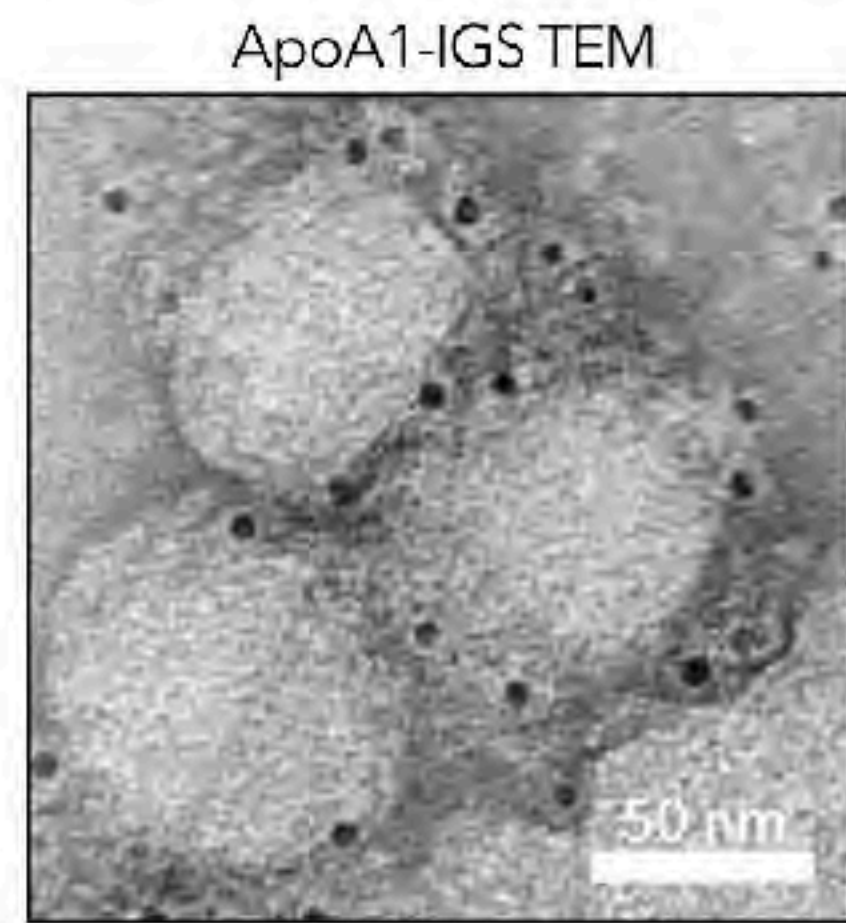
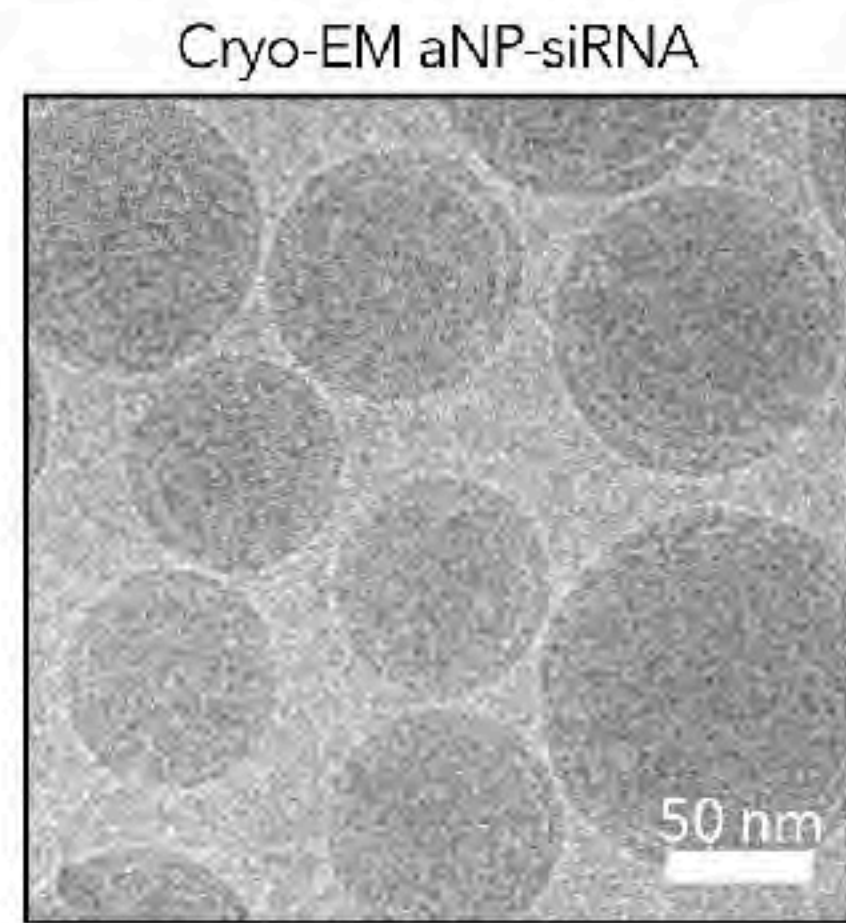
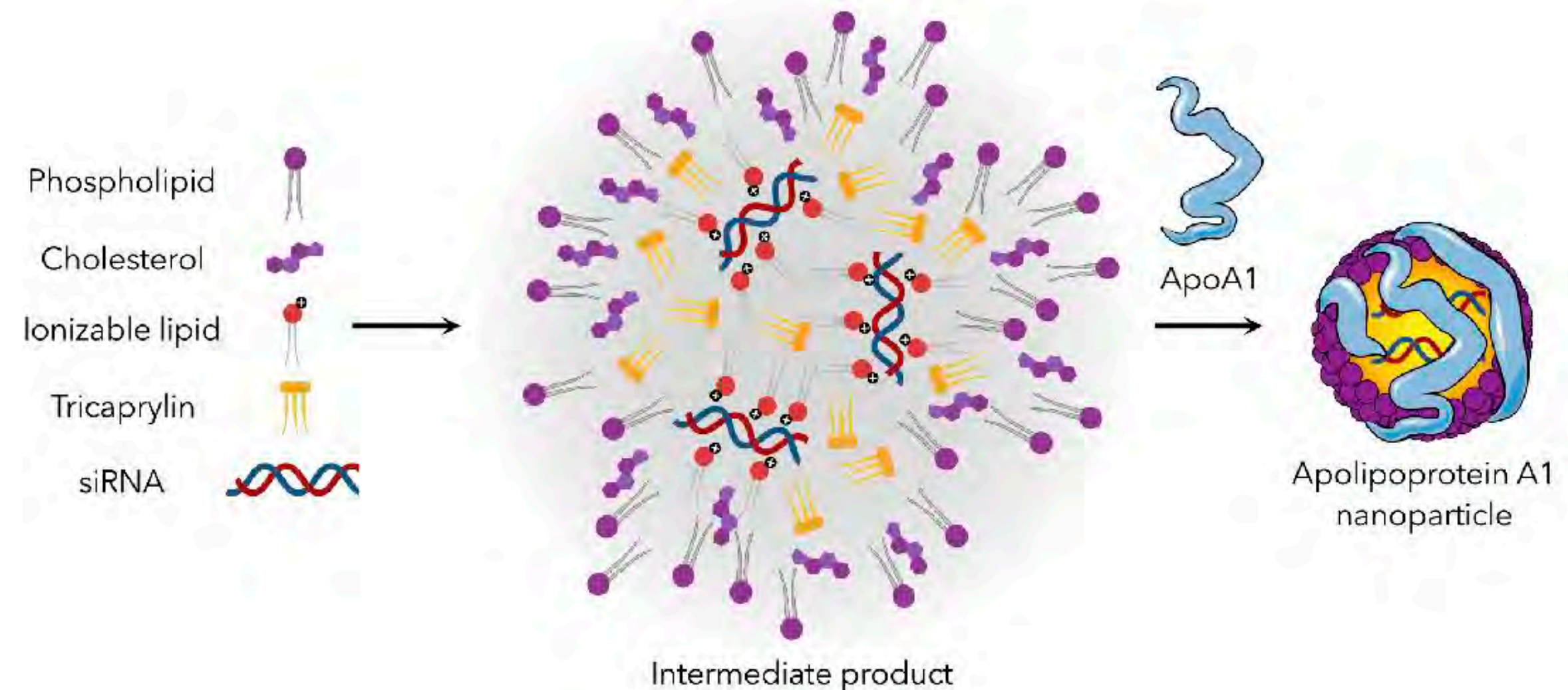
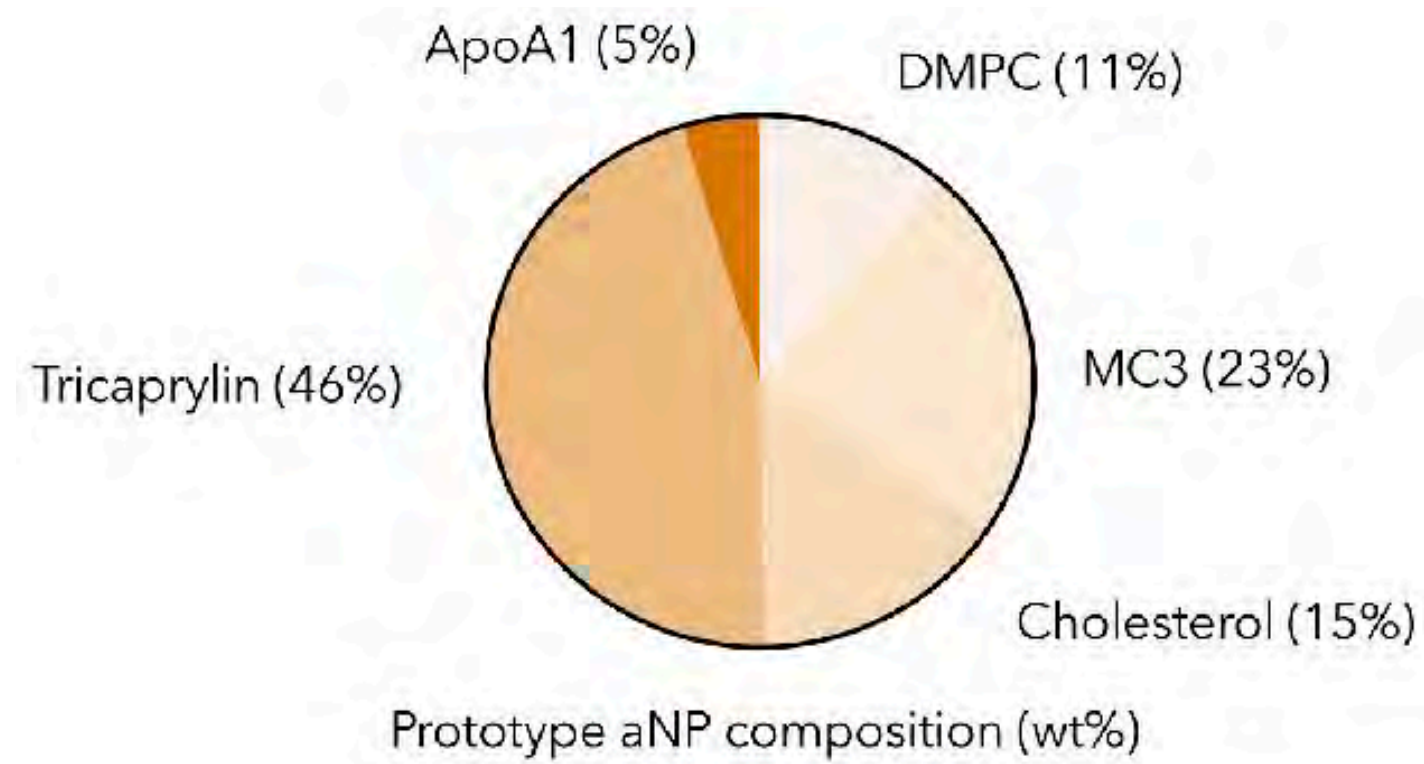
Myeloid cells & HPSCs



Production procedure

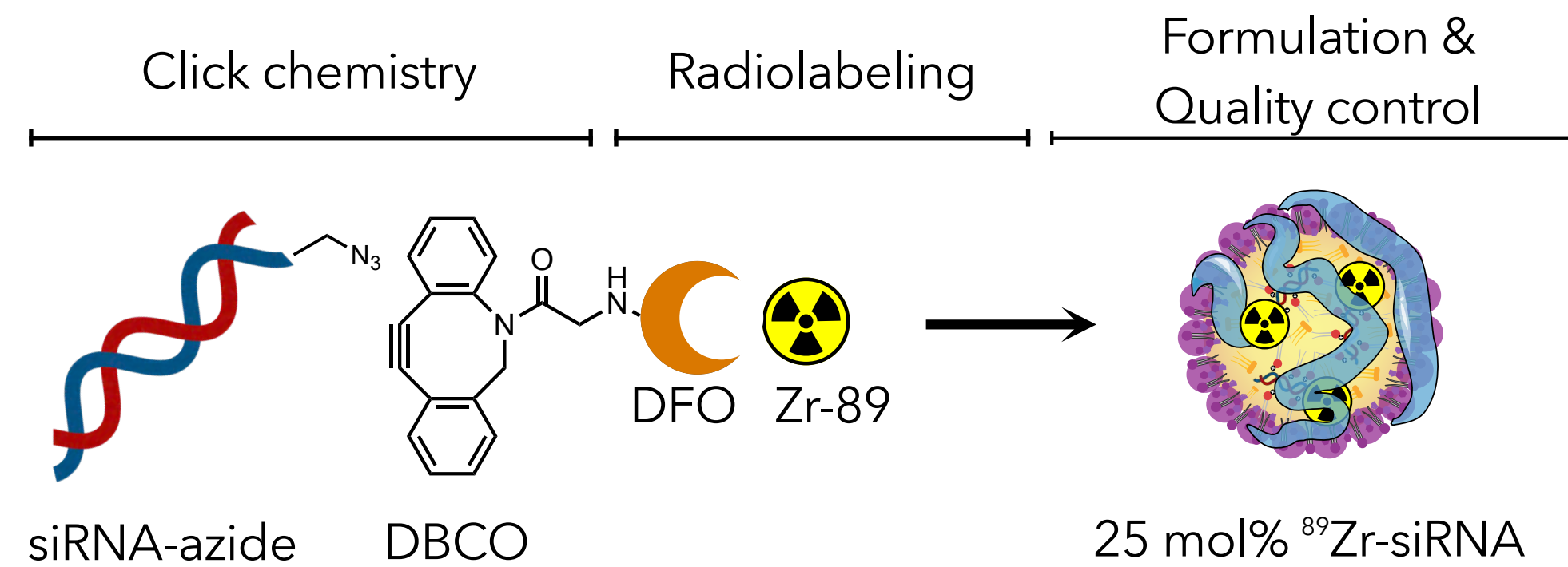
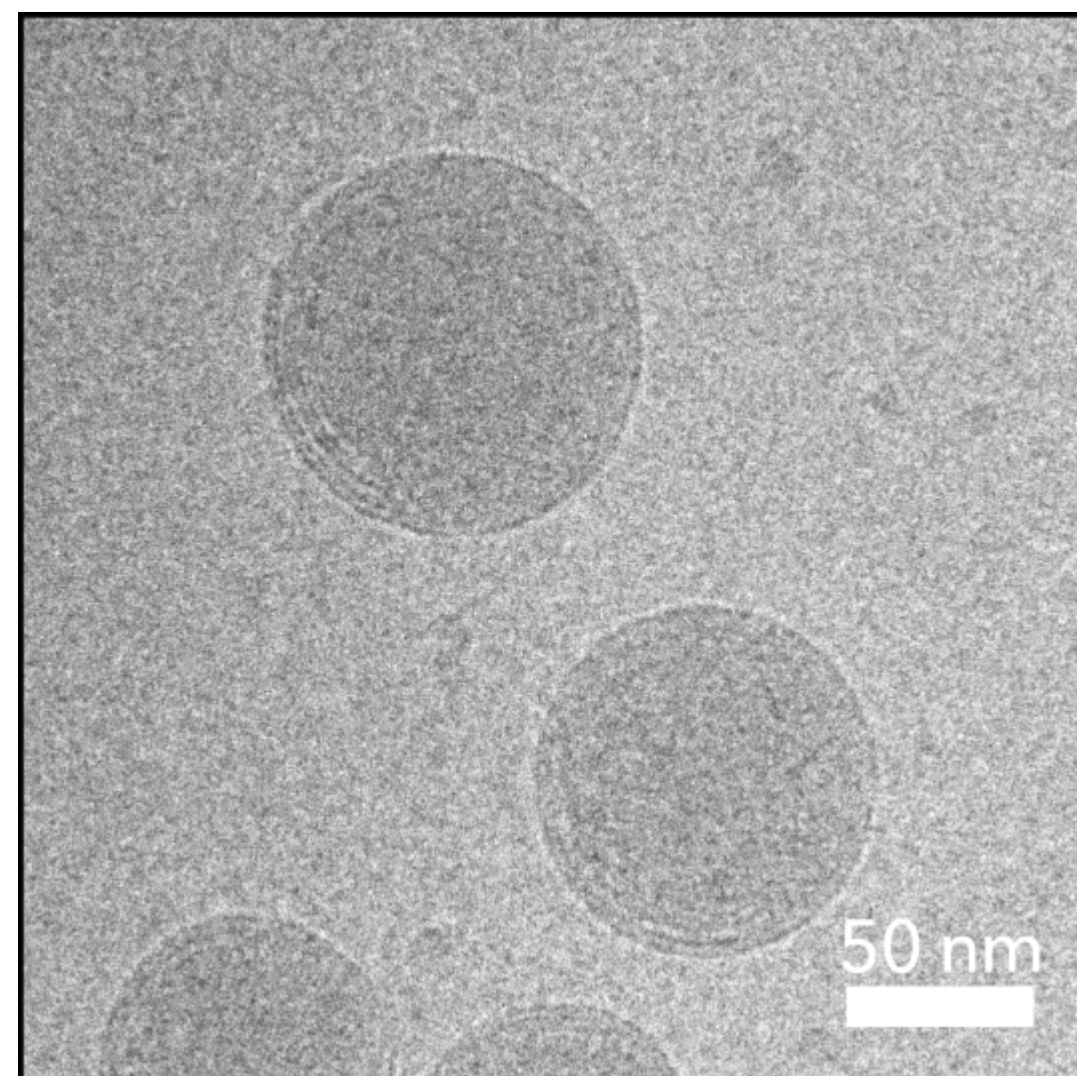


aNP-siRNA prototype



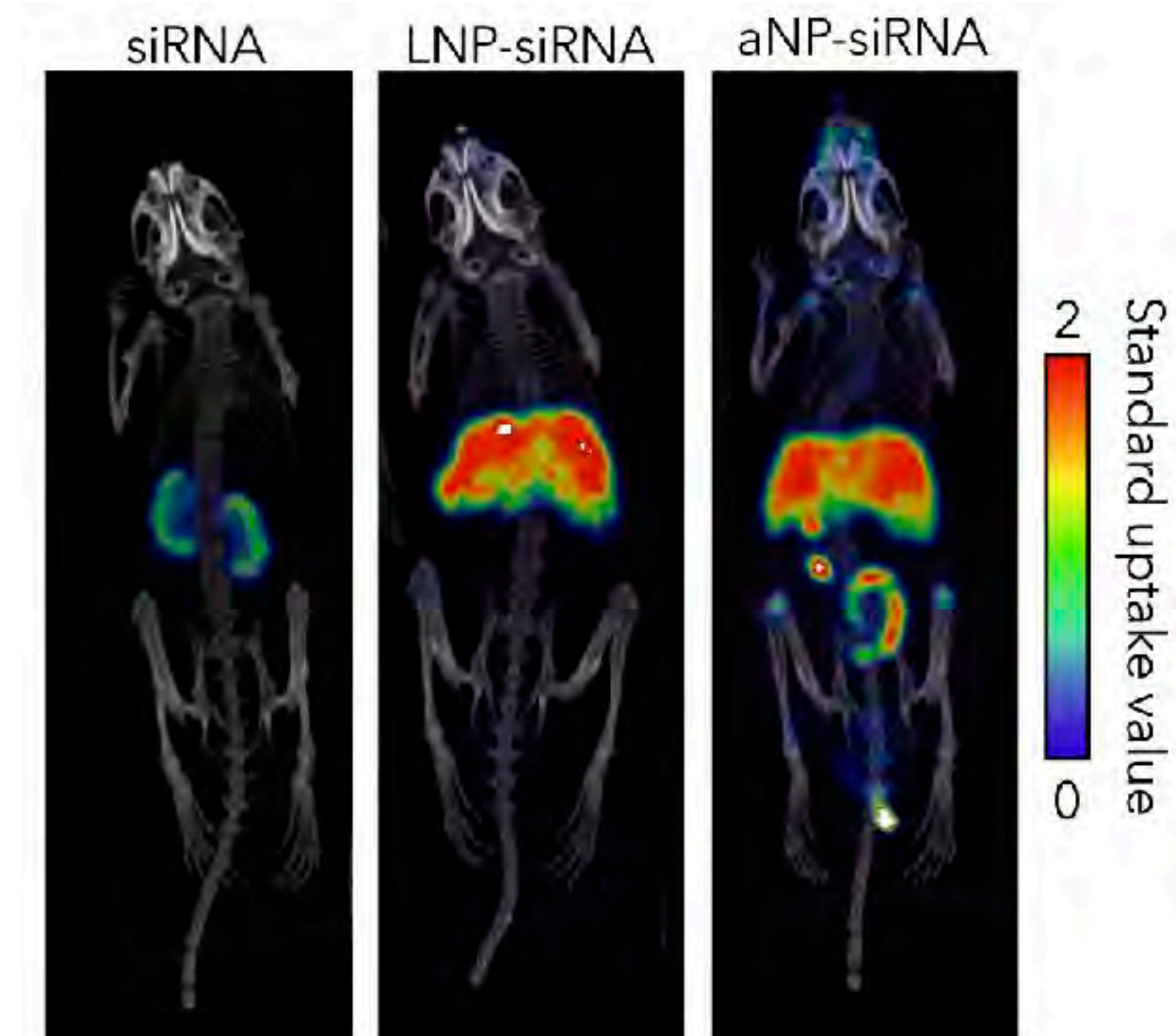
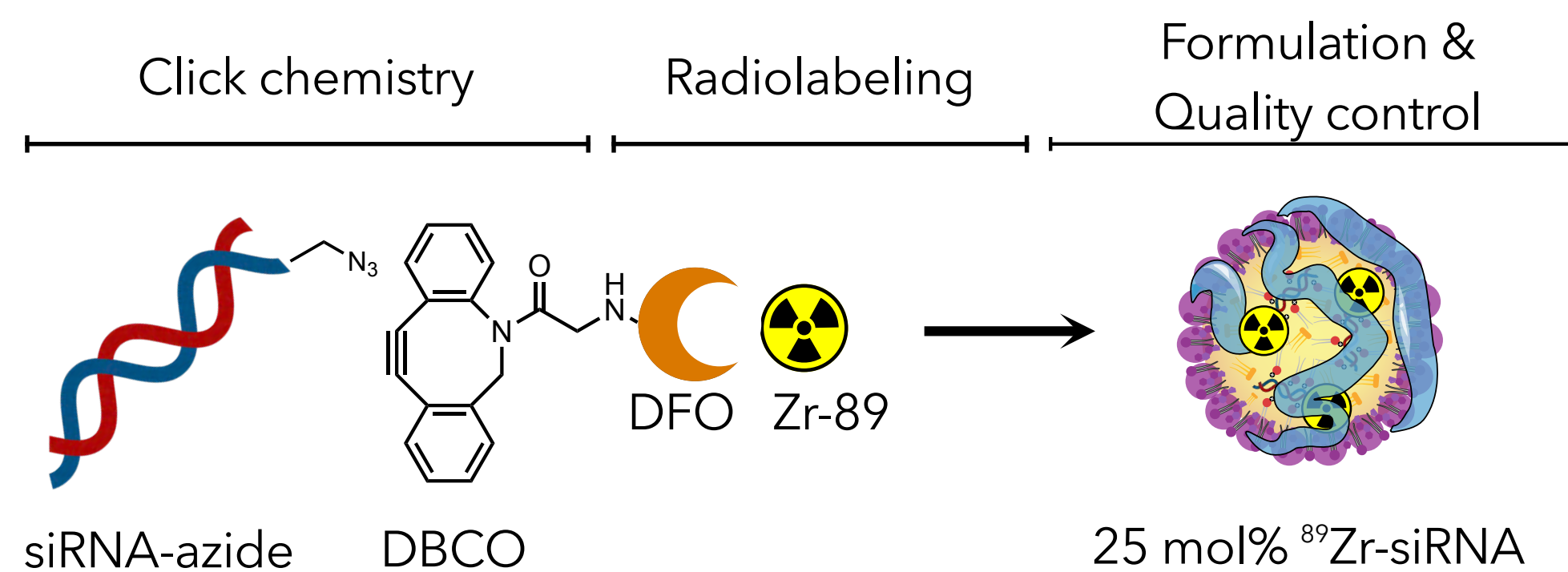
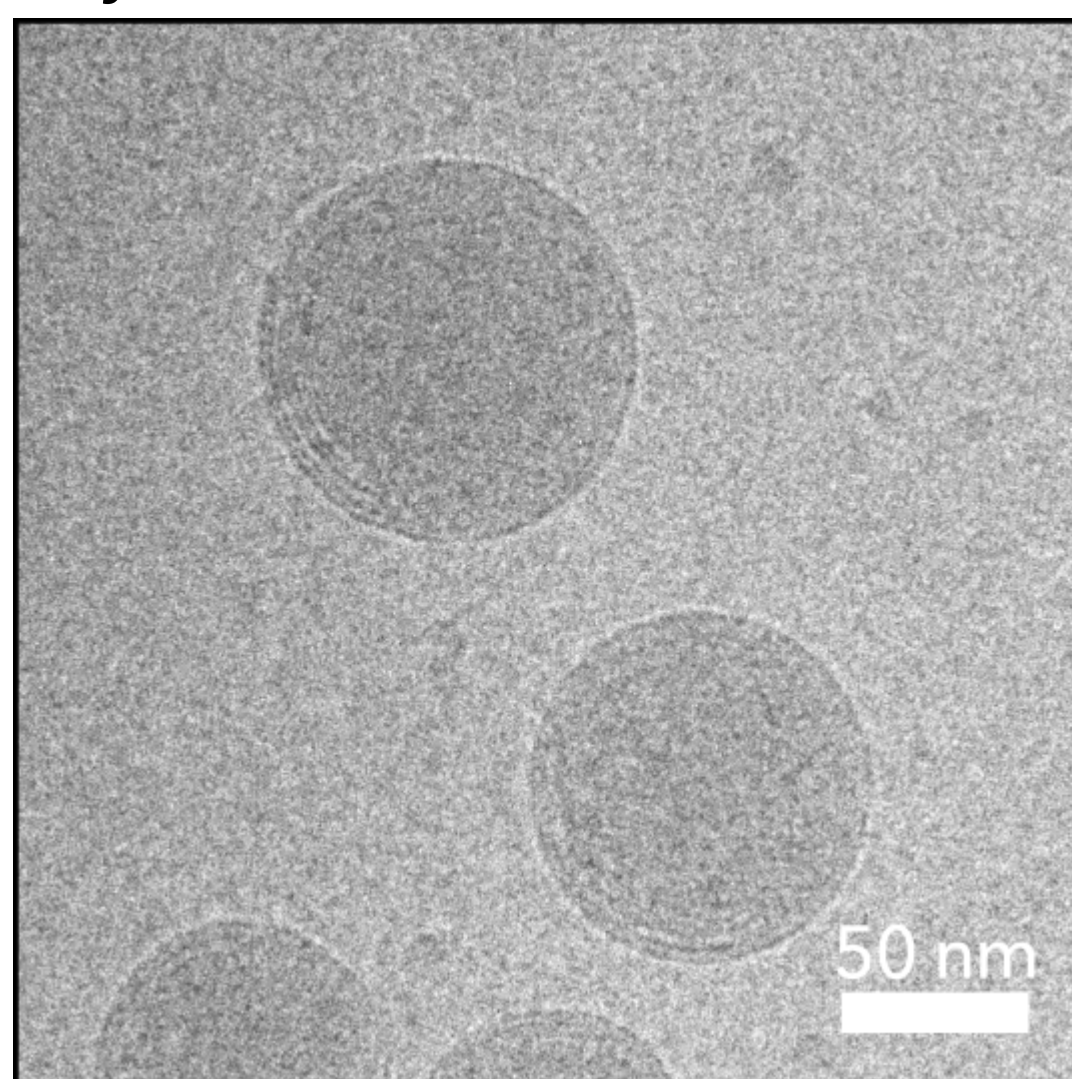
aNP-siRNA prototype

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



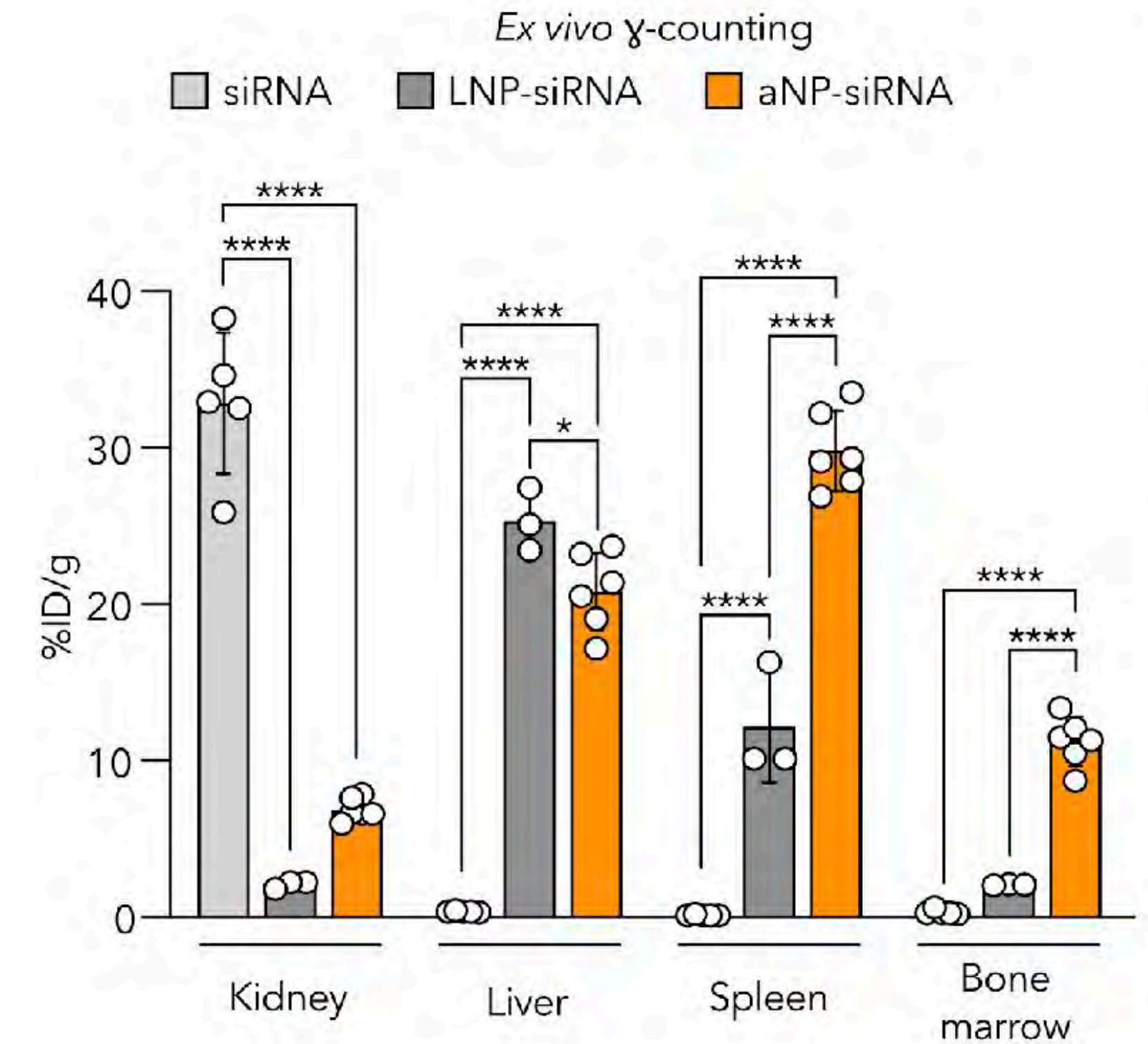
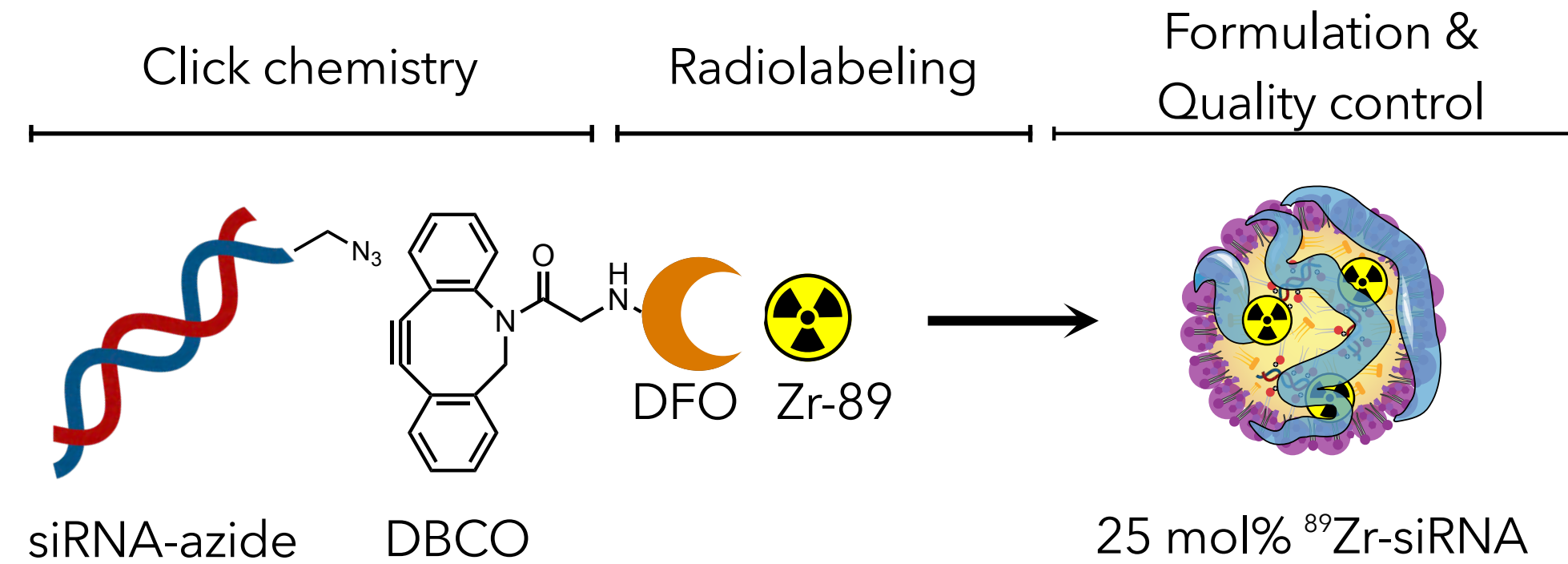
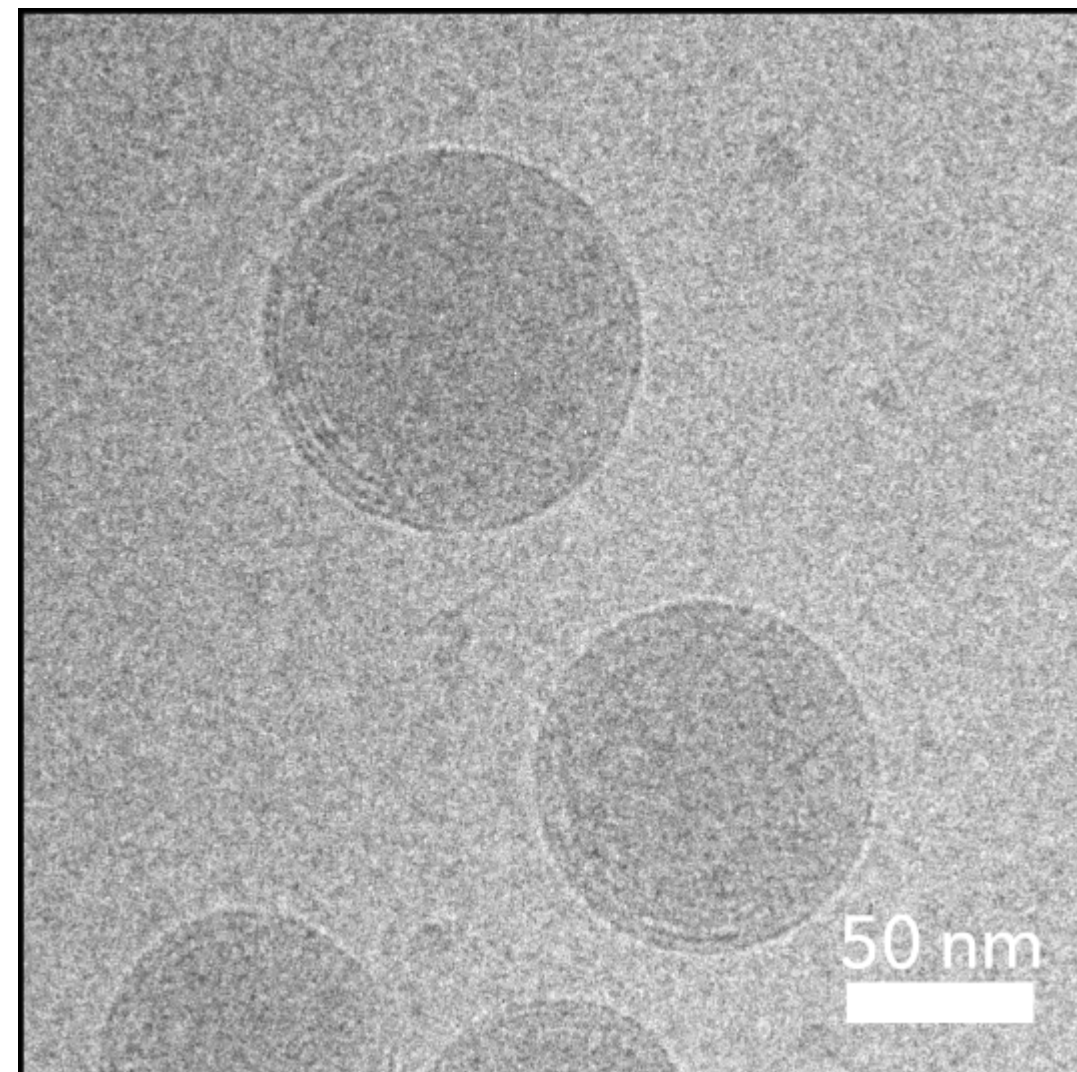
aNP-siRNA prototype

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



aNP-siRNA prototype

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

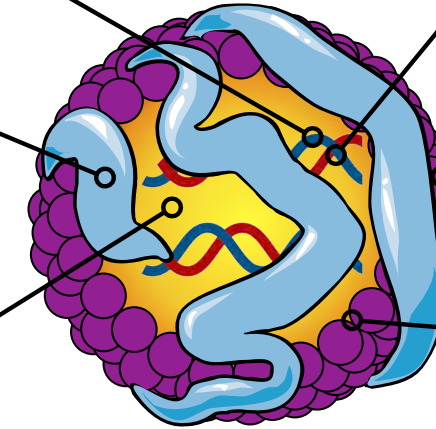


aNP-siRNA library establishment

MC3 (**N**itrogen) - Variable N/P: 3, 6, 9, 12

ApoA1 - Constant: 1 mg

Tricaprylin - Variable: 0, 5, 10 mg

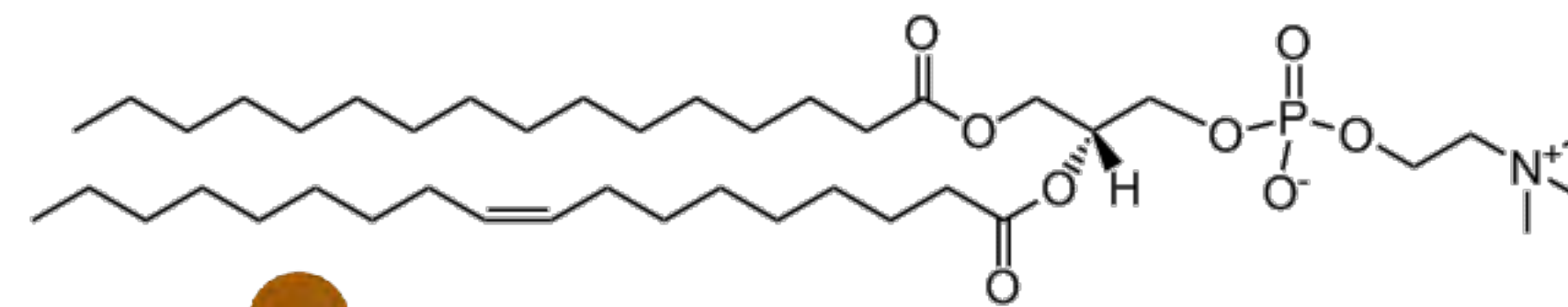
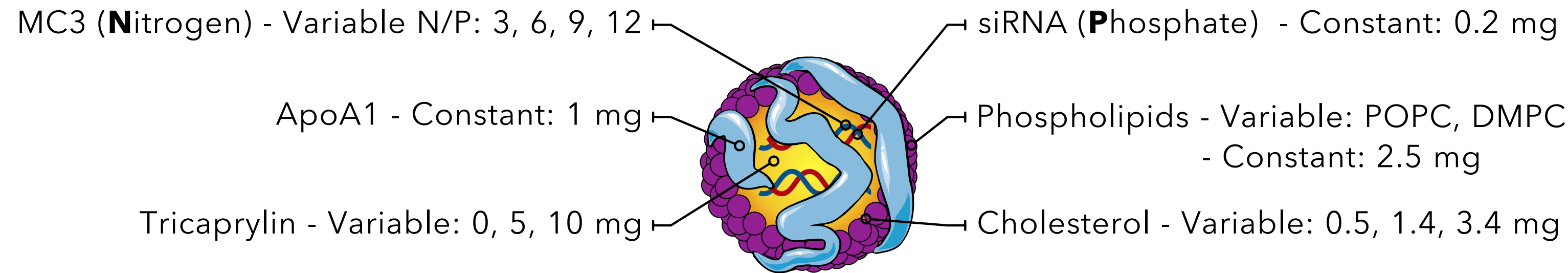


siRNA (**P**hosphate) - Constant: 0.2 mg

Phospholipids - Variable: POPC, DMPC
- Constant: 2.5 mg

Cholesterol - Variable: 0.5, 1.4, 3.4 mg

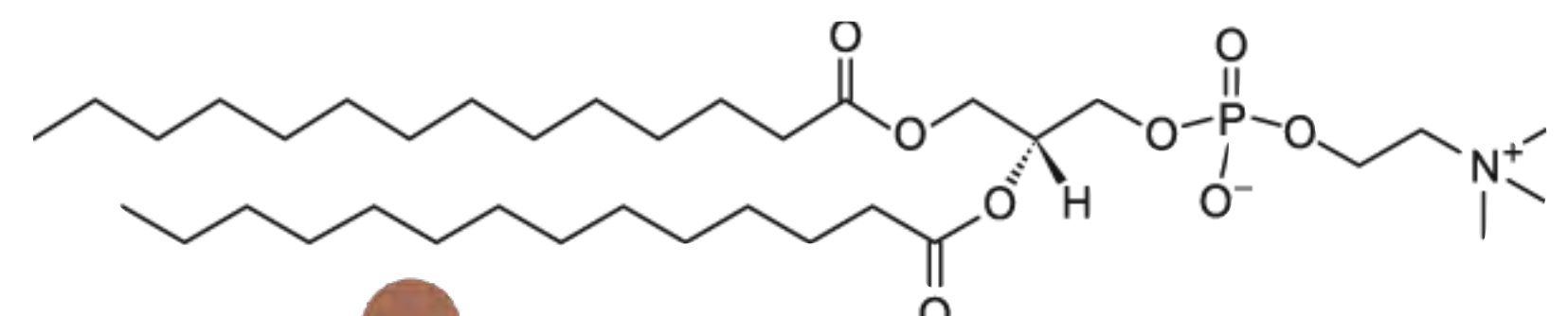
aNP-siRNA library establishment



POPC-based aNPs

Nitrogen-to-Phosphate ratio

3 6 9 12



DMPC-based aNPs

Nitrogen-to-Phosphate ratio

3 6 9 12

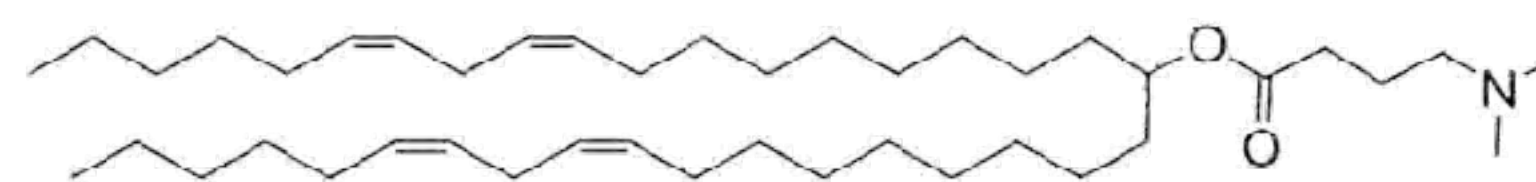


Tricaprylin {
None
Med
Hi

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

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

Lo Med Hi →
Cholesterol

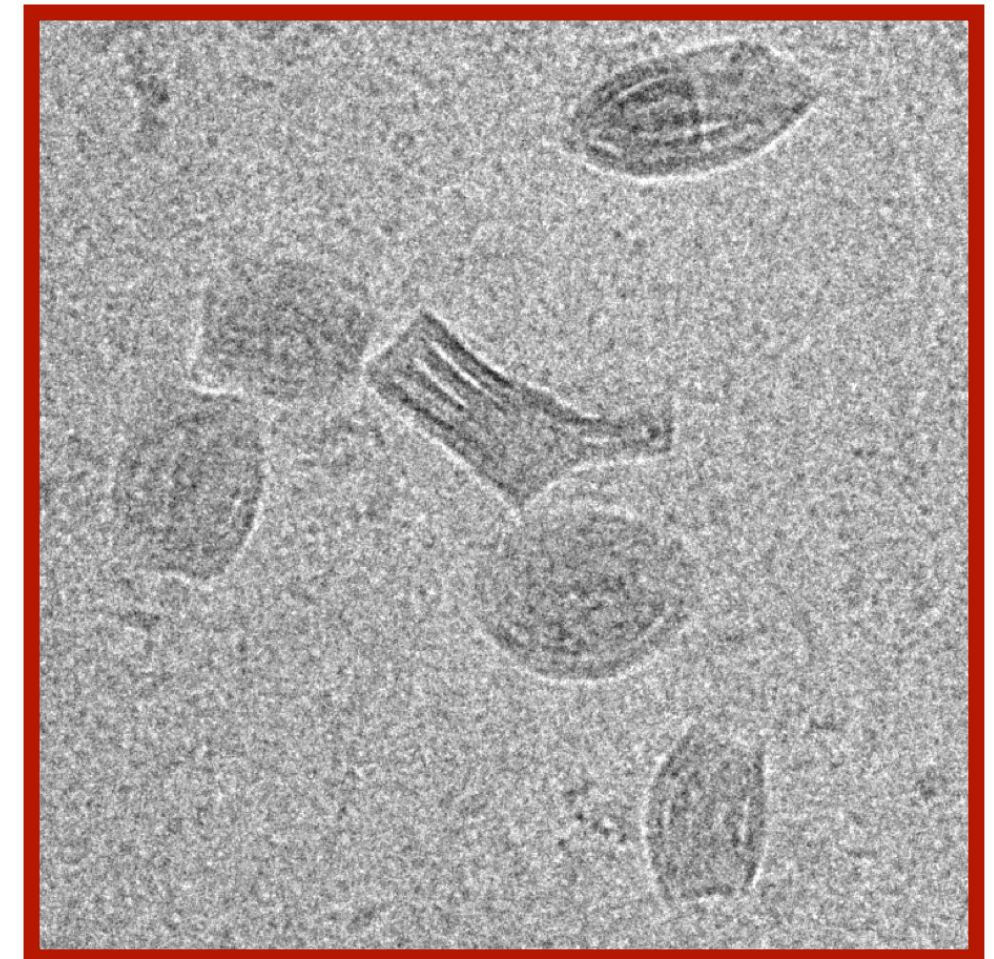
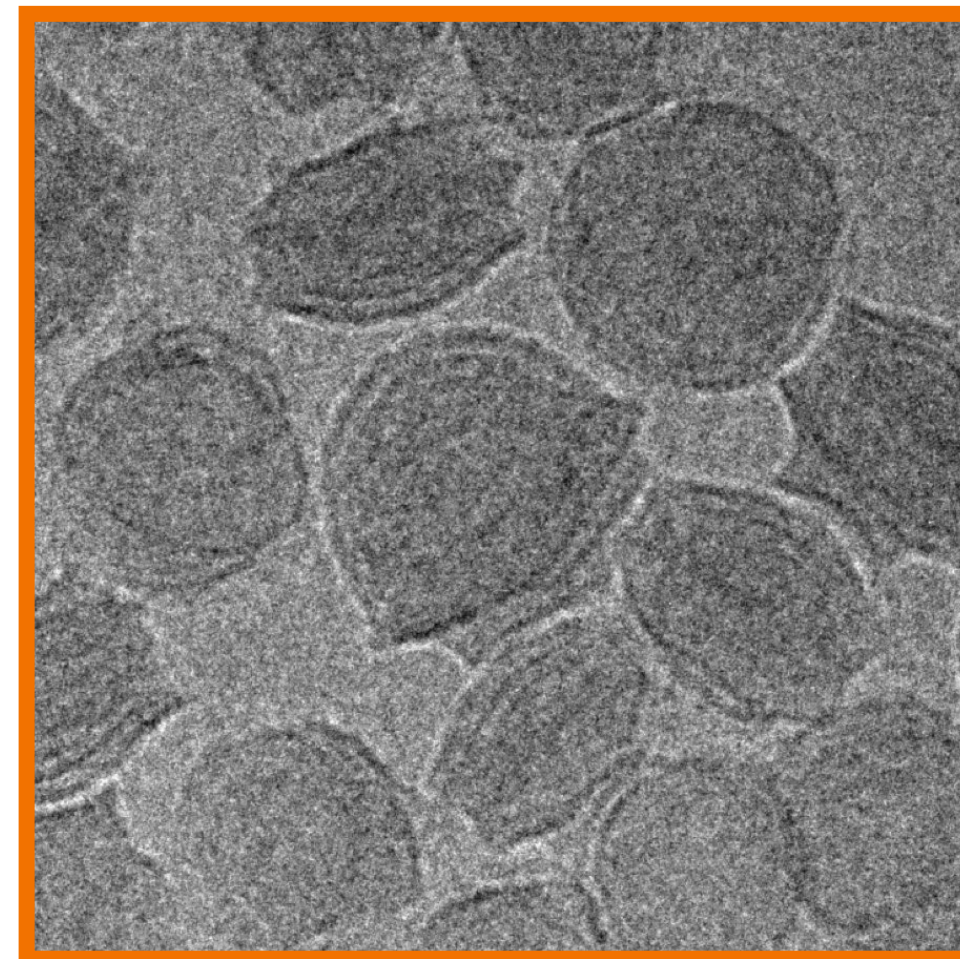
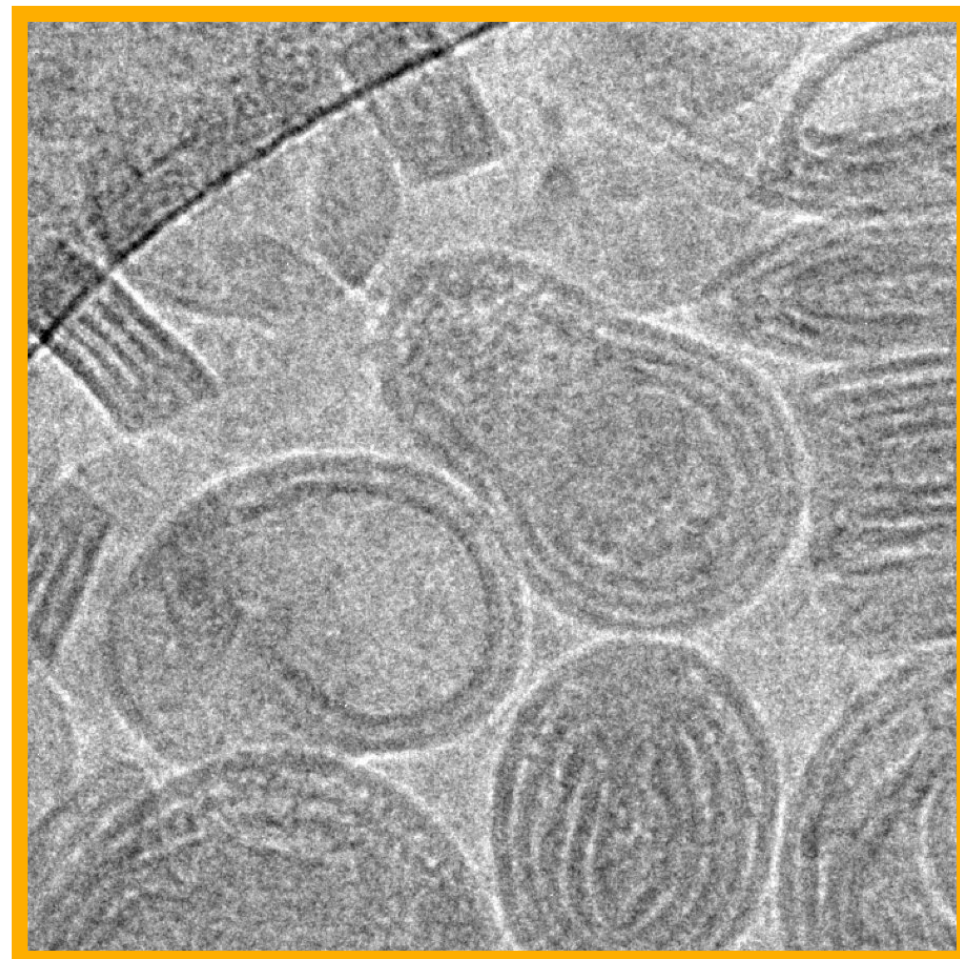
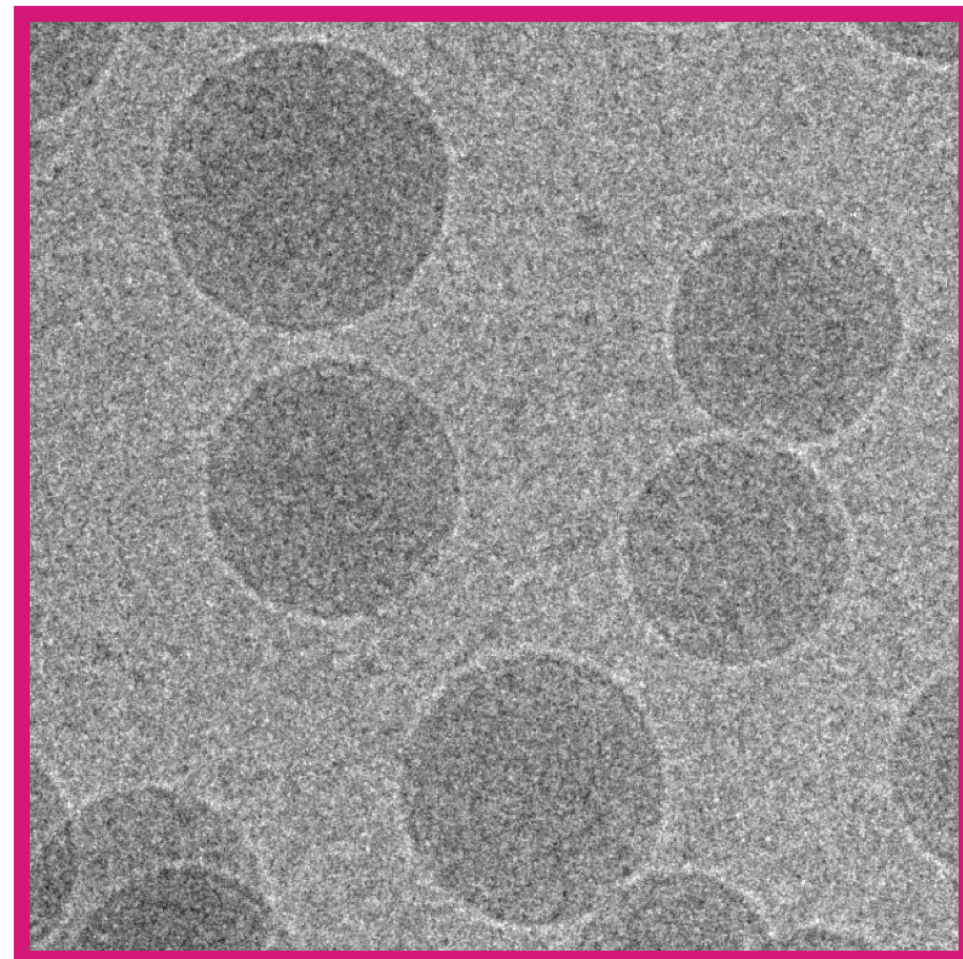
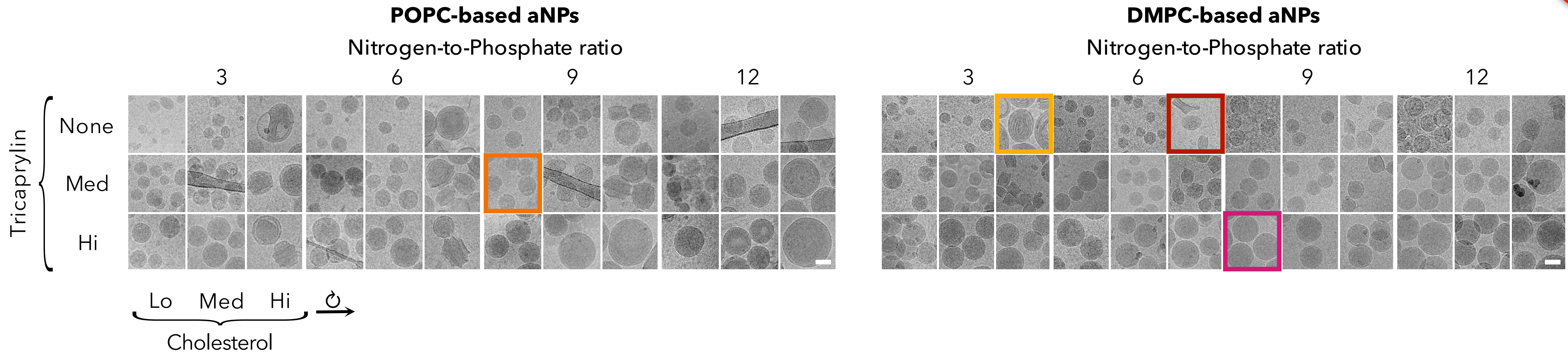


DLIn-MC3-DMA

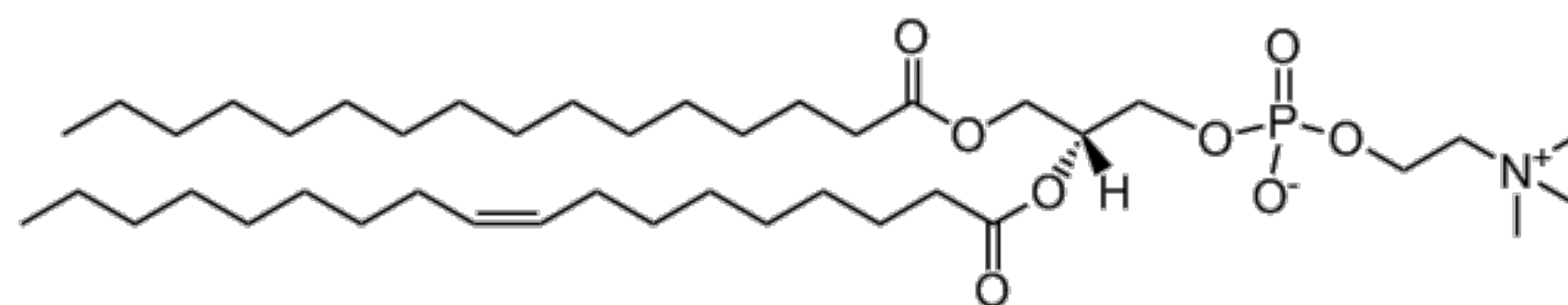
aNP-siRNA library characterization



Ewelina



aNP-siRNA library establishment



POPC-based aNPs

Nitrogen-to-Phosphate ratio

3 6 9 12



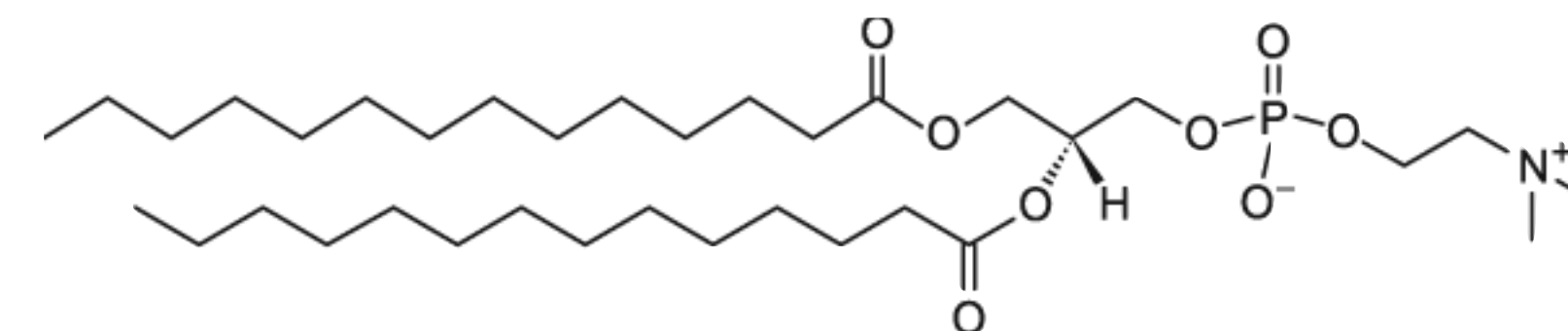
Tricaprylin

None
Med
Hi

1	2	3	4	5	6	7	8	9	10	11	12
25	26	27	28	29	30	31	32	33	34	35	36
49	50	51	52	53	54	55	56	57	58	59	60

Lo Med Hi →

Cholesterol



DMPC-based aNPs

Nitrogen-to-Phosphate ratio

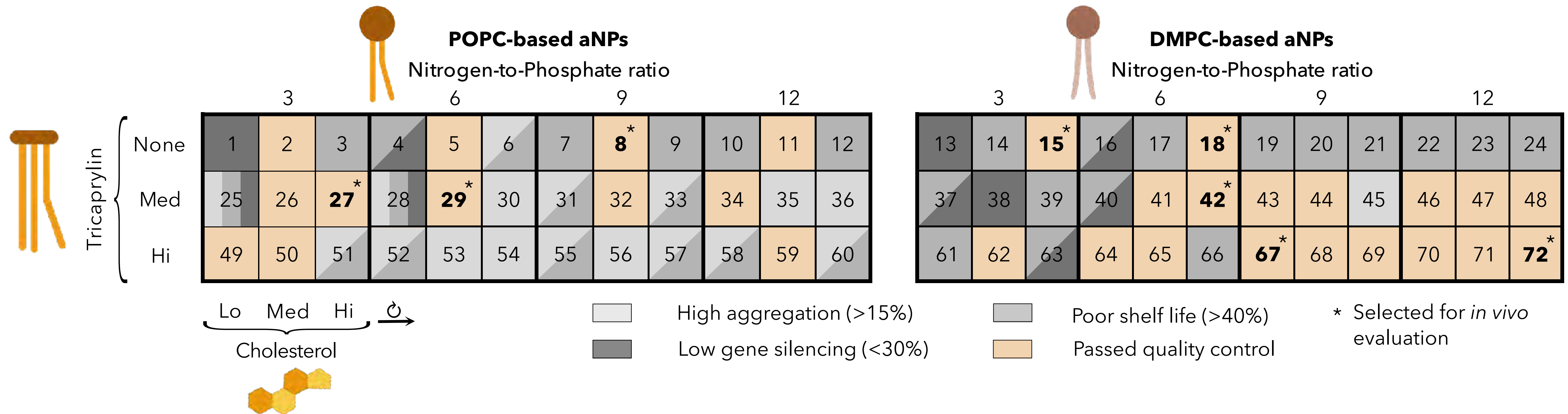
3 6 9 12

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



DLIn-MC3-DMA

aNP-siRNA selection for *in vivo* evaluation



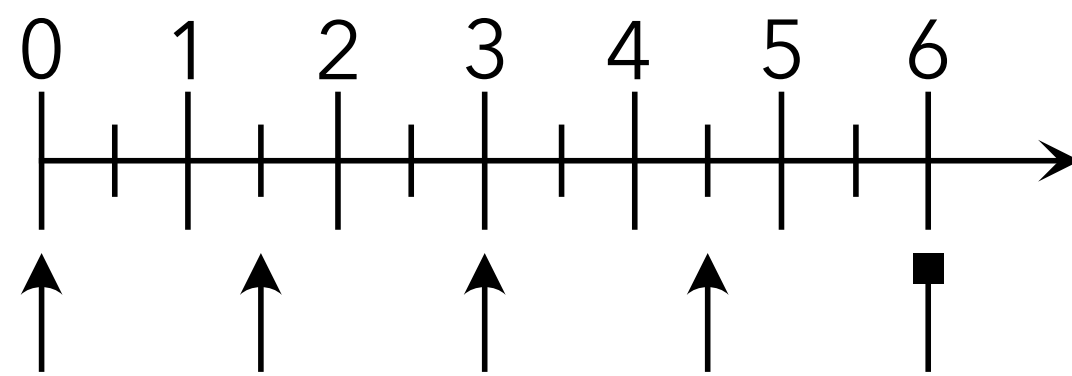
LAMP-1 silencing in mice with aNP-siRNA

LAMP1 - Lysosomal associated membrane protein 1



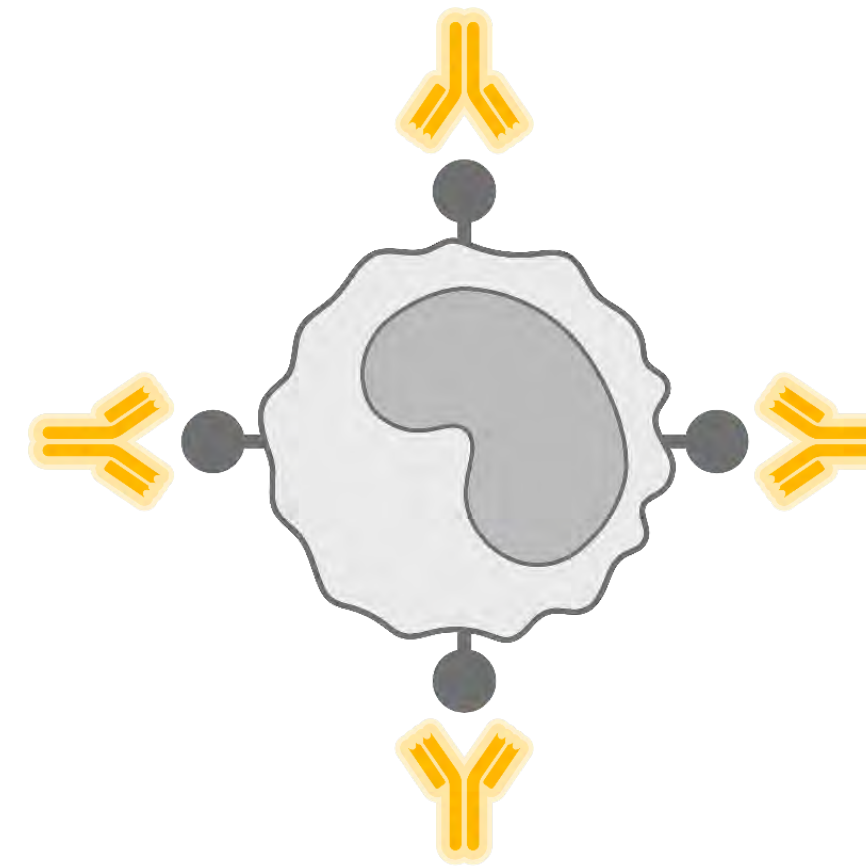
Wildtype C57/BL6 mice

Days



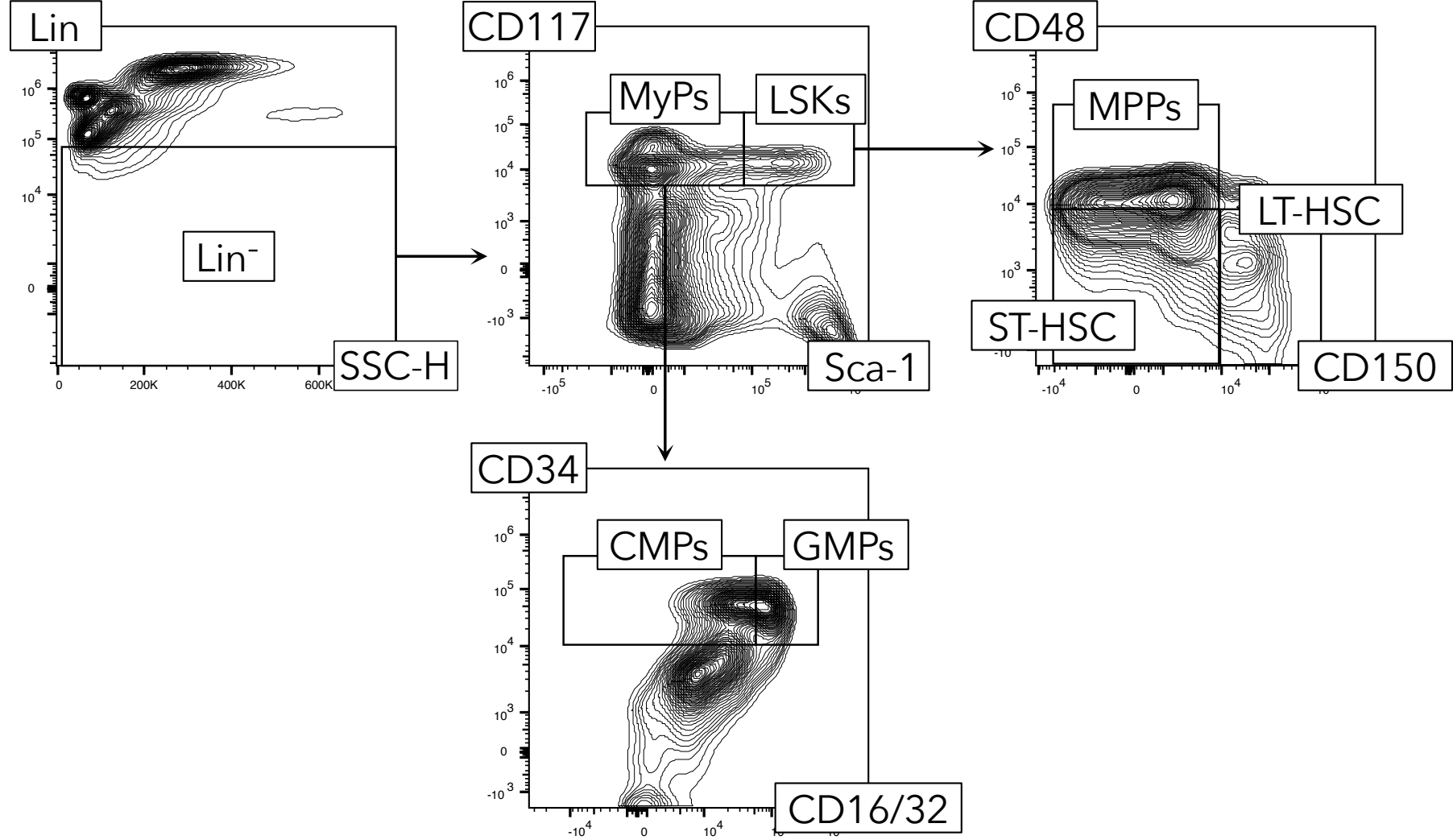
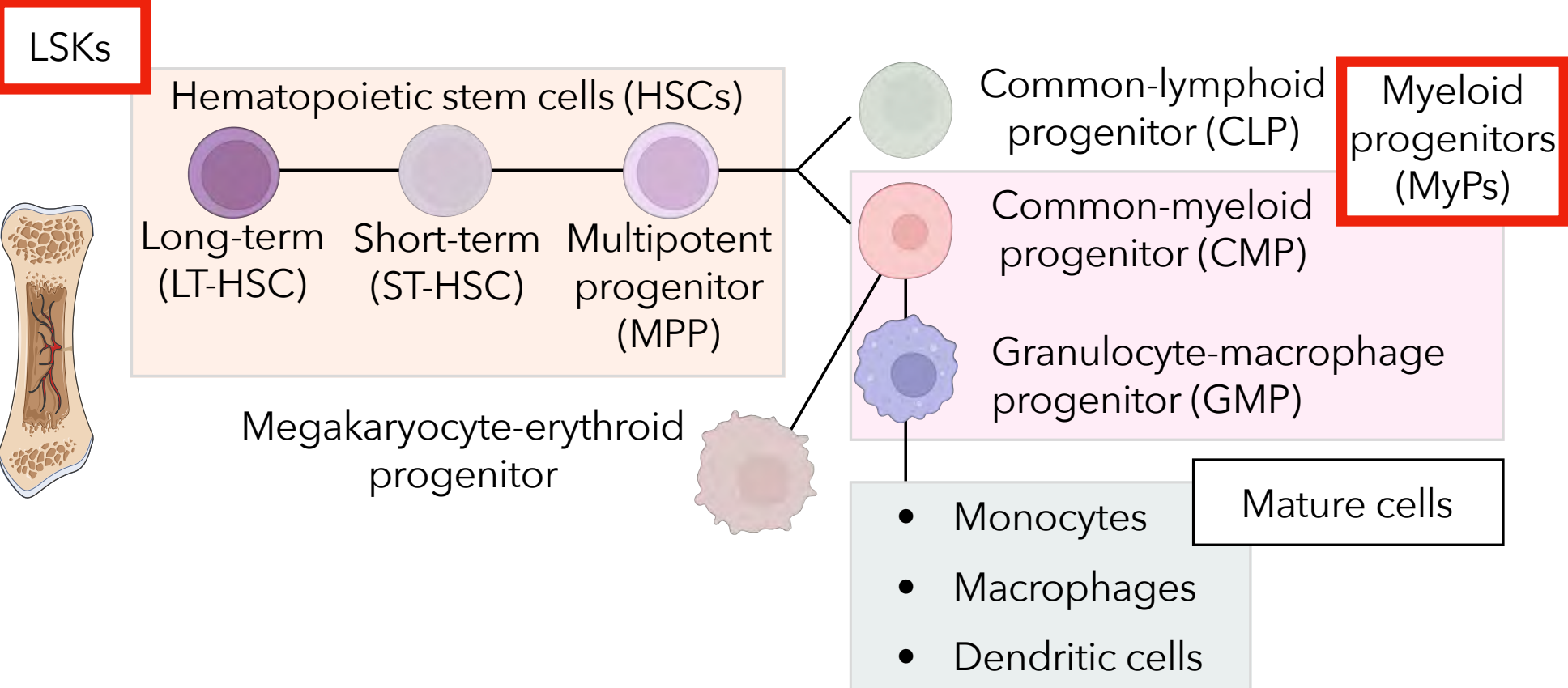
↑ 0.5 mg/kg LAMP1 siRNA

▣ Euthanasia and analysis



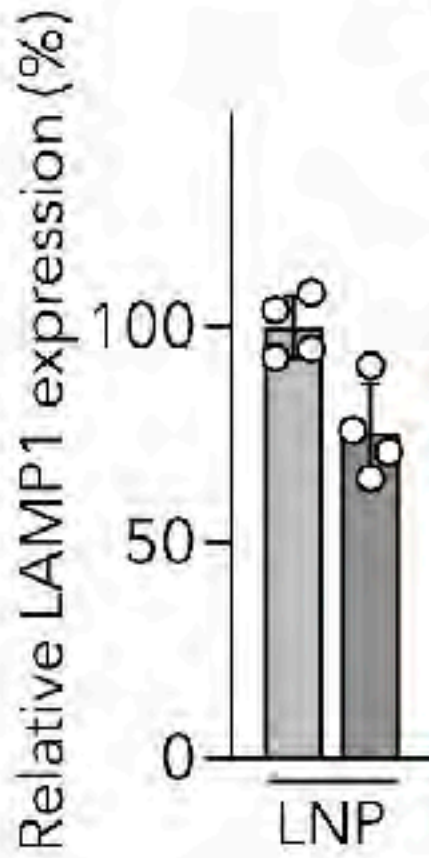
- Membrane bound protein
- Widely expressed
- Function taken over by LAMP2

Gene silencing in (myeloid) progenitor cells

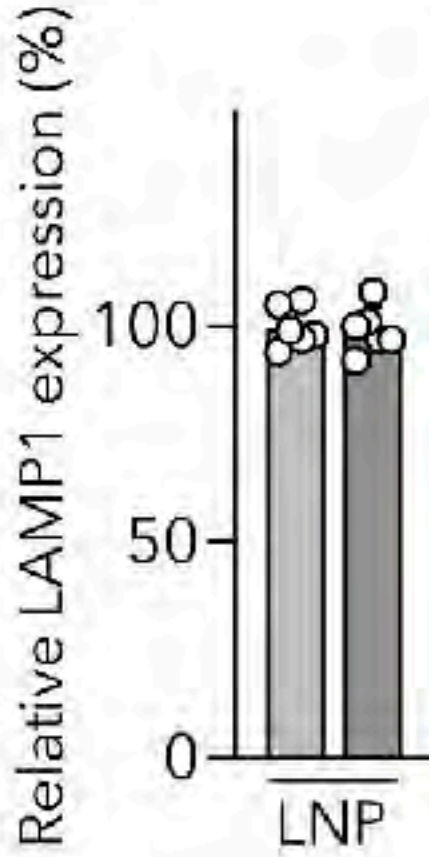


□ LNP-siCtrl ■ LNP-siLAMP1

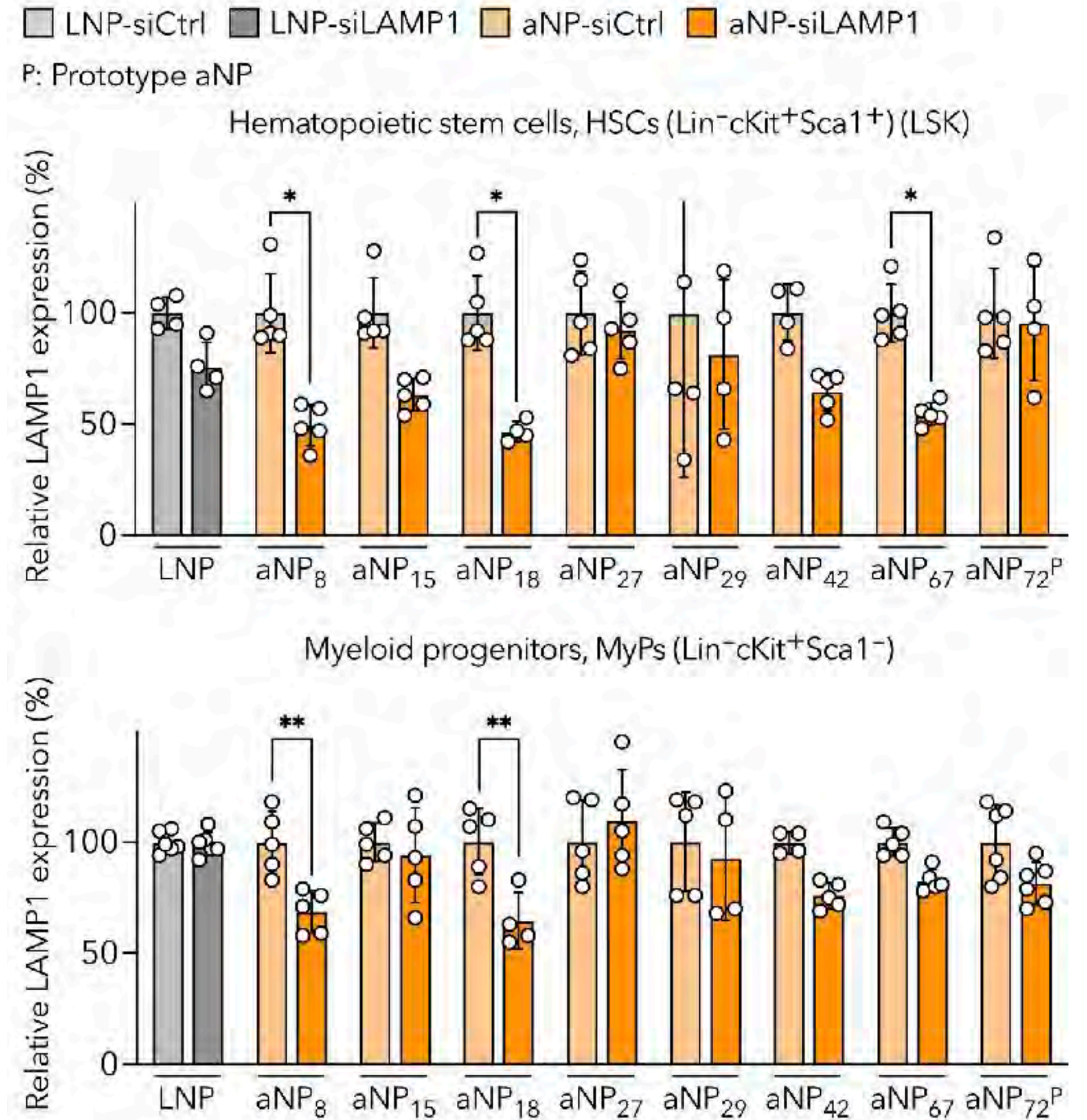
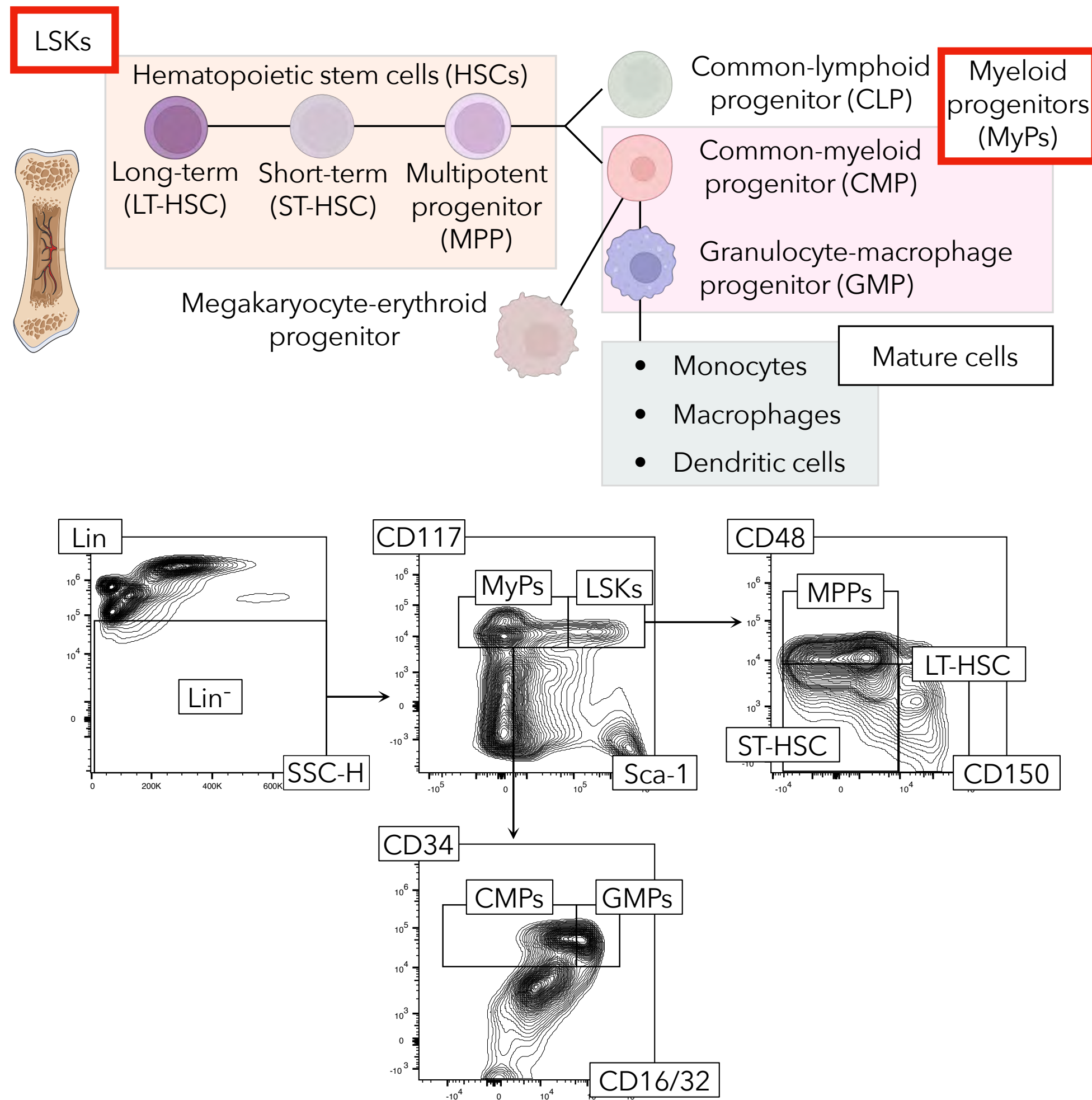
Hematopoietic stem cells, HSCs (Lin⁻cKit⁺Sca1⁺) (LSK)



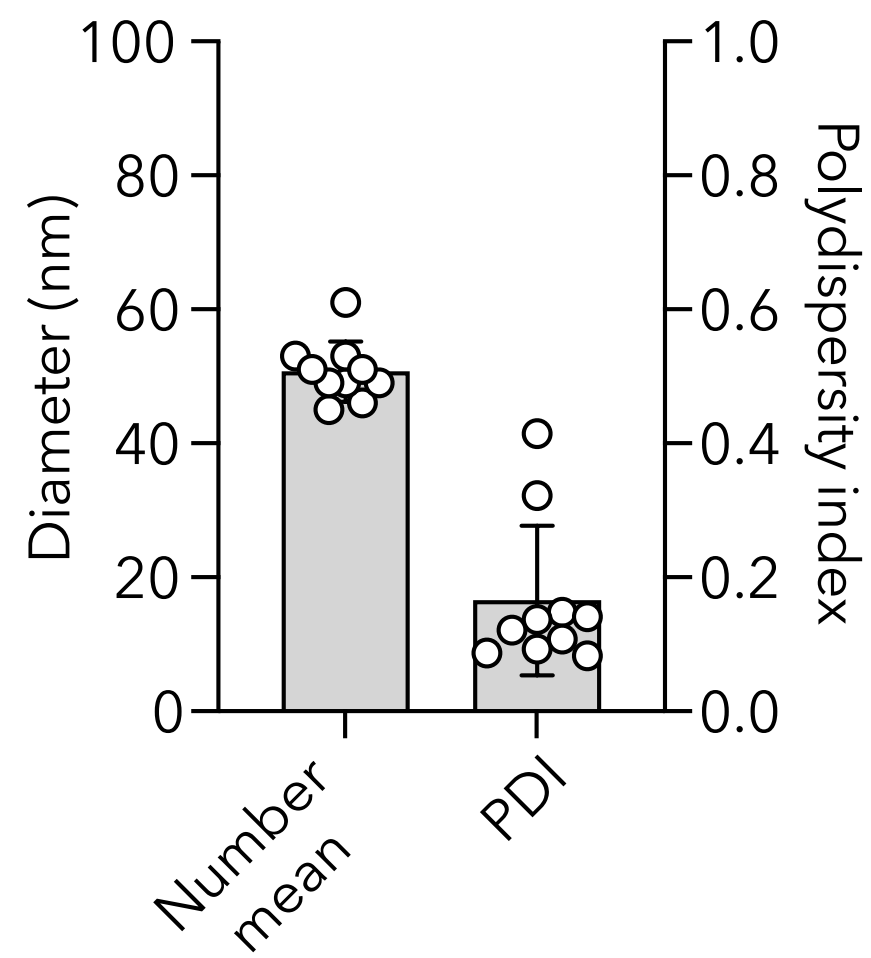
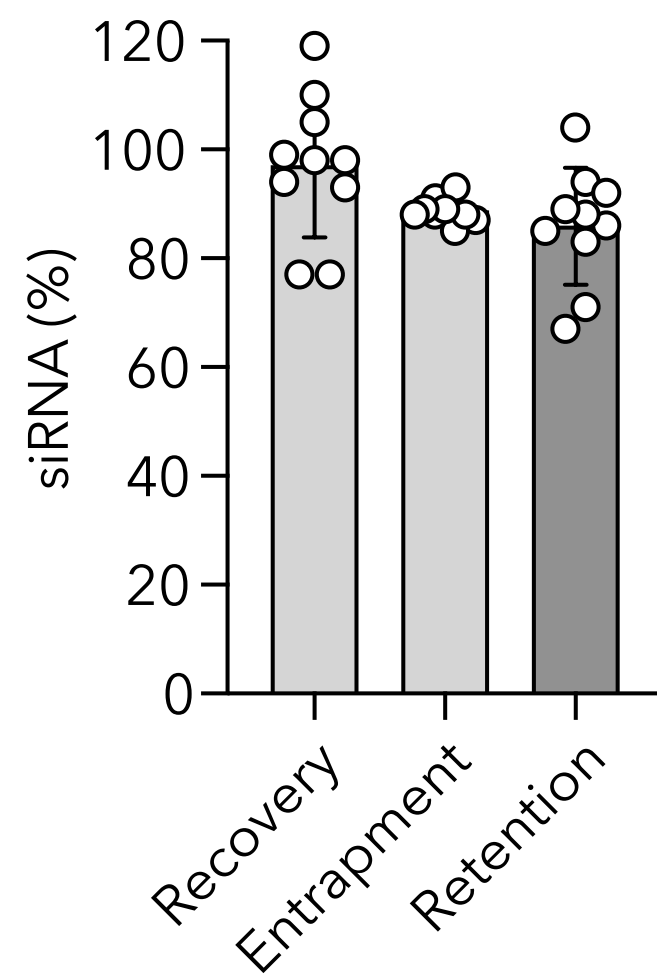
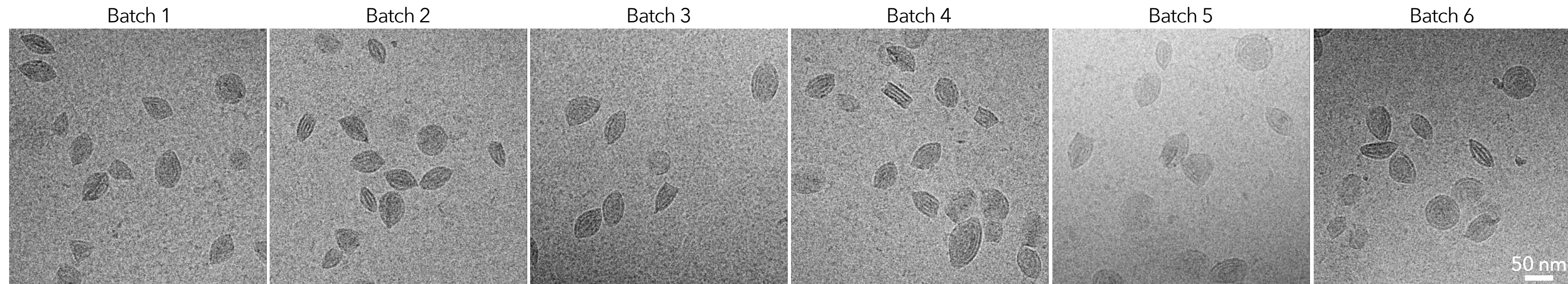
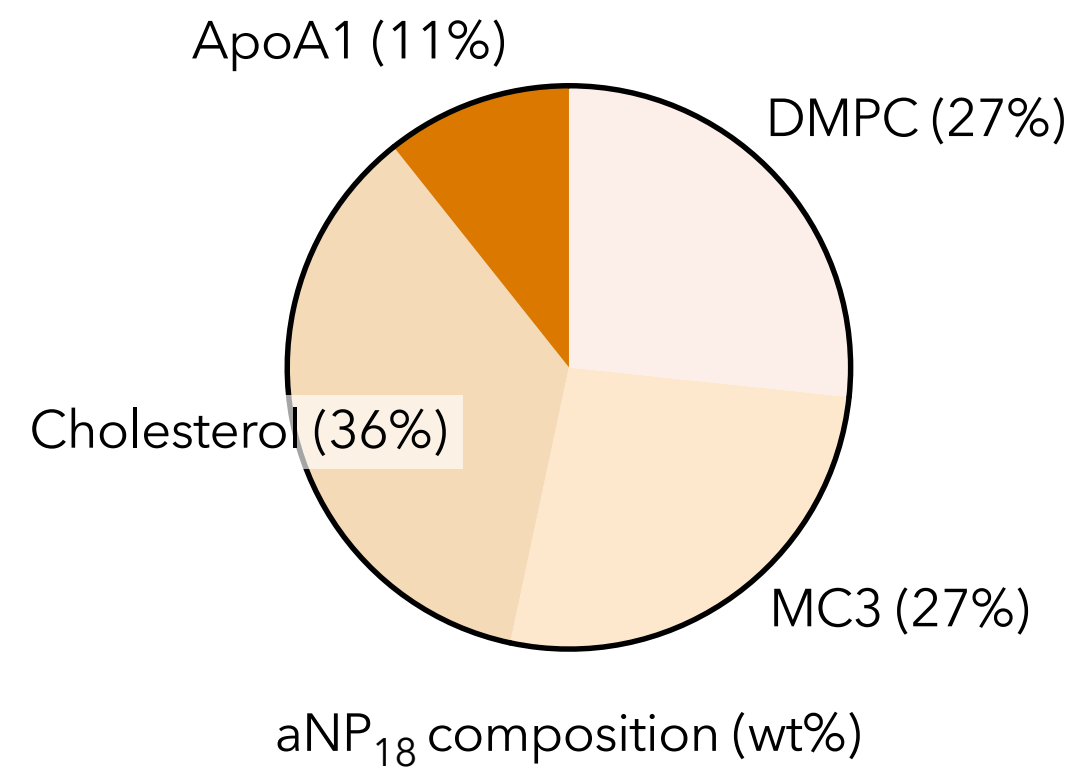
Myeloid progenitors, MyPs (Lin⁻cKit⁺Sca1⁻)



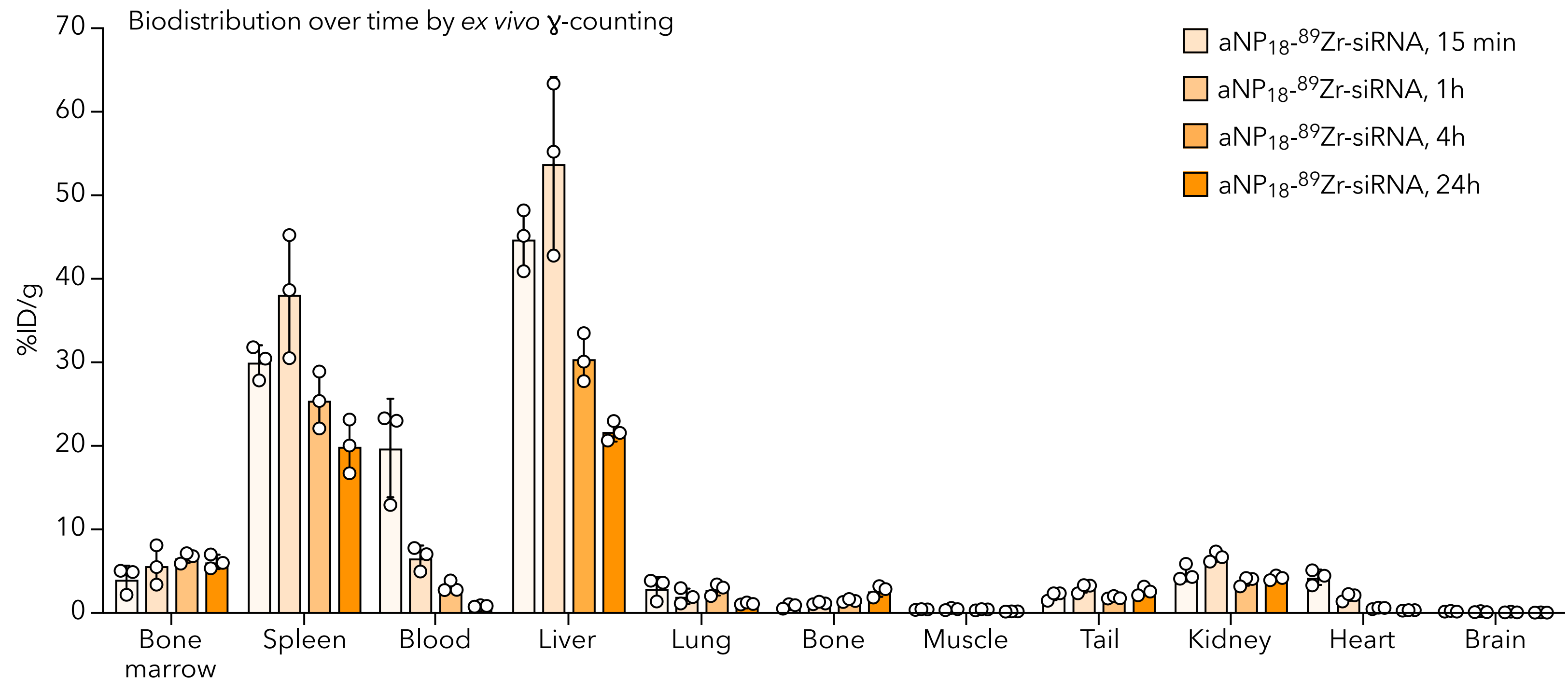
Gene silencing in (myeloid) progenitor cells



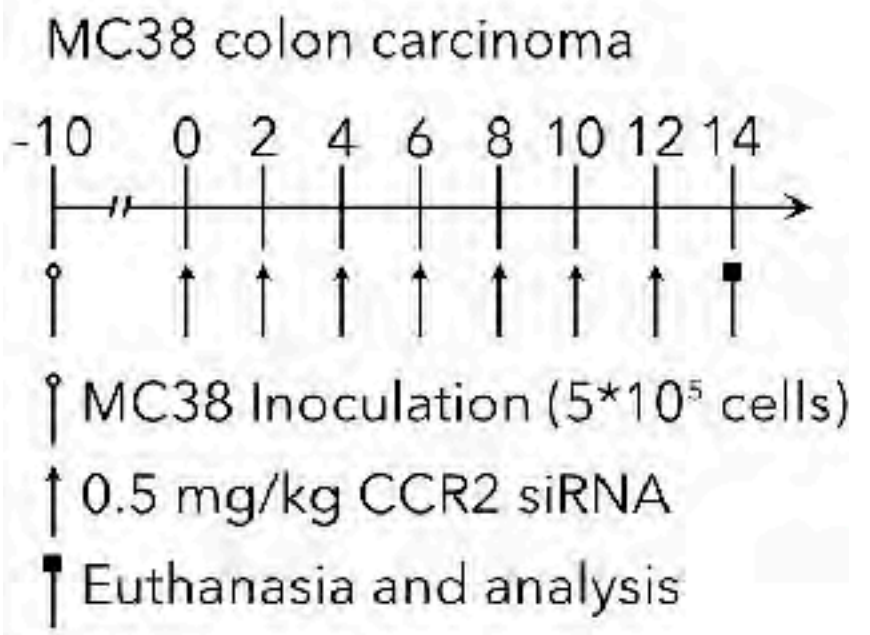
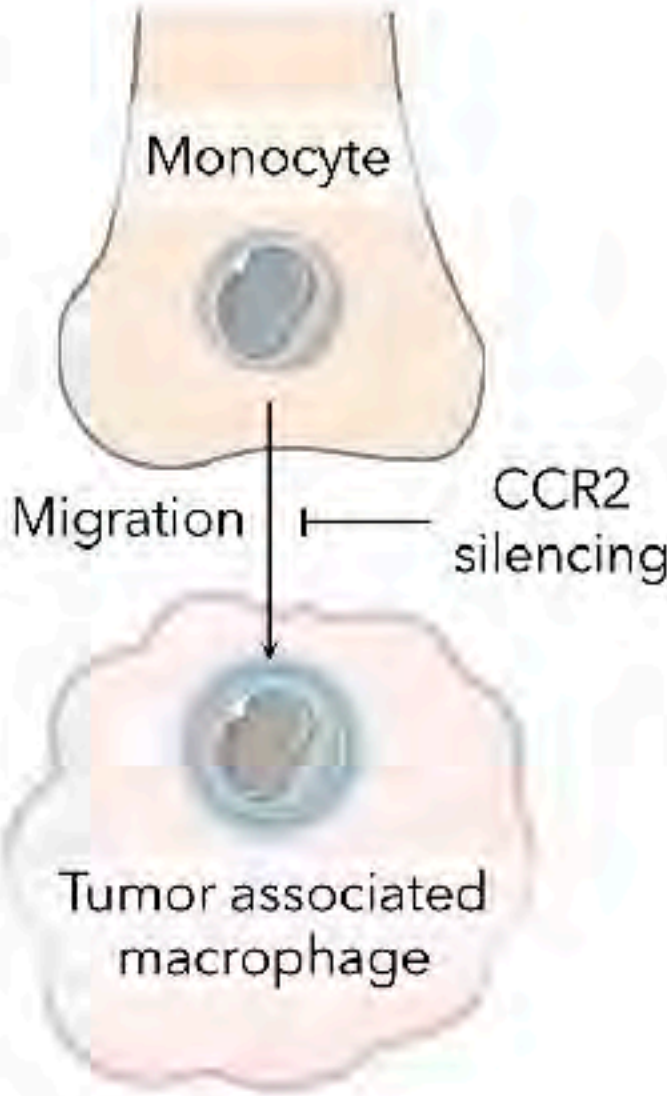
Lead aNP-RNA analysis



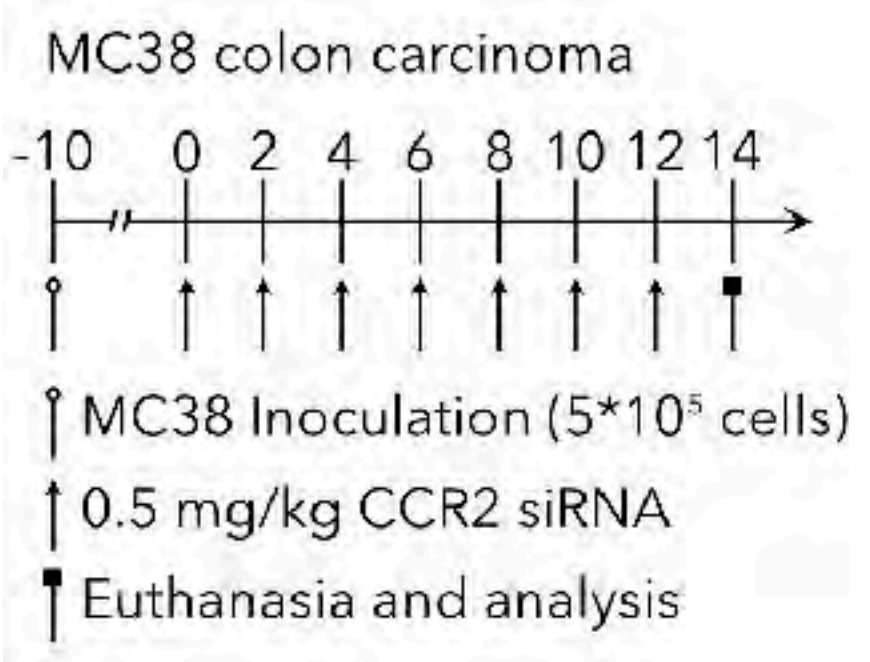
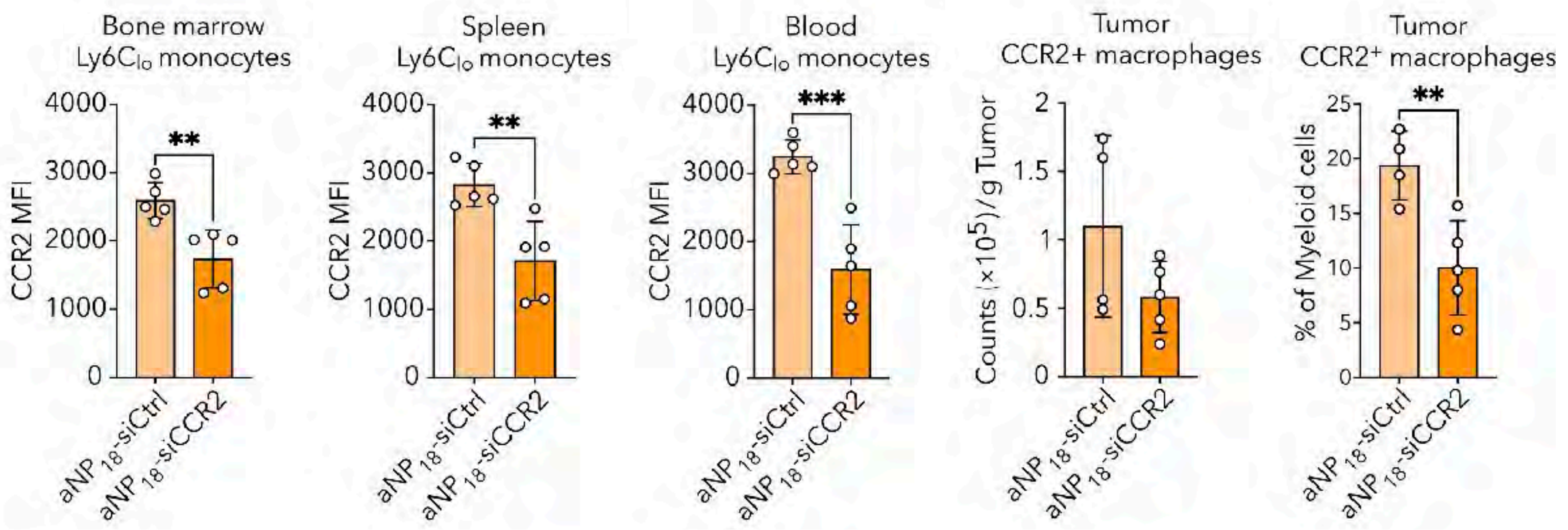
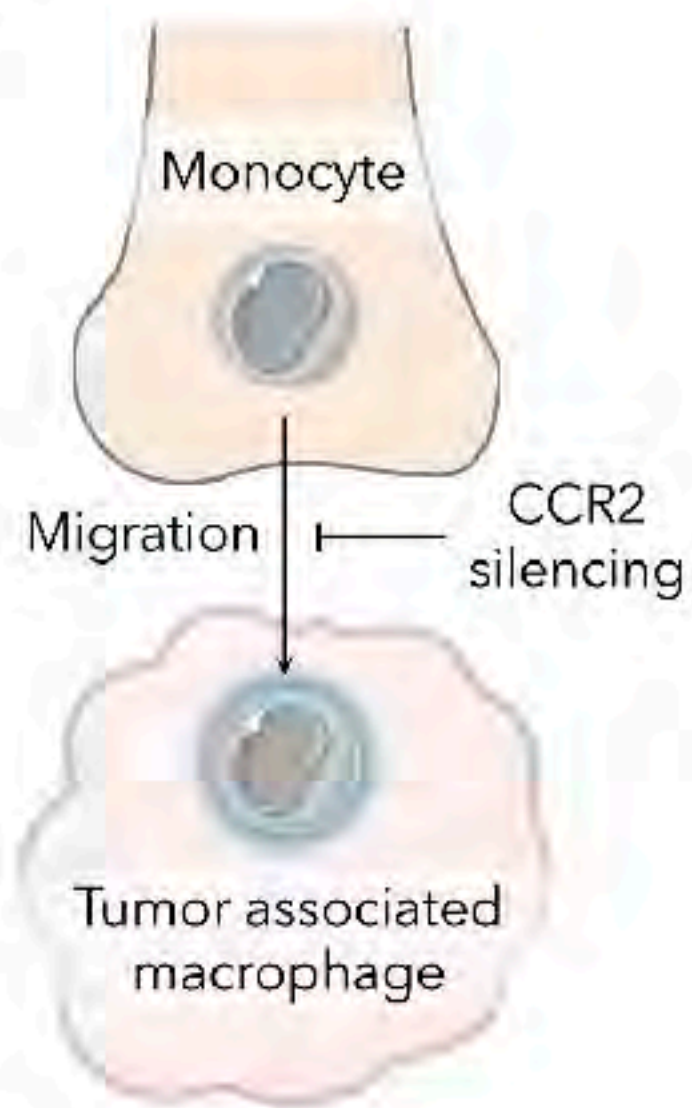
Biodistribution over time by ex vivo γ -counting



Inhibiting immunosuppressive monocyte migration

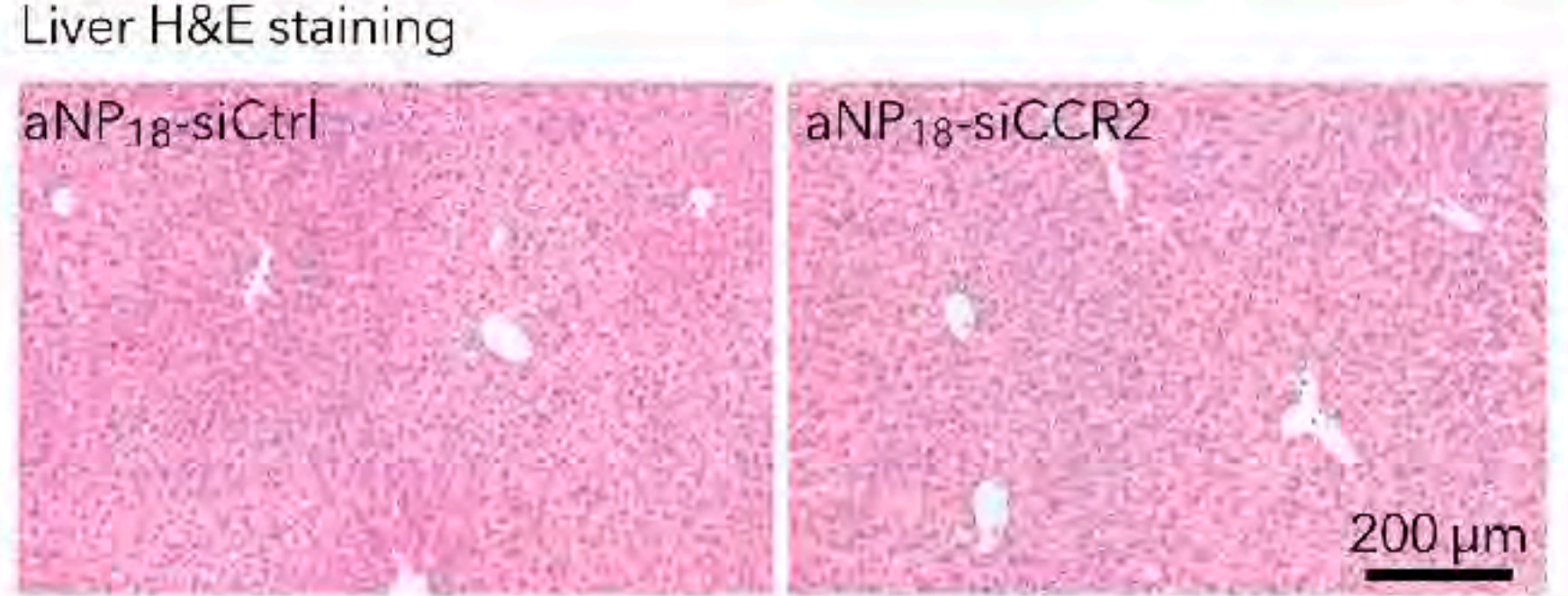
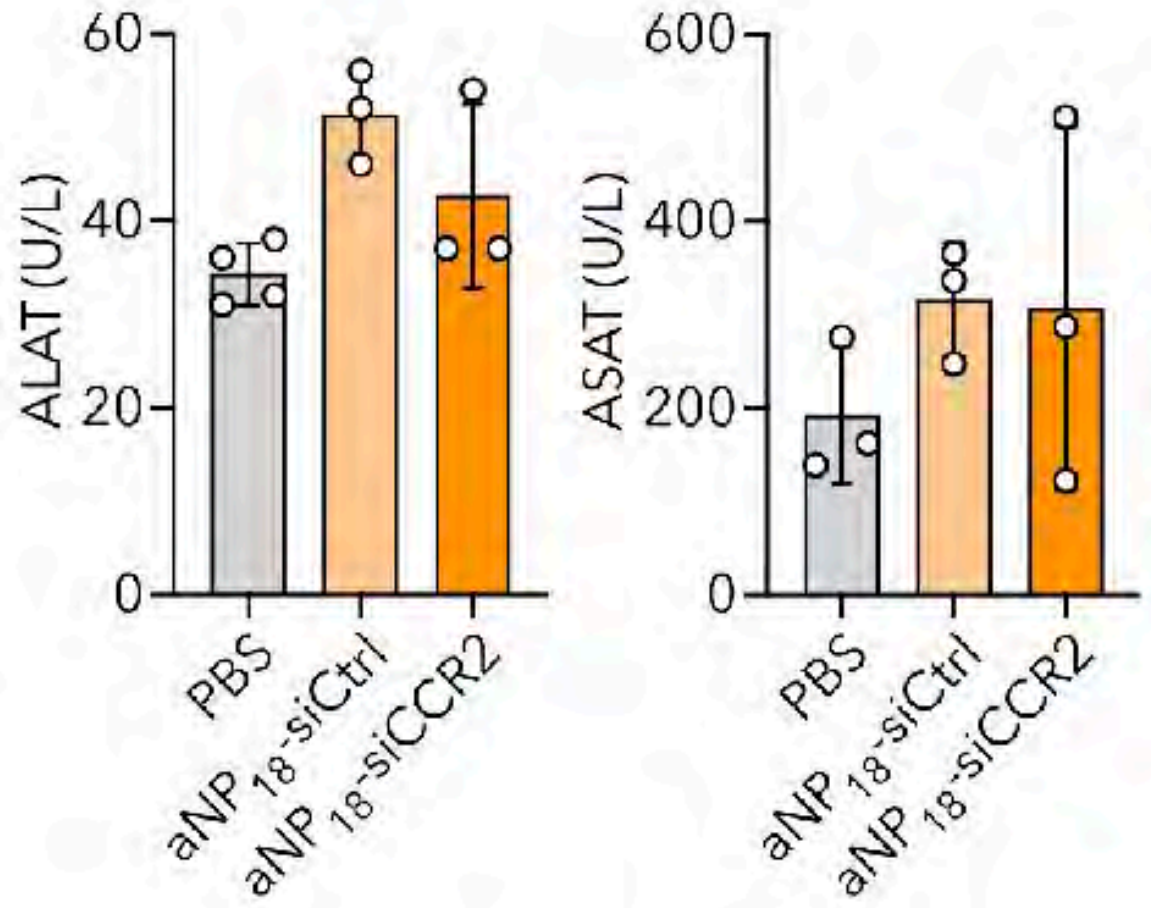
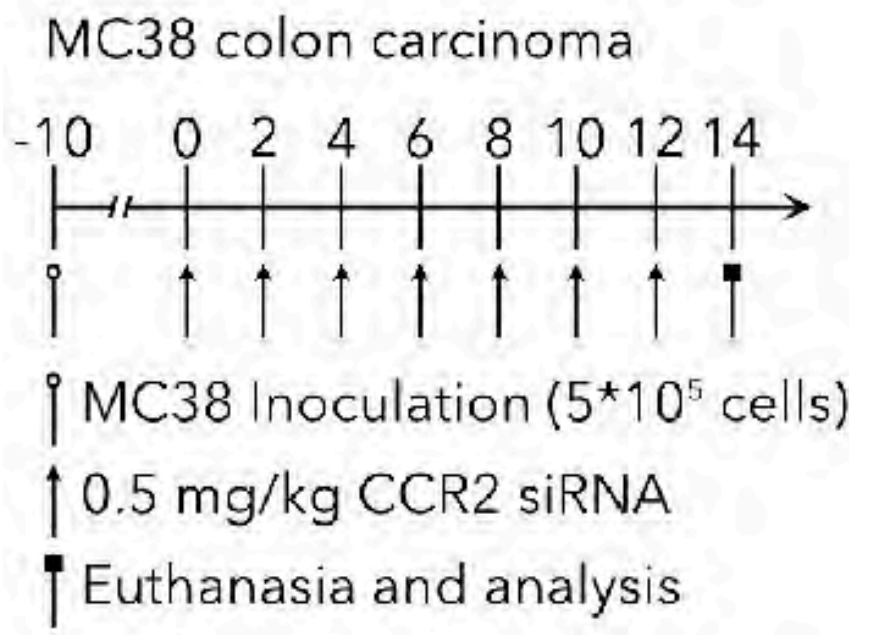
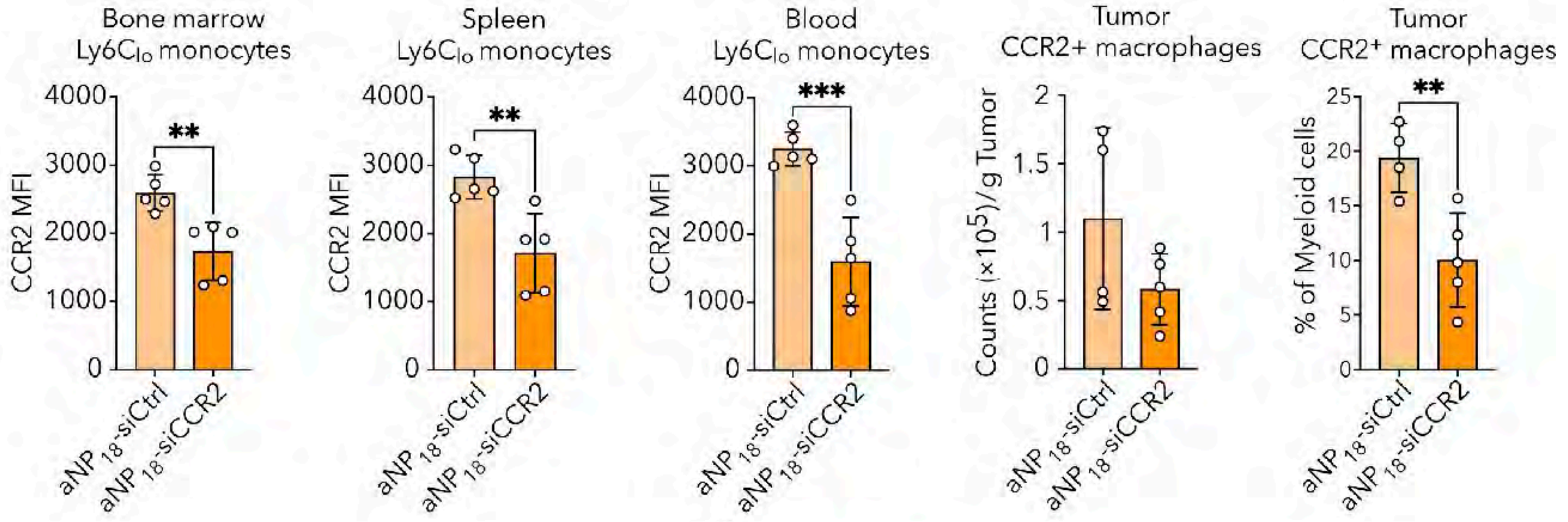
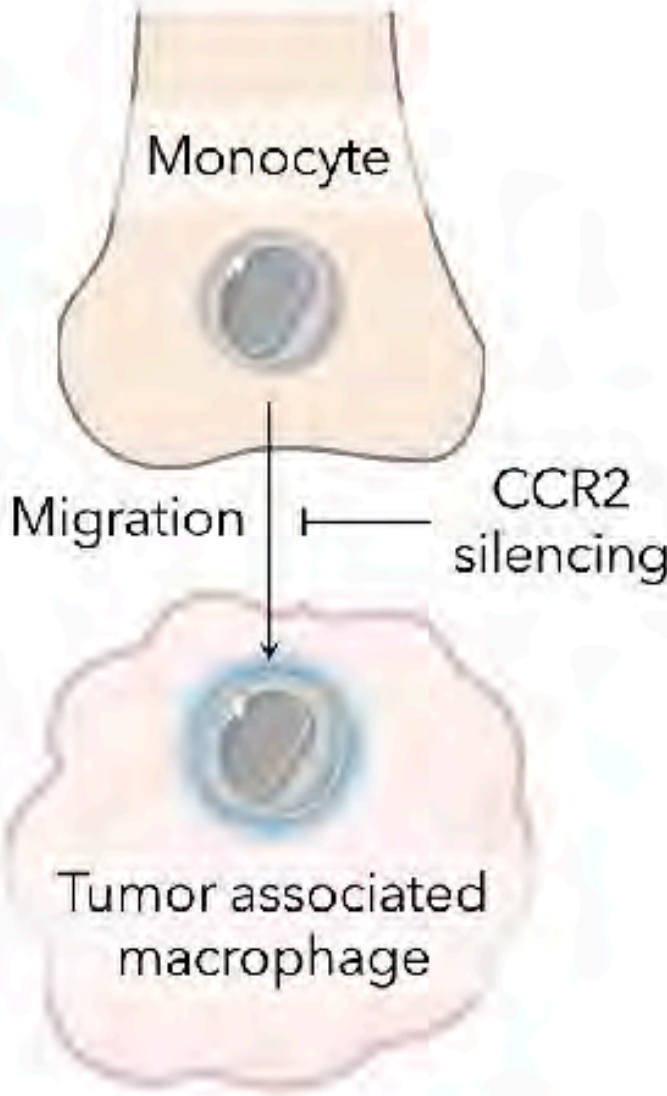


Inhibiting immunosuppressive monocyte migration



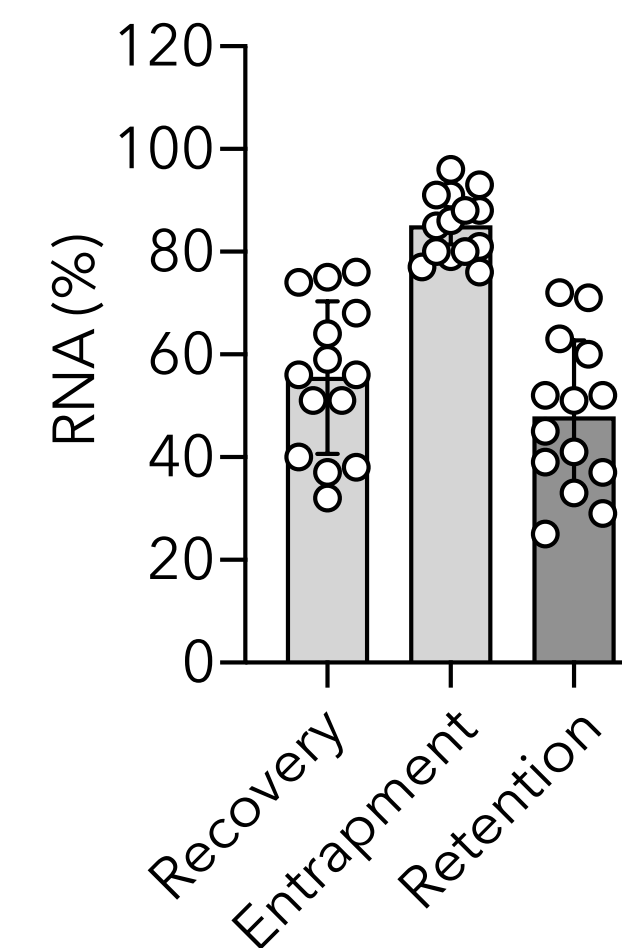
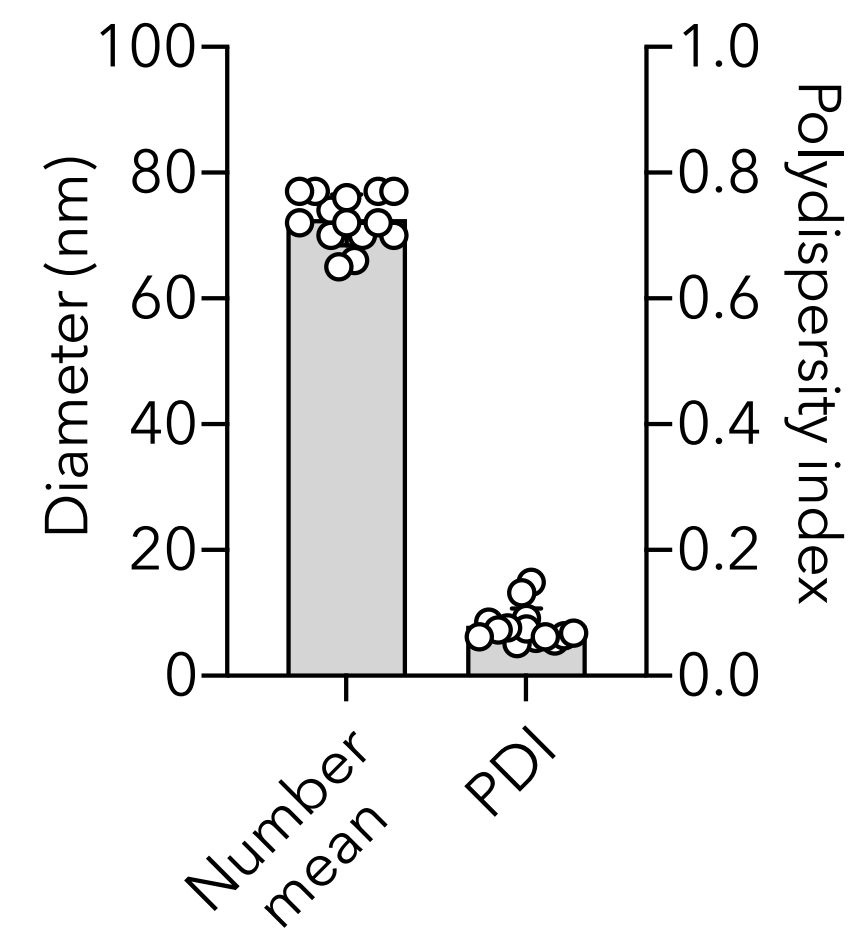
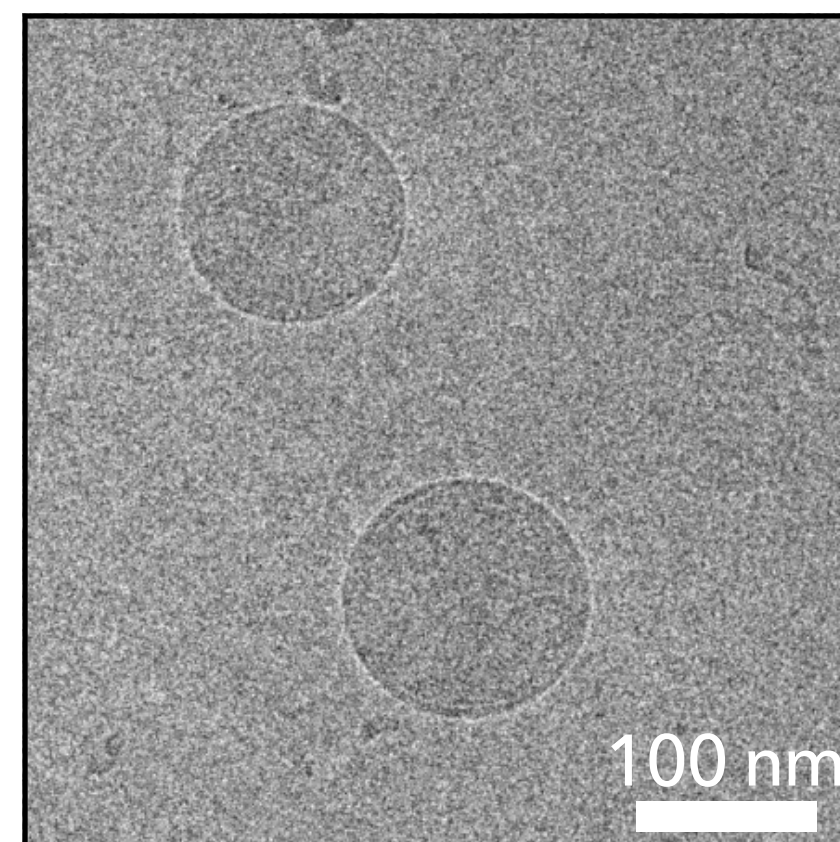
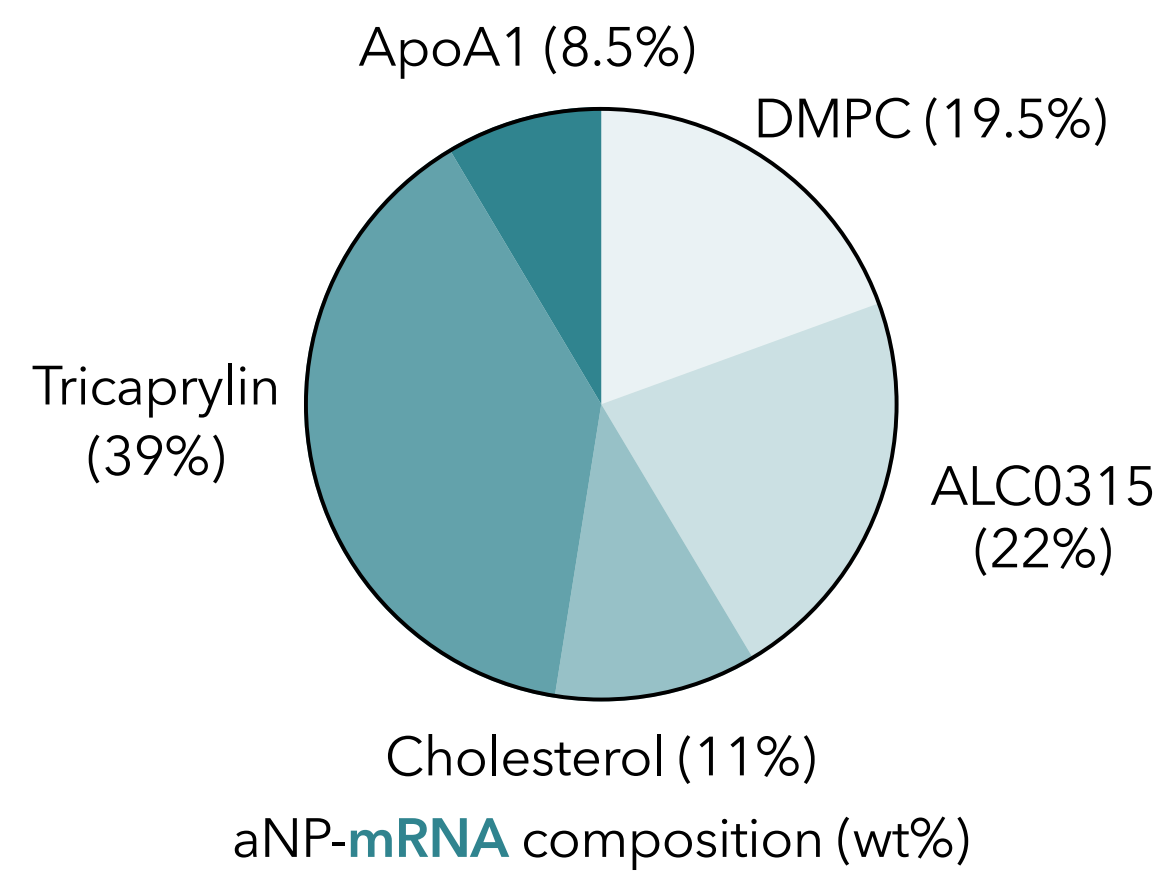
Data represented as mean ± SD, each data point represents one animal. Student t-test (**: $p < 0.01$, ***: $p < 0.001$). Hofstraat, Anbergen, Zwolsman *et al.*, Nat Nanotechnol, 2025

Inhibiting immunosuppressive monocyte migration

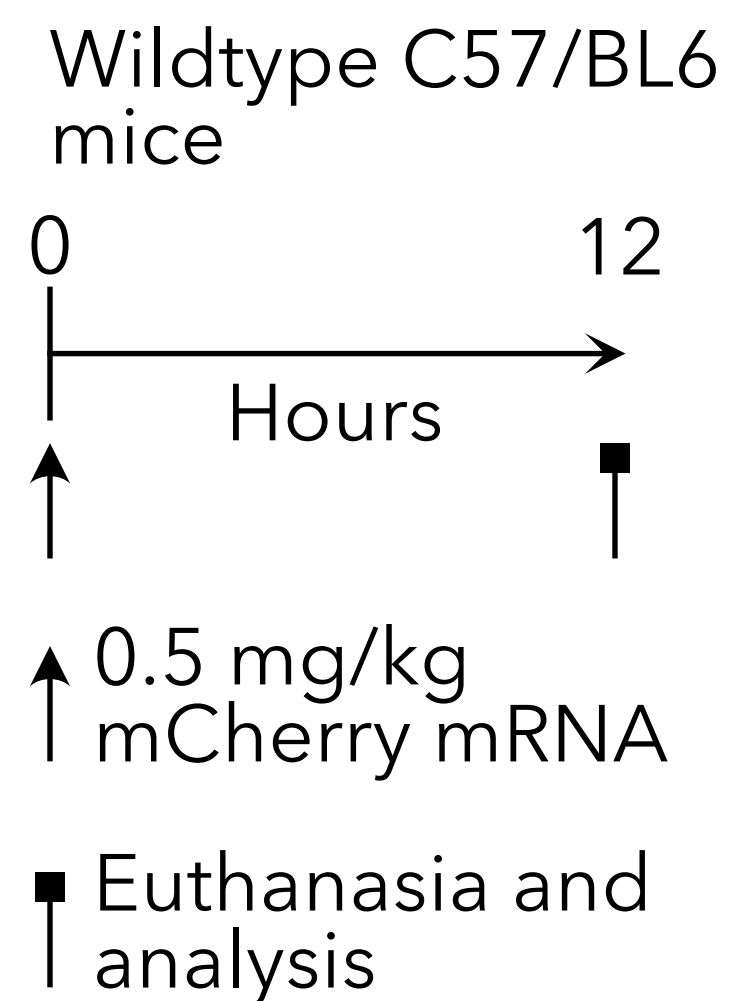
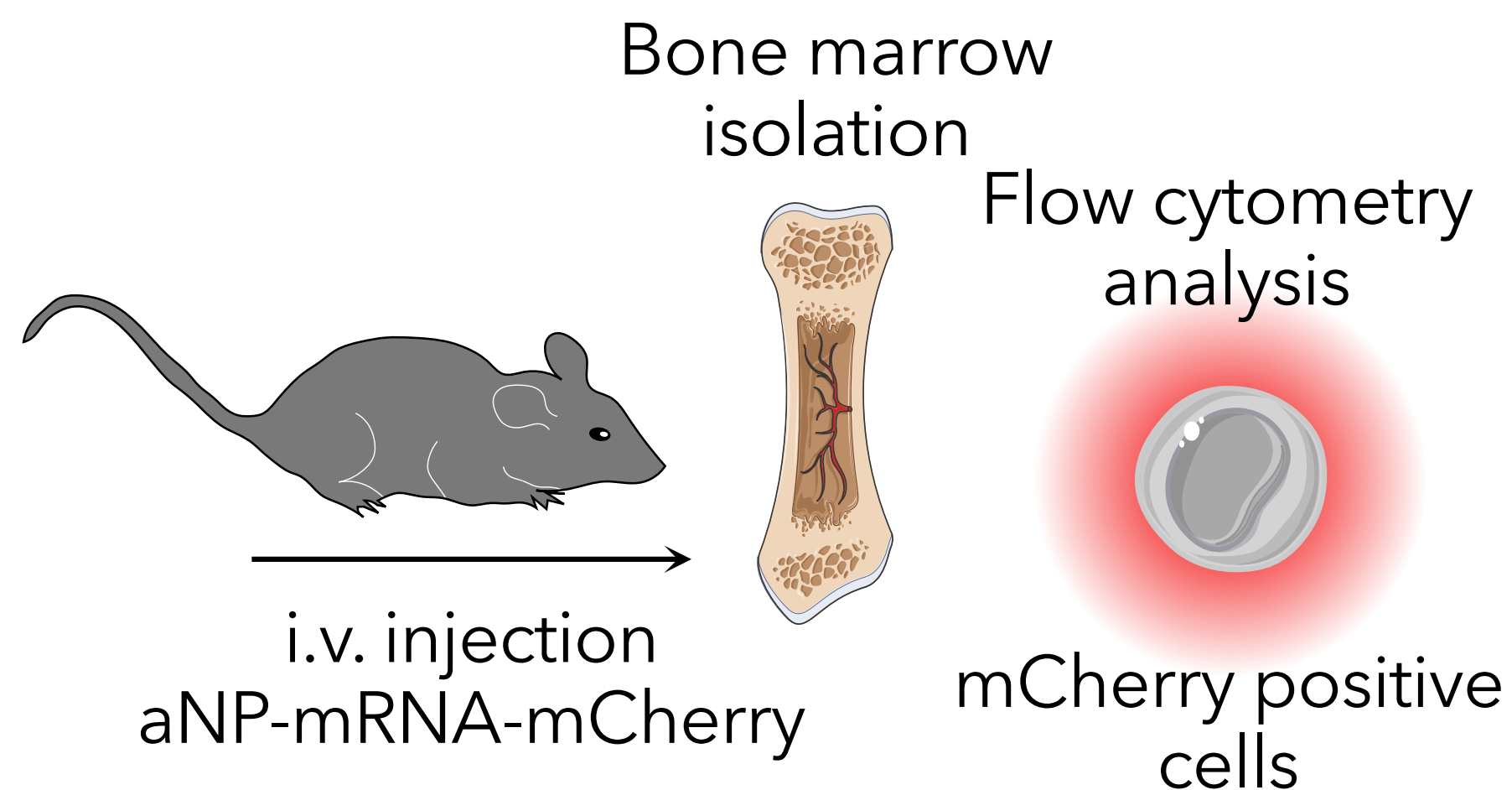
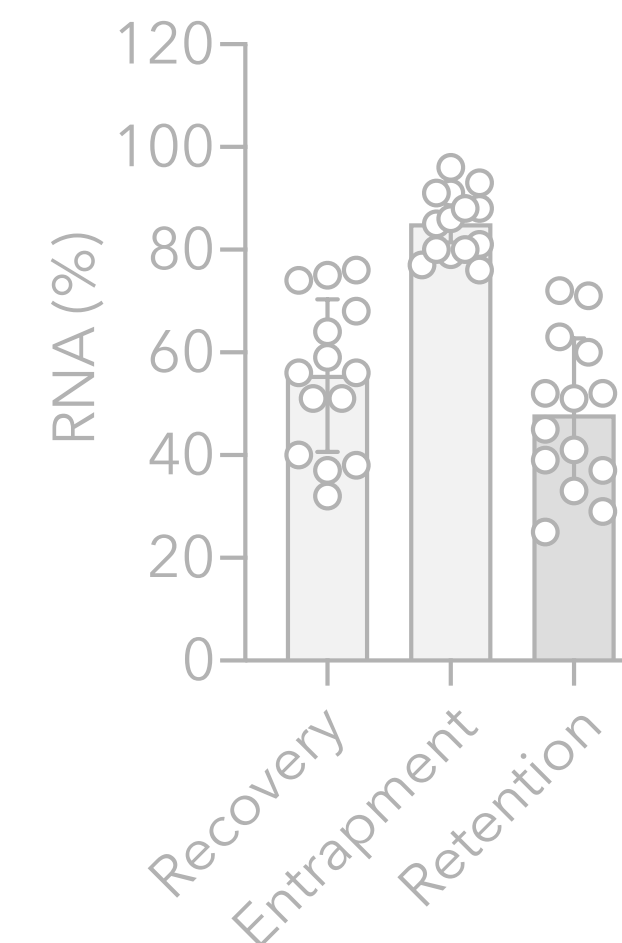
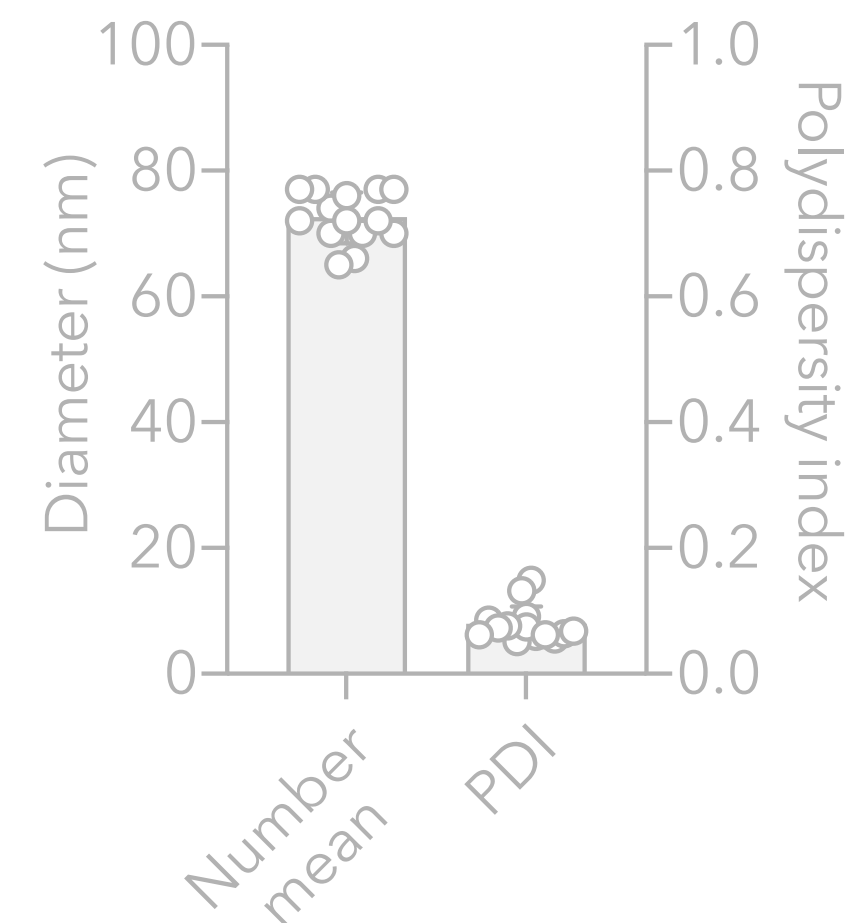
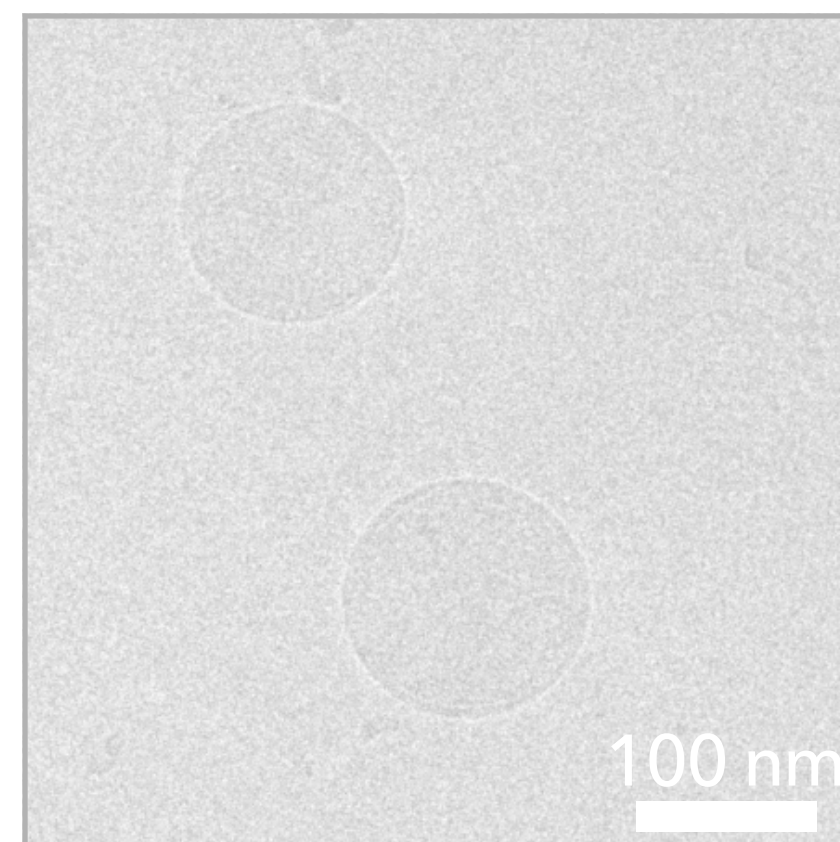
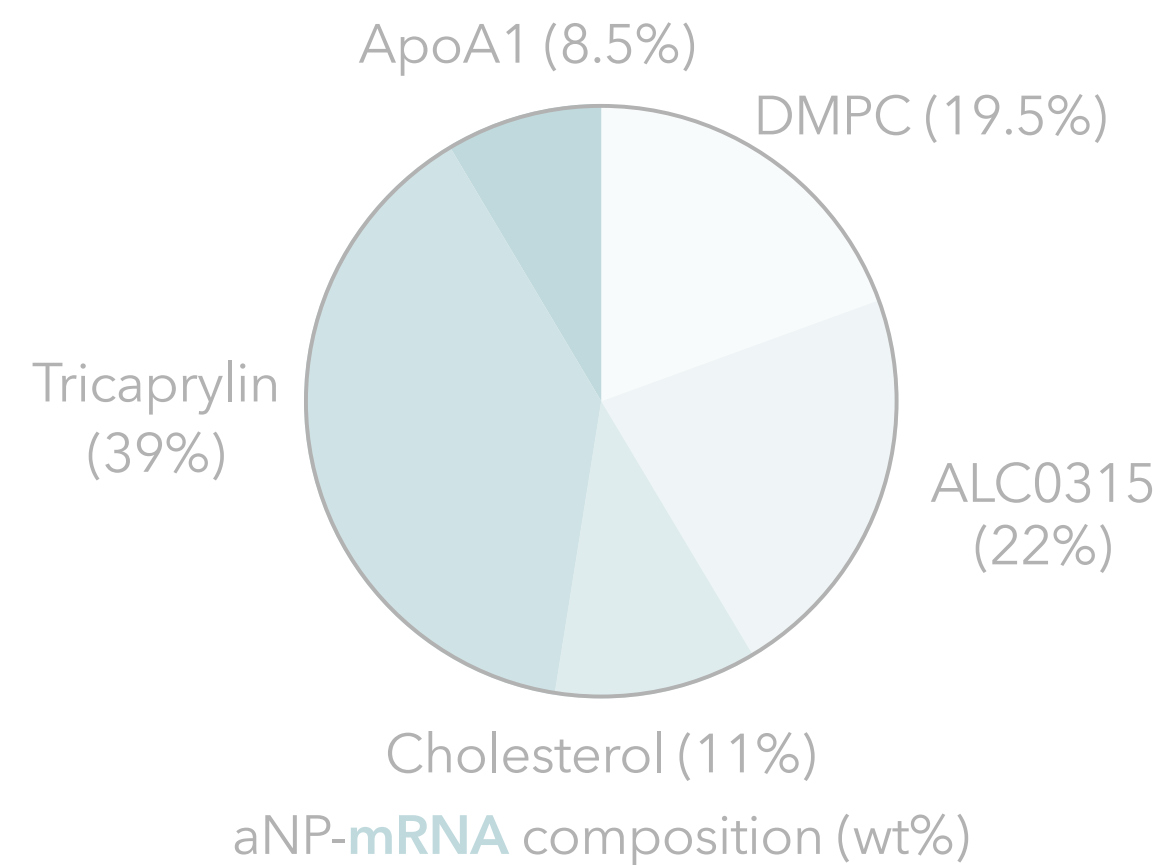


Data represented as mean ± SD, each data point represents one animal. Student t-test (**: p<0.01, ***: p<0.001). Hofstraat, Anbergen, Zwolsman *et al.*, Nat Nanotechnol, 2025

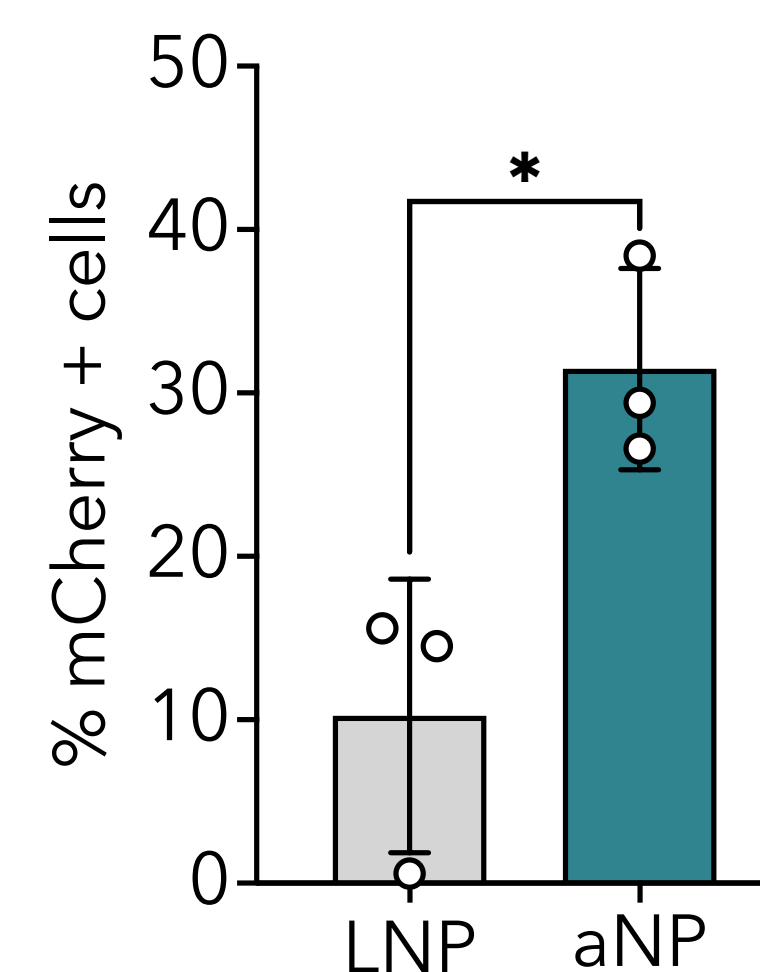
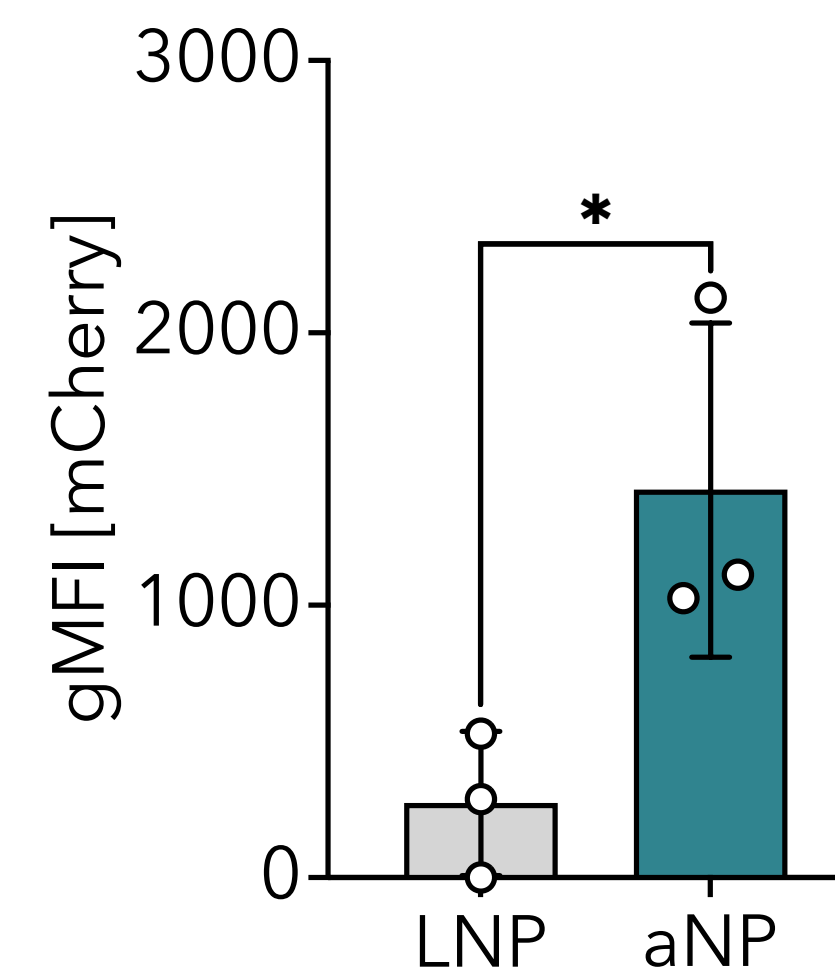
Reporter gene expression in myeloid progenitor cells



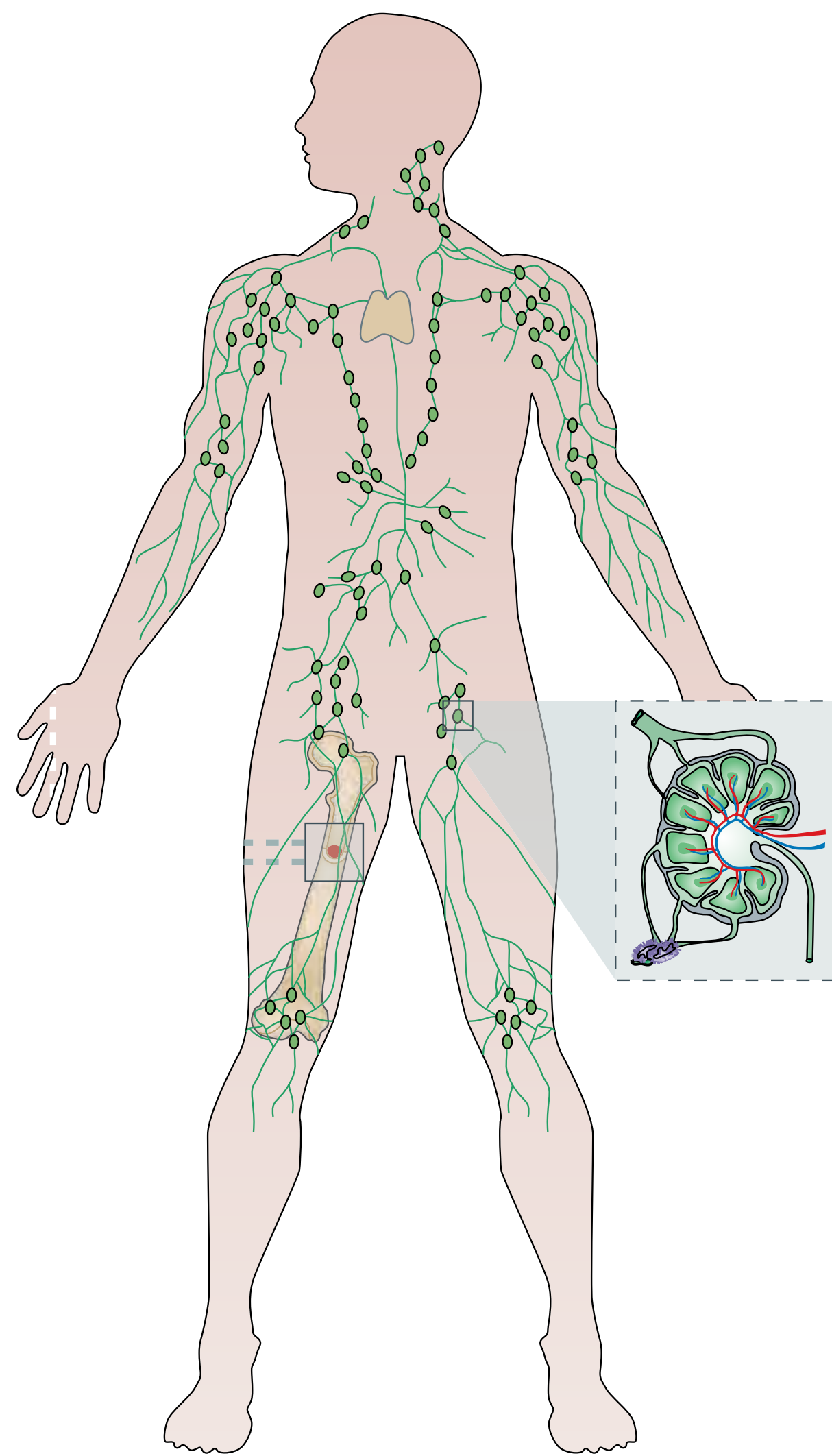
Reporter gene expression in myeloid progenitor cells



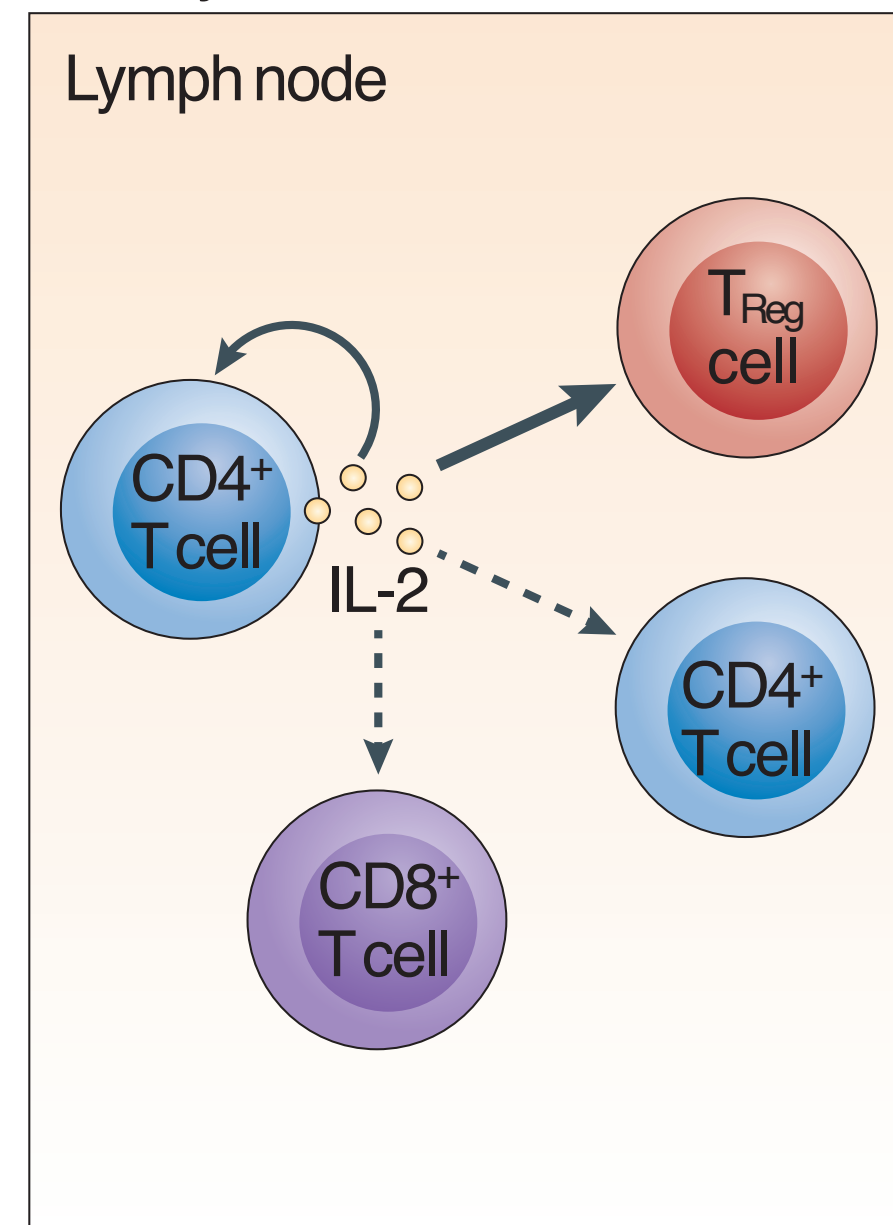
Myeloid progenitors, MyPs ($Lin^-cKit^+Sca1^-$)



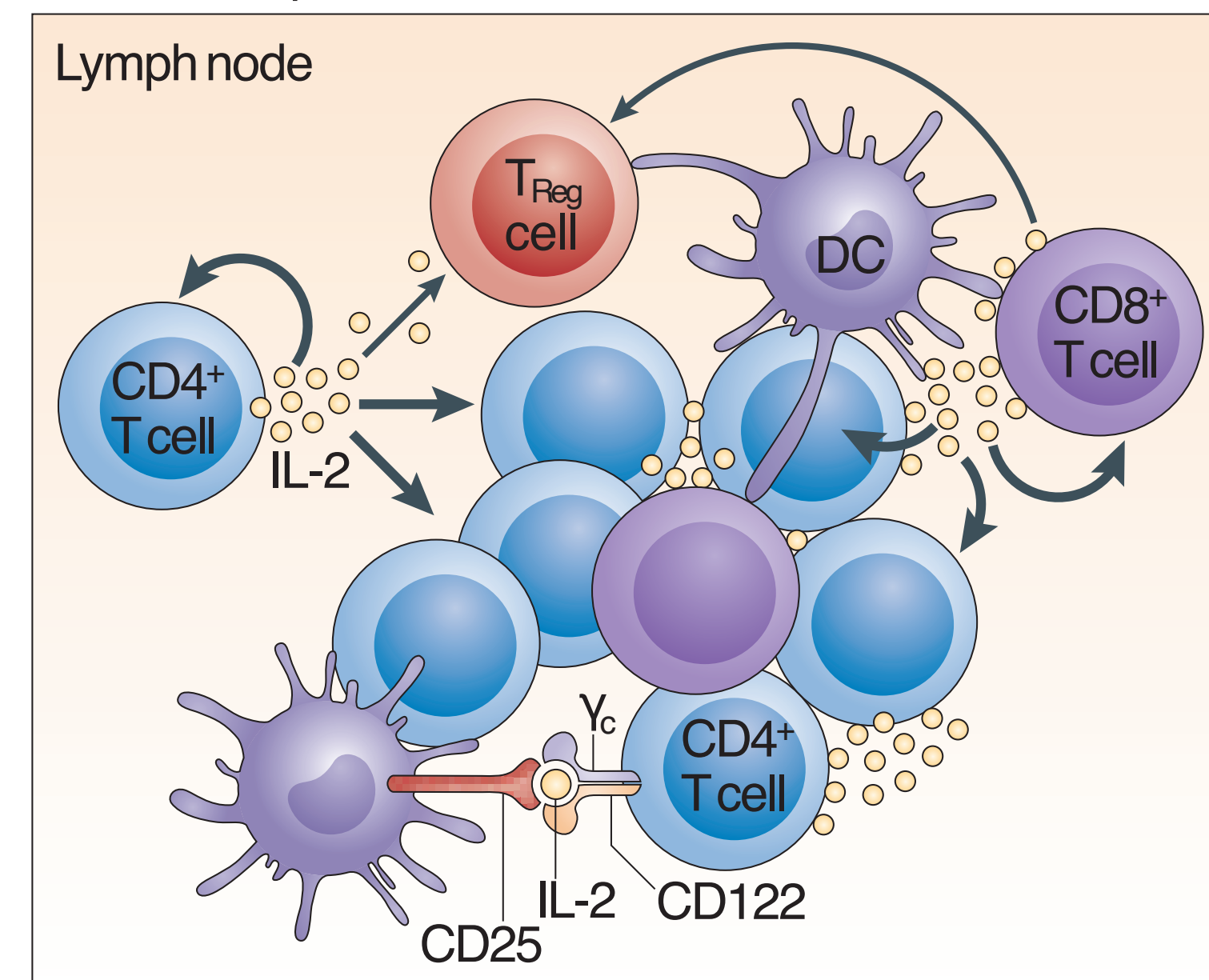
Delivering IL-2 mRNA to secondary lymphoid organs



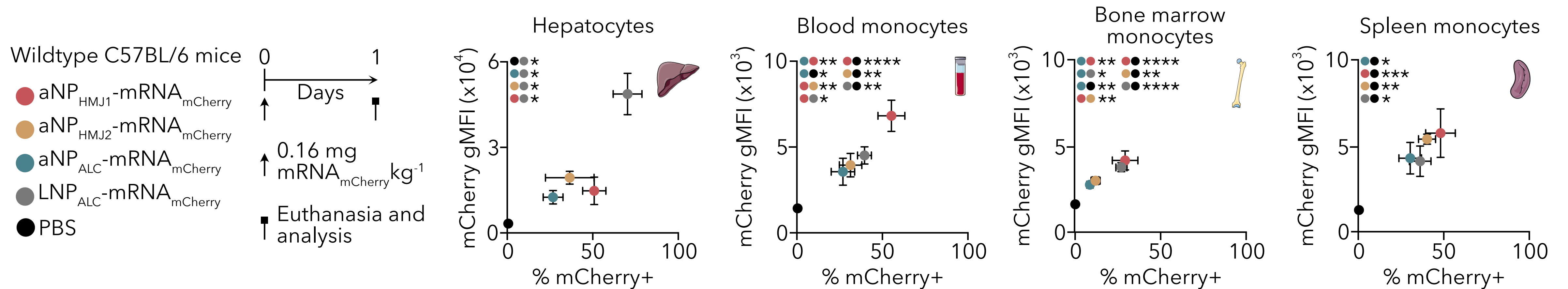
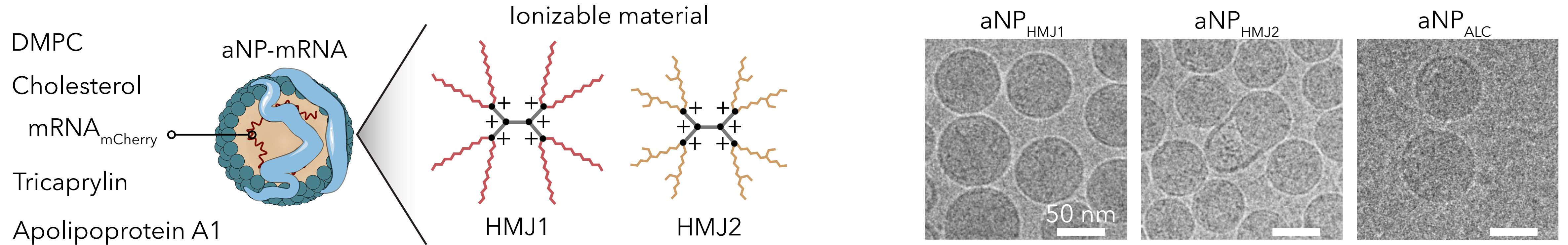
Steady state



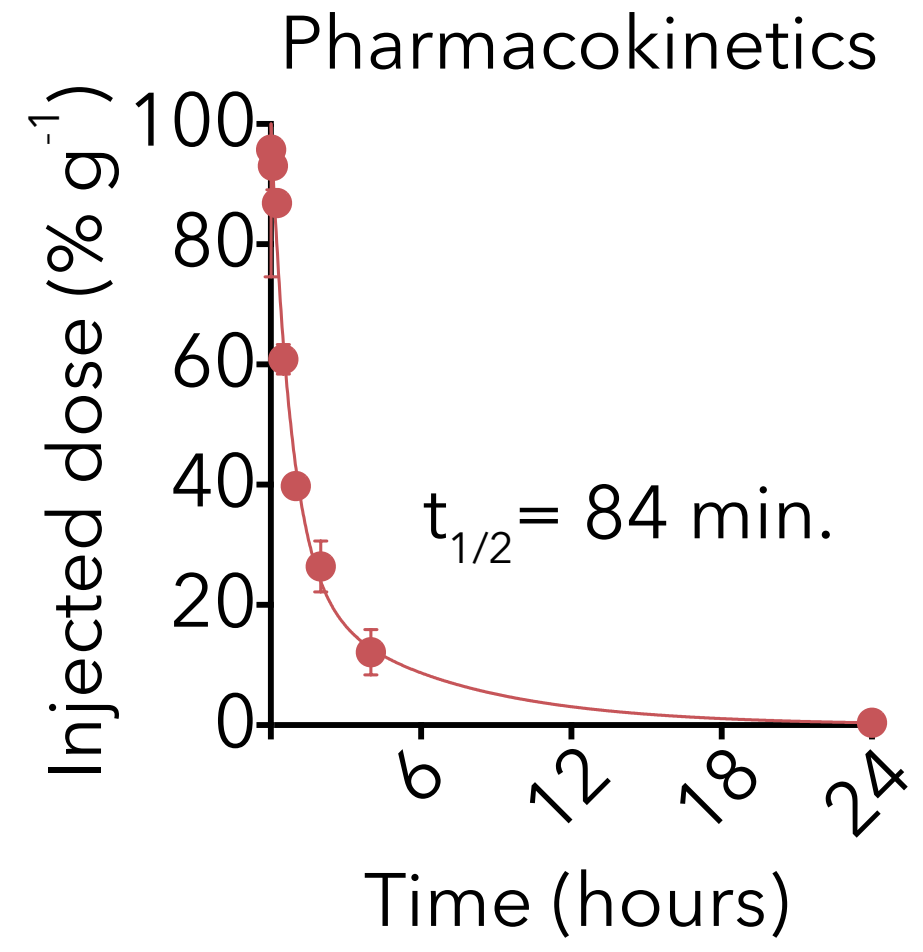
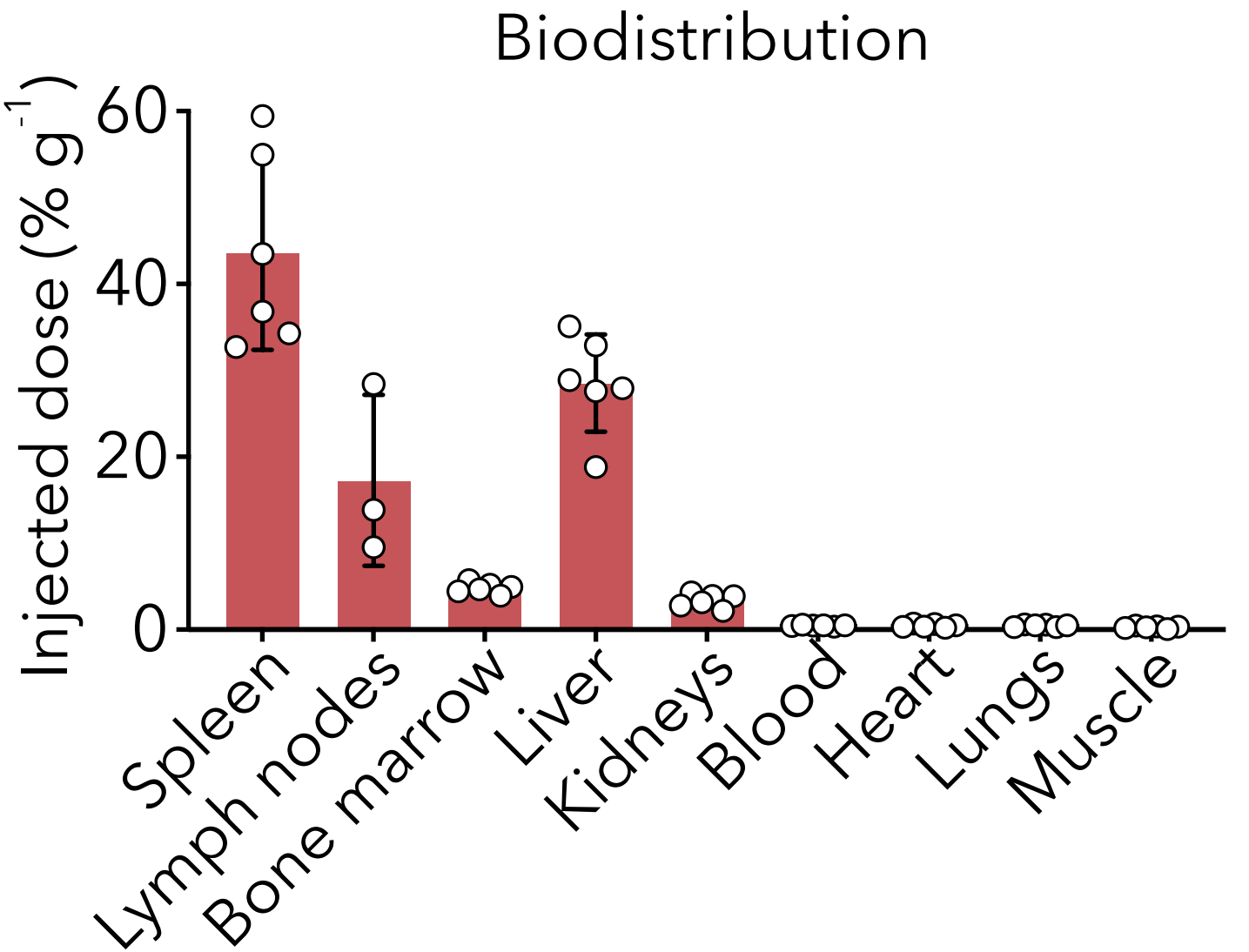
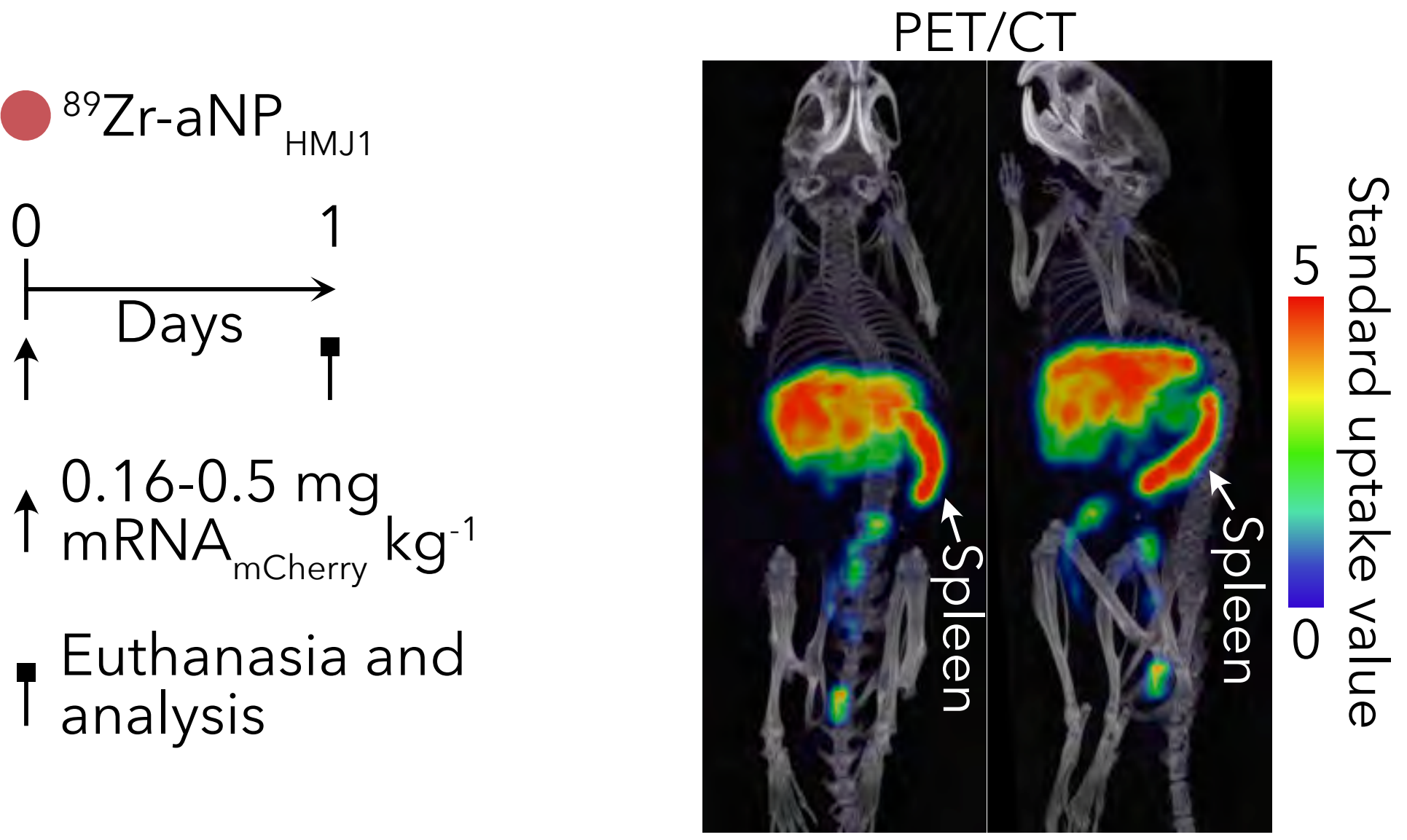
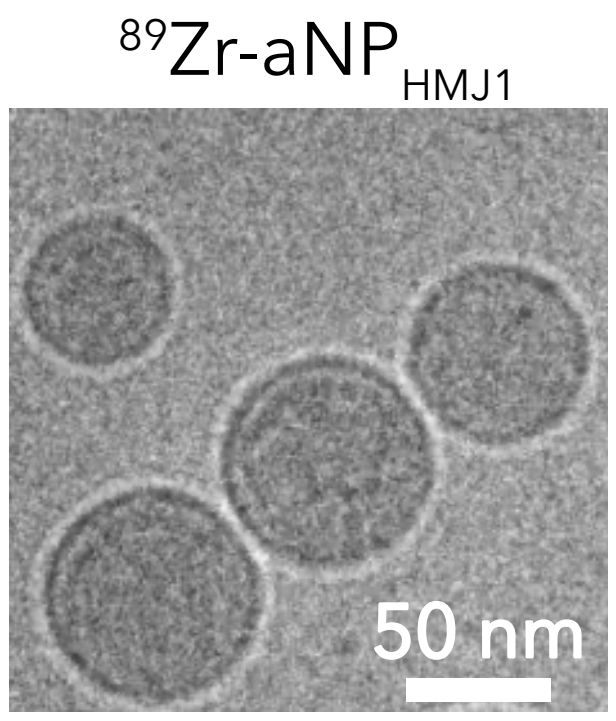
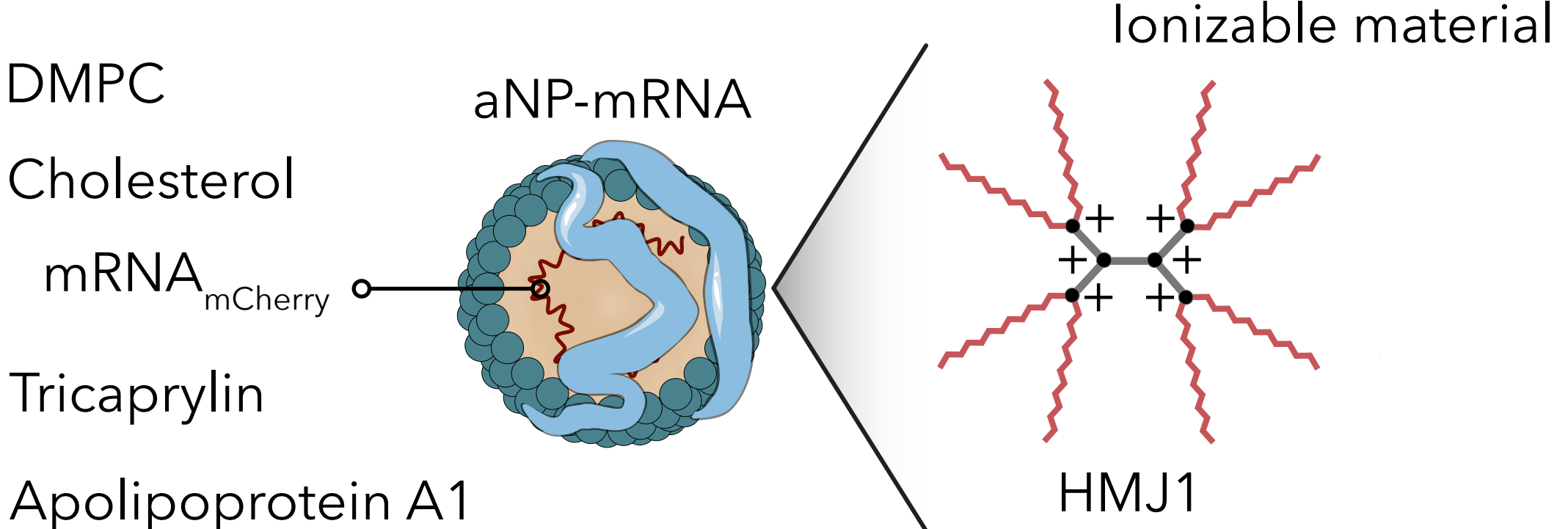
Immune response



Developing aNP with tropism for lymphoid organs

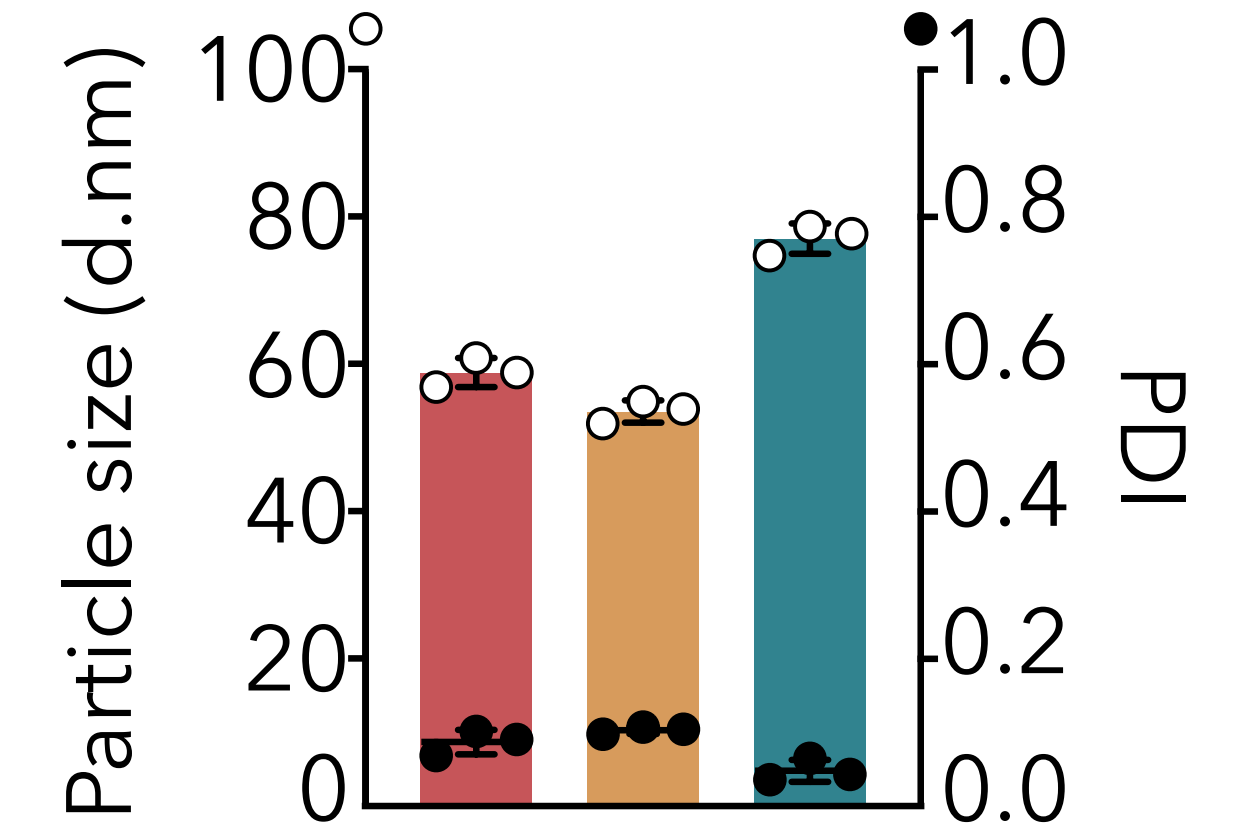
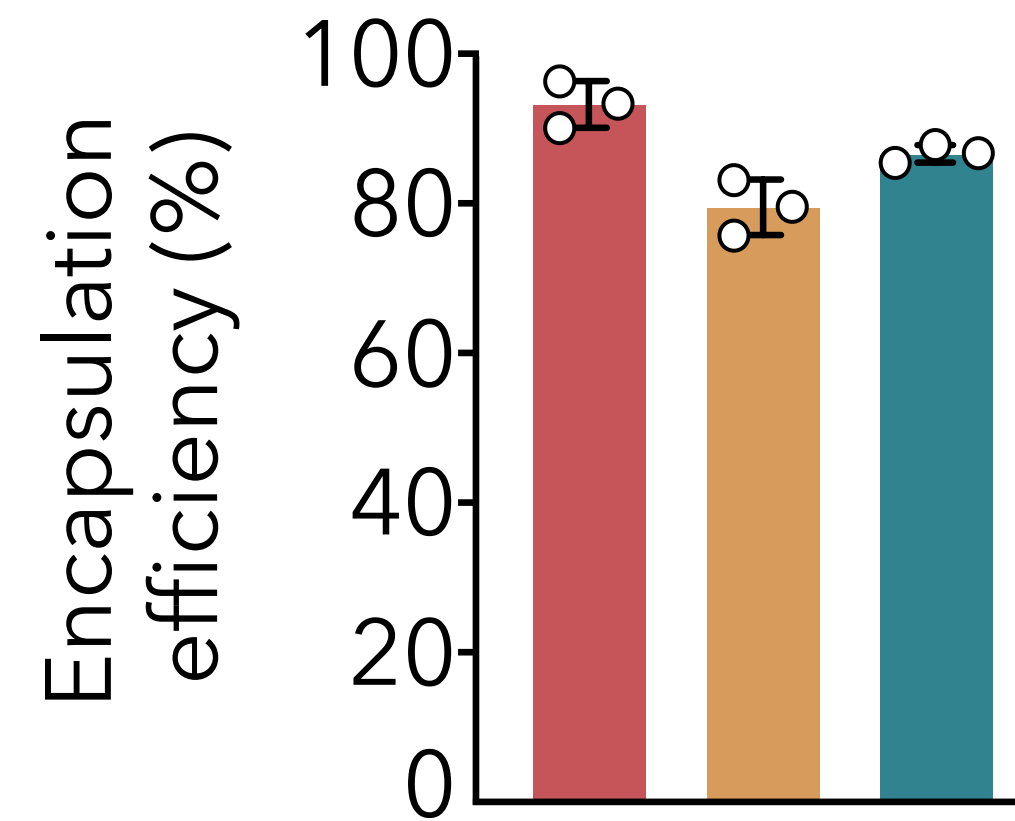


Quantitative biodistribution by *in vivo* PET imaging

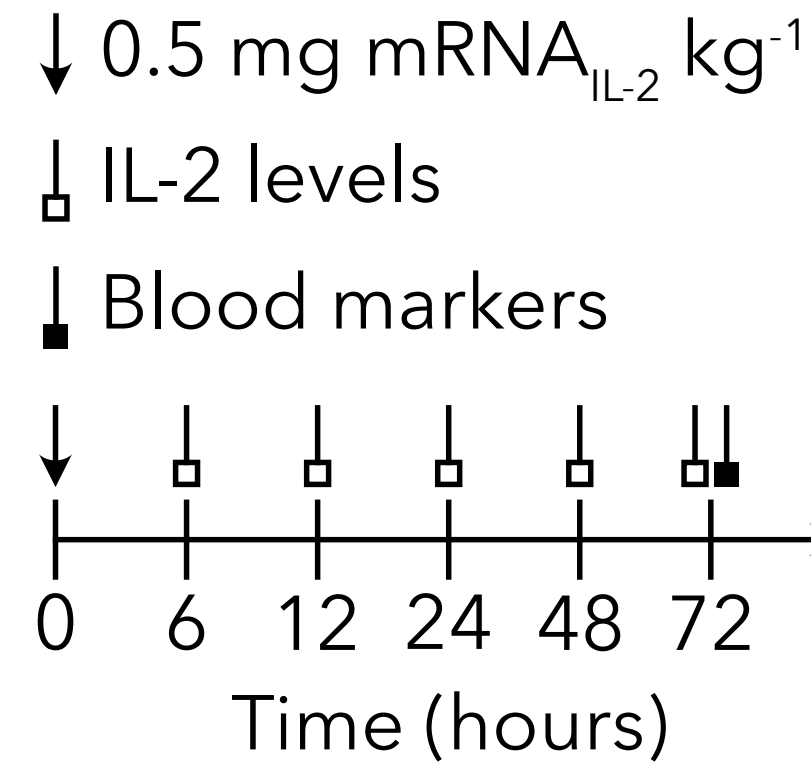


In vivo IL-2 production using aNP-mRNA

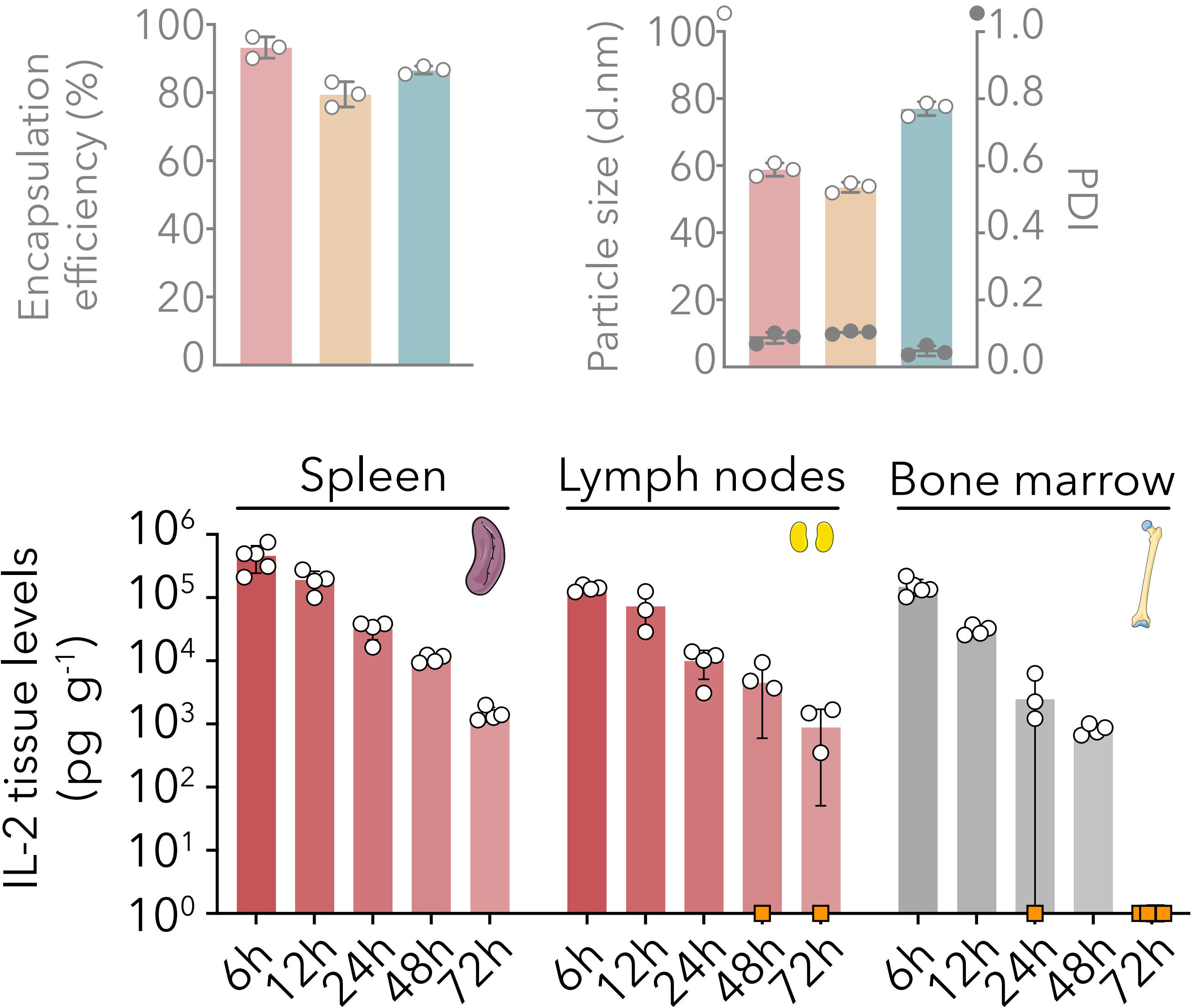
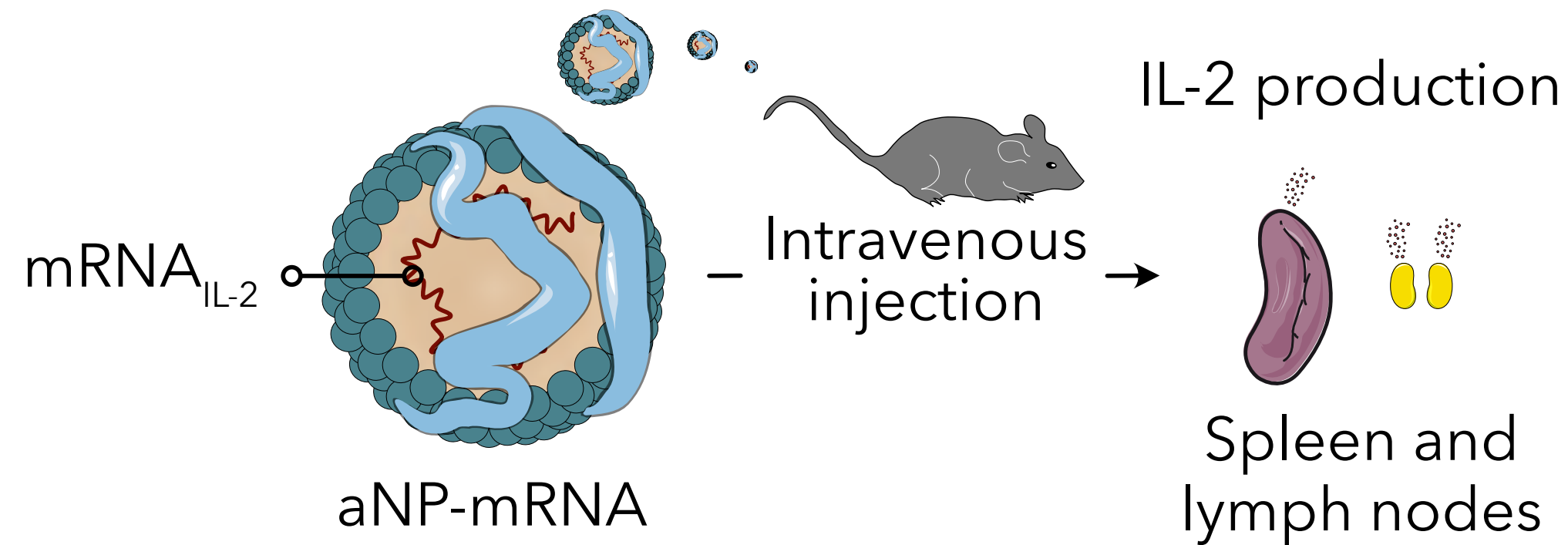
- aNP_{HMJ1}-mRNA_{IL-2}
- aNP_{HMJ2}-mRNA_{IL-2}
- aNP_{ALC}-mRNA_{IL-2}



In vivo IL-2 production using aNP-mRNA

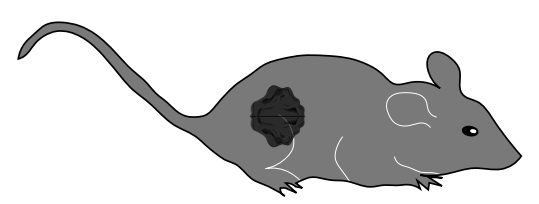
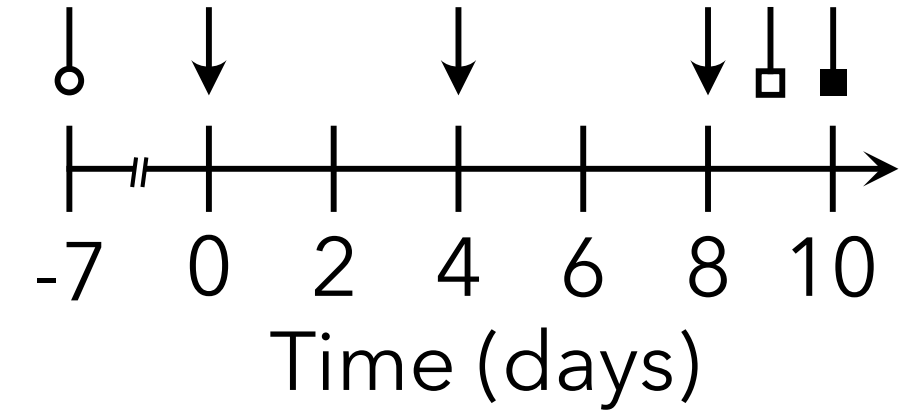


● aNP_{HMJ1}-mRNA_{IL-2}

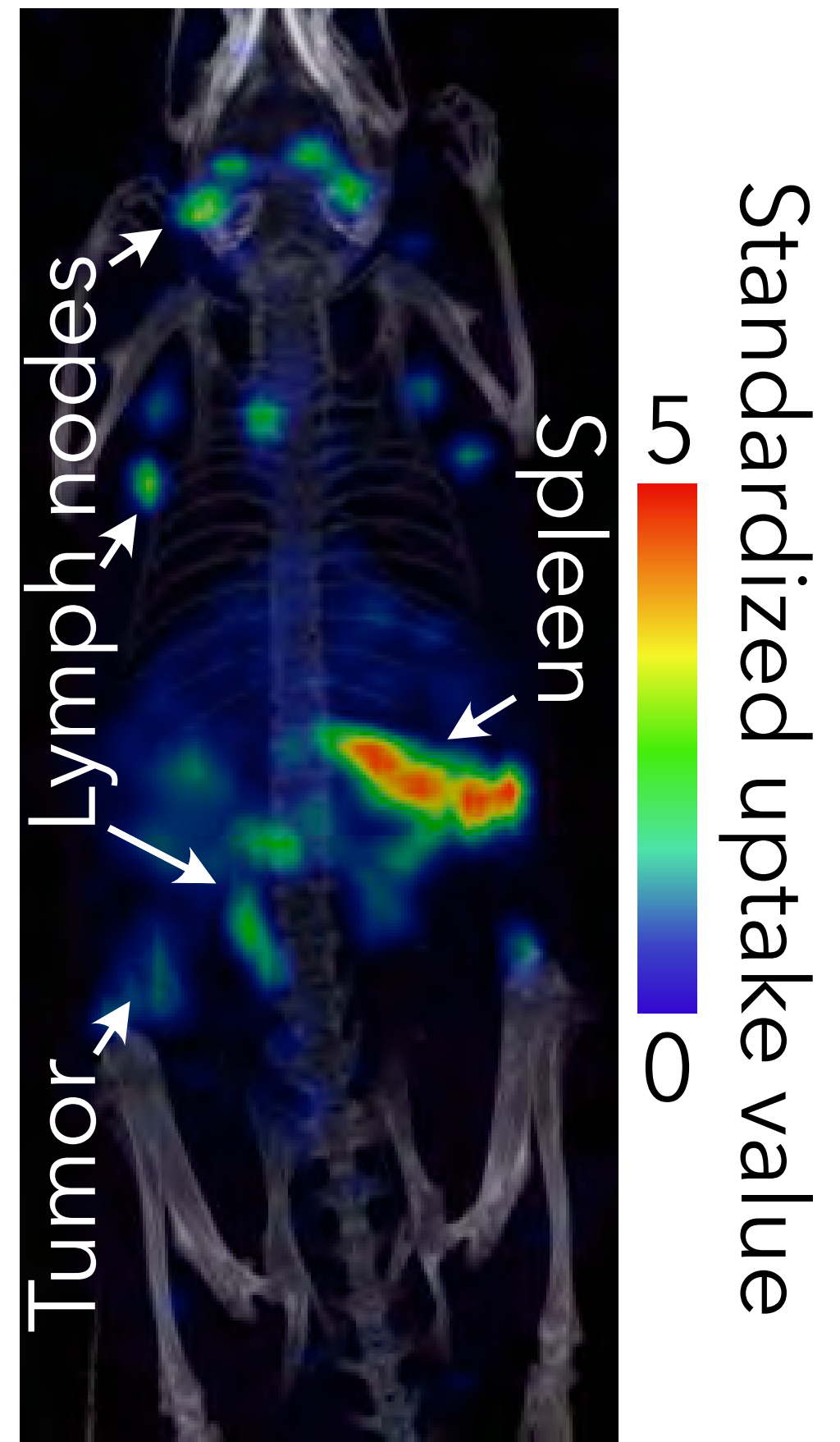


Imaging CD8 expansion in lymph nodes and tumor

↓ B16F10 inoculation
↓ aNP-mRNA injection
↓ ⁸⁹Zr-CD8-nanobody injection
↓ Euthanasia and CD8 T cell analysis

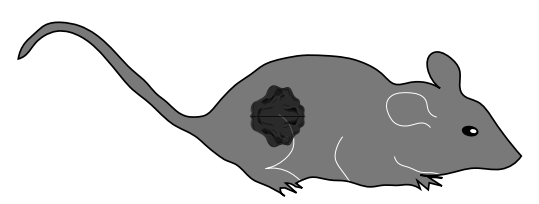
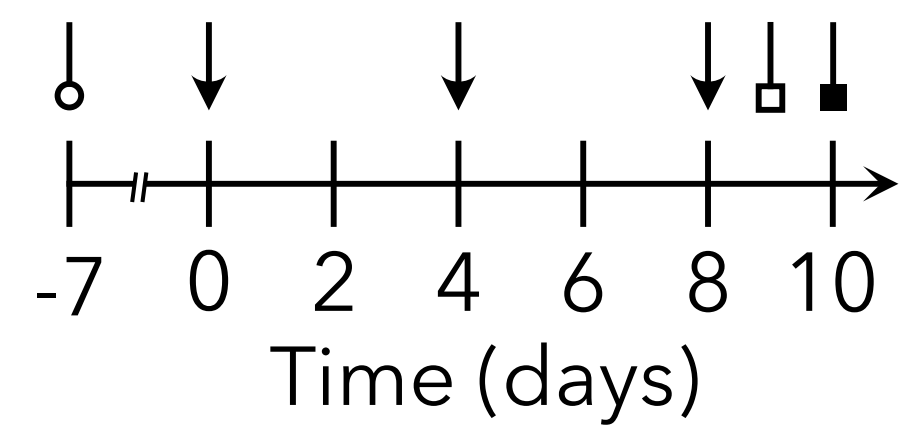


- aNP_{HMJ1}-mRNA_{IL-2}
- 1x0.5 mg kg⁻¹
 - 3x0.125 mg kg⁻¹
 - PBS

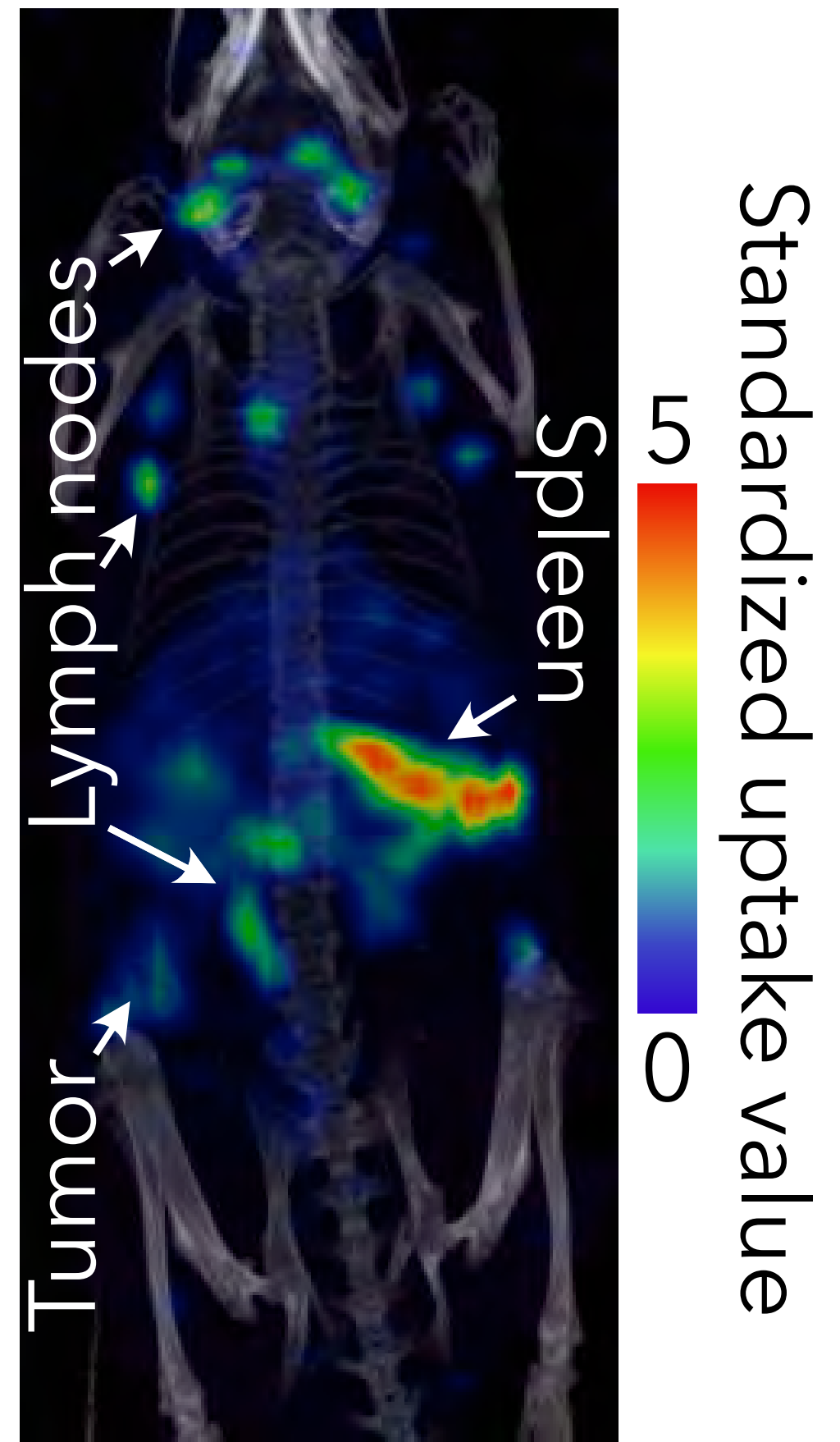


Imaging CD8 expansion in lymph nodes and tumor

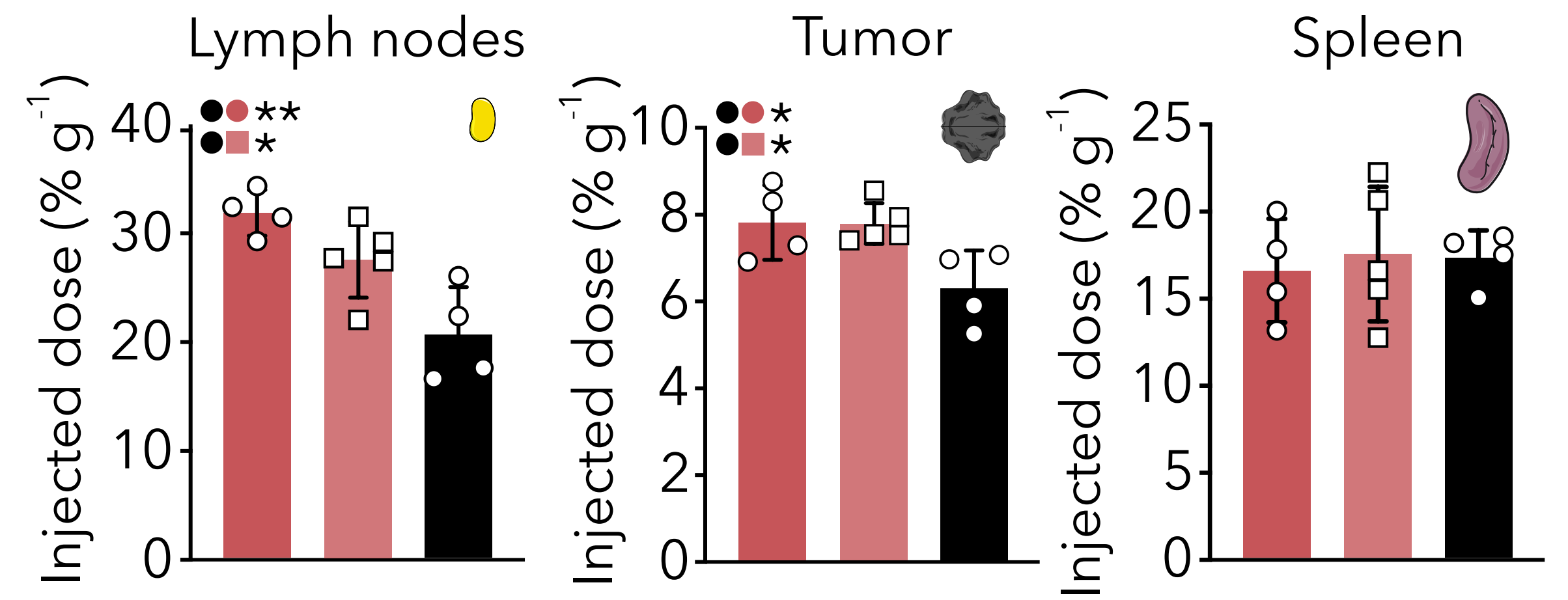
↓ B16F10 inoculation
 ↓ aNP-mRNA injection
 ↓ ⁸⁹Zr-CD8-nanobody injection
 ↓ Euthanasia and CD8 T cell analysis



aNP_{HMJ1}-mRNA_{IL-2}
 ● 1x0.5 mg kg⁻¹
 ■ 3x0.125 mg kg⁻¹
 ● PBS

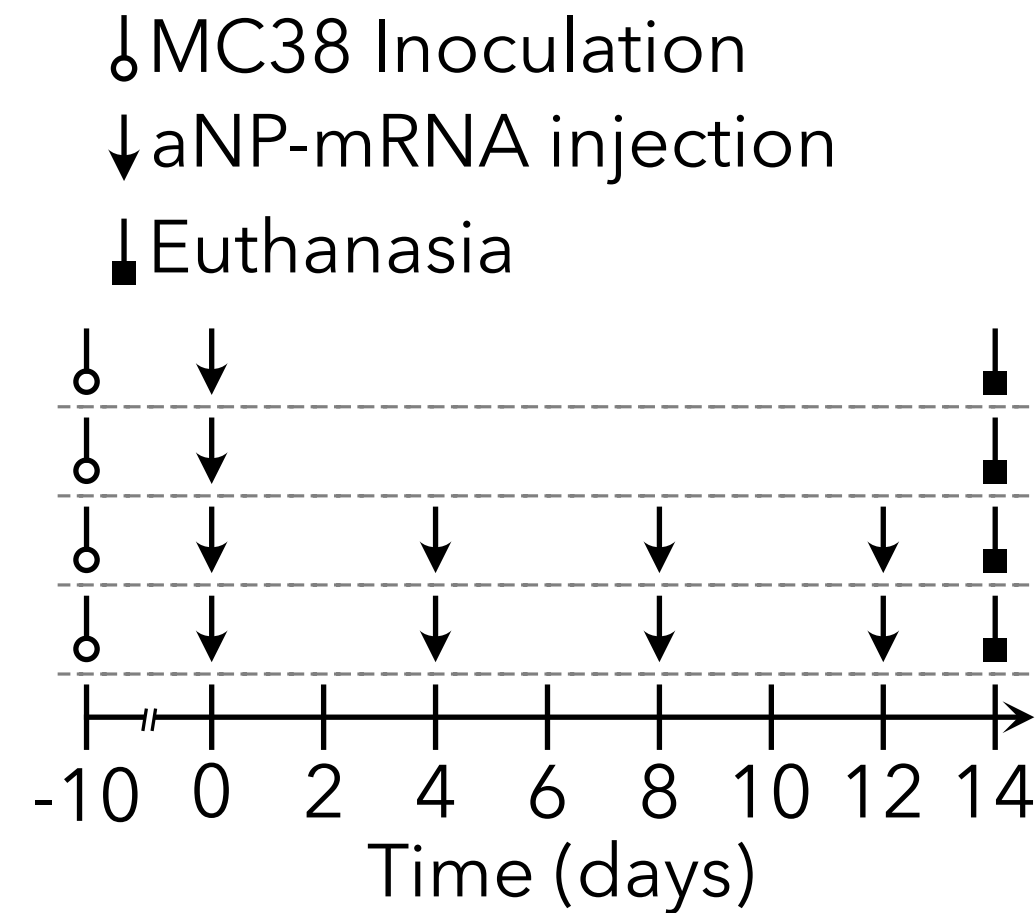


Day 10
γ-counting



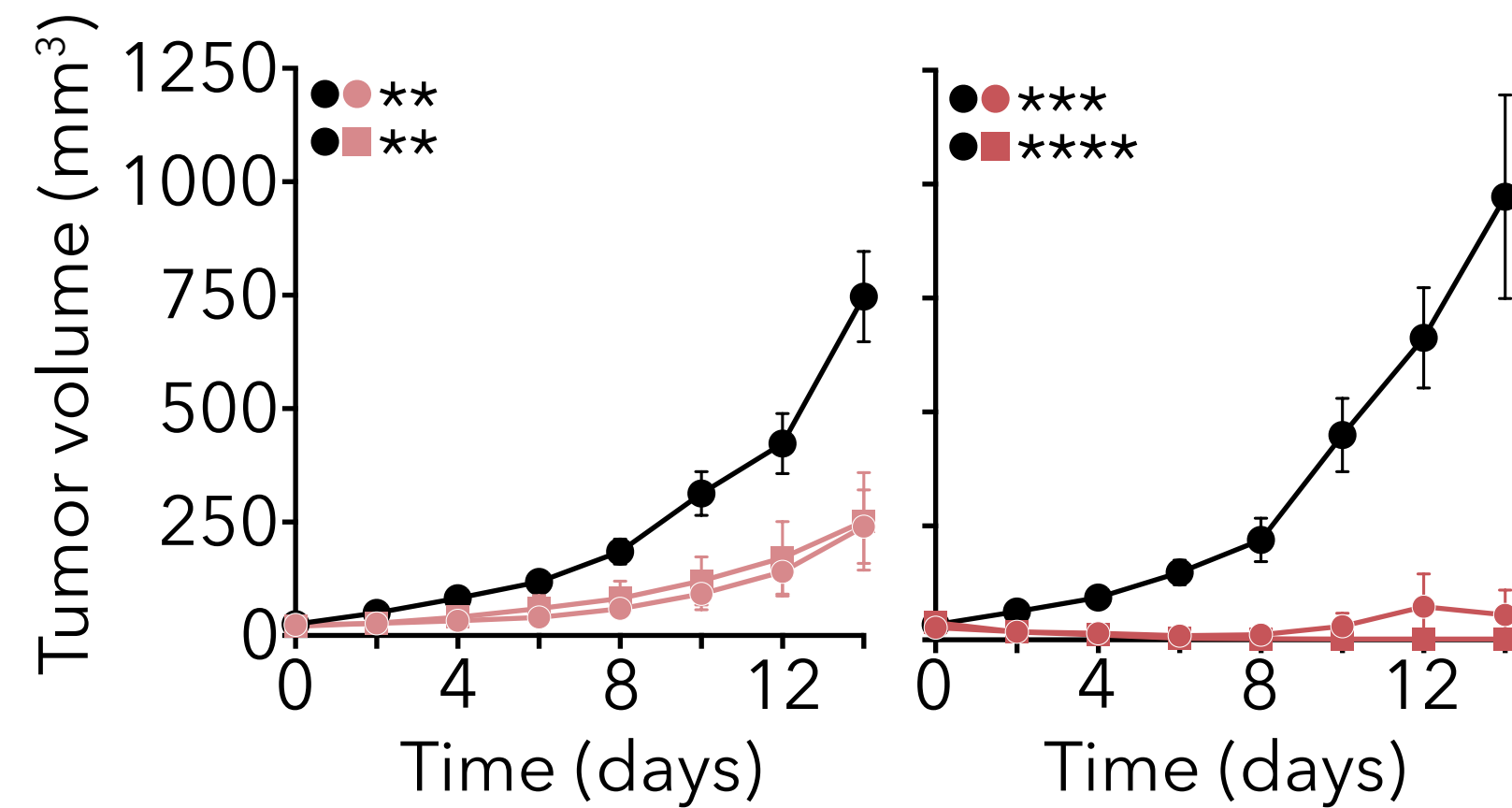
IL-2 immunotherapy using aNP-mRNA

MC38 colorectal cancer model



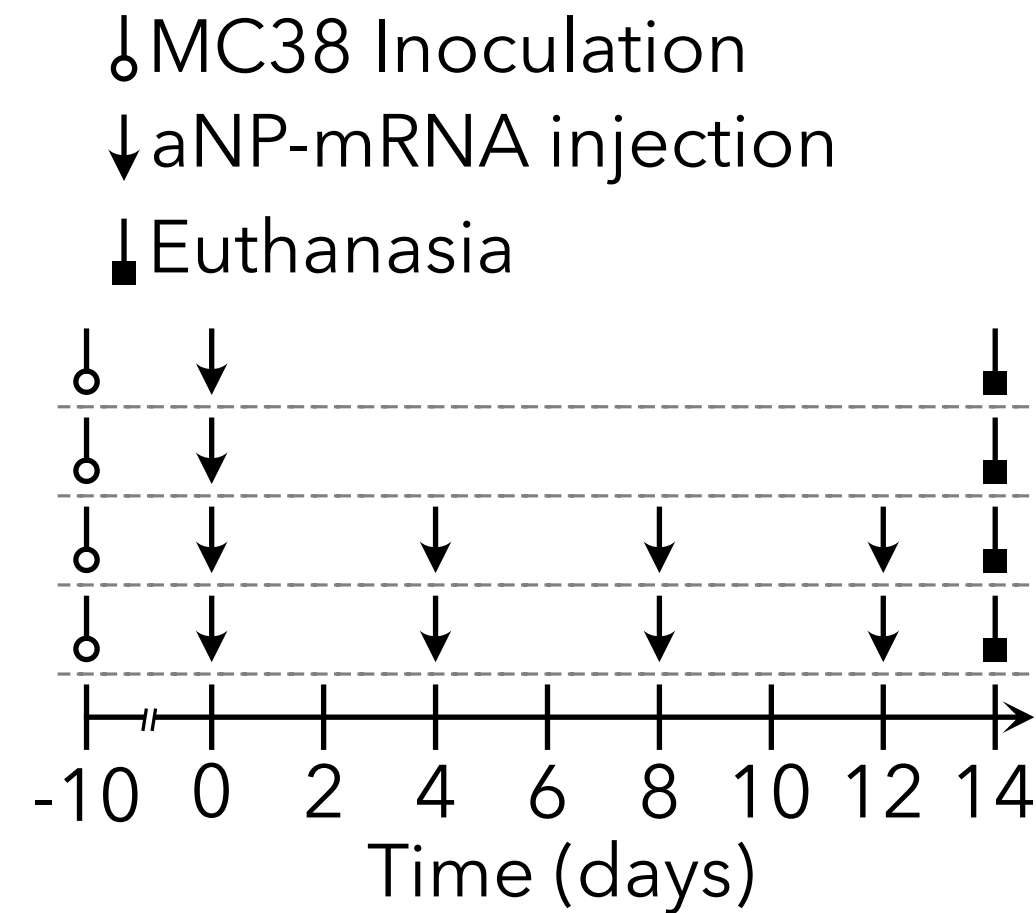
aNP_{HMJ1}-mRNA_{IL-2}

- 1x0.5 mg kg⁻¹
- 4x0.125 mg kg⁻¹
- 1x0.16 mg kg⁻¹
- 4x0.04 mg kg⁻¹
- PBS



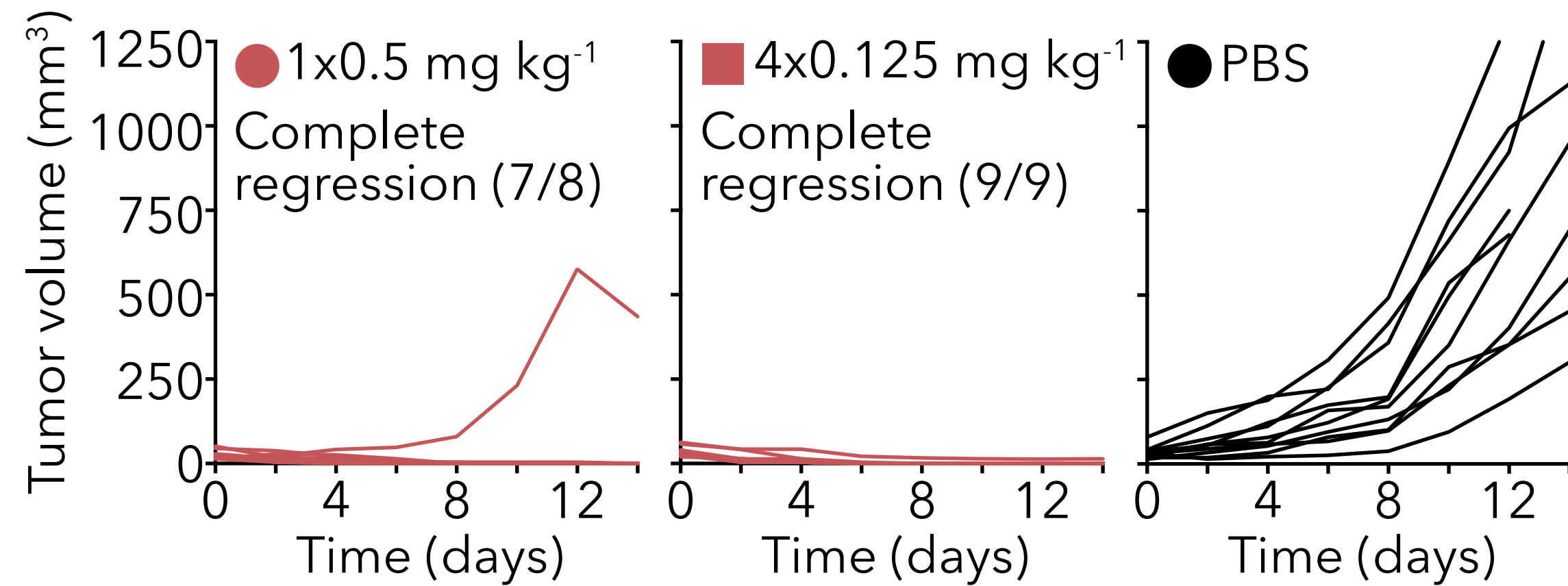
IL-2 immunotherapy using aNP-mRNA

MC38 colorectal cancer model



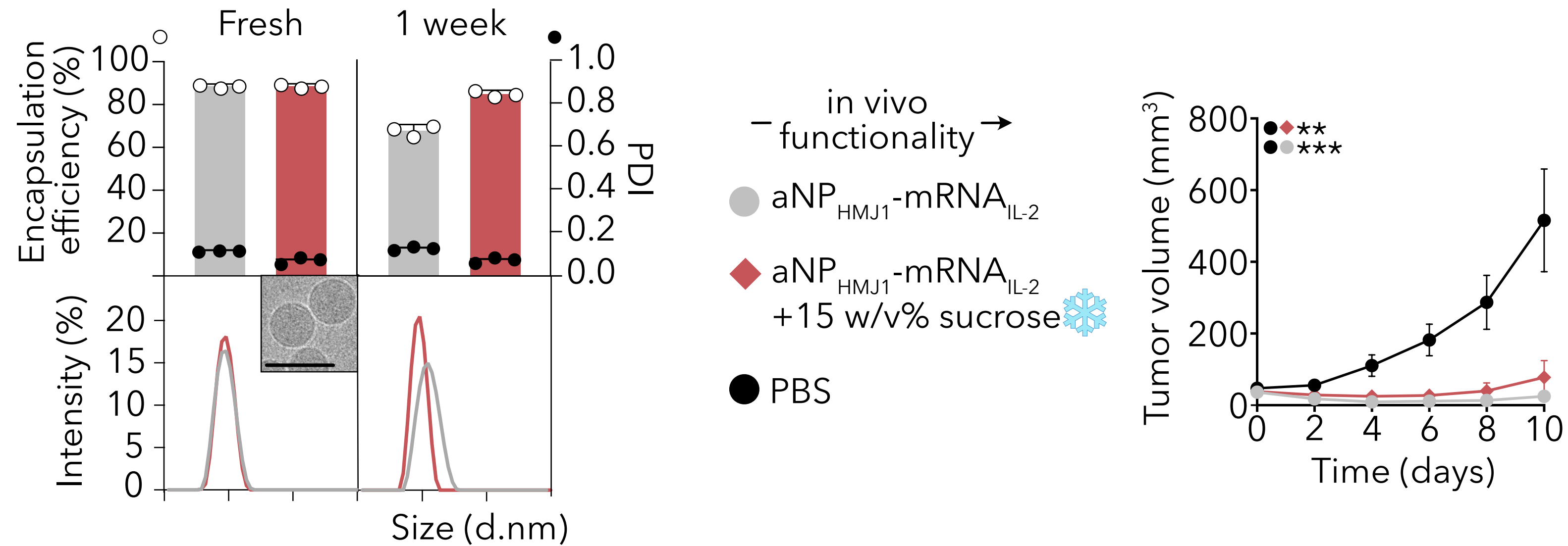
aNP_{HMJ1}-mRNA_{IL-2}

- 1x0.5 mg kg⁻¹
- 4x0.125 mg kg⁻¹
- 1x0.16 mg kg⁻¹
- 4x0.04 mg kg⁻¹
- PBS



IL-2 immunotherapy using aNP-mRNA

MC38 colorectal cancer model



IL-2 immunotherapy using aNP-mRNA

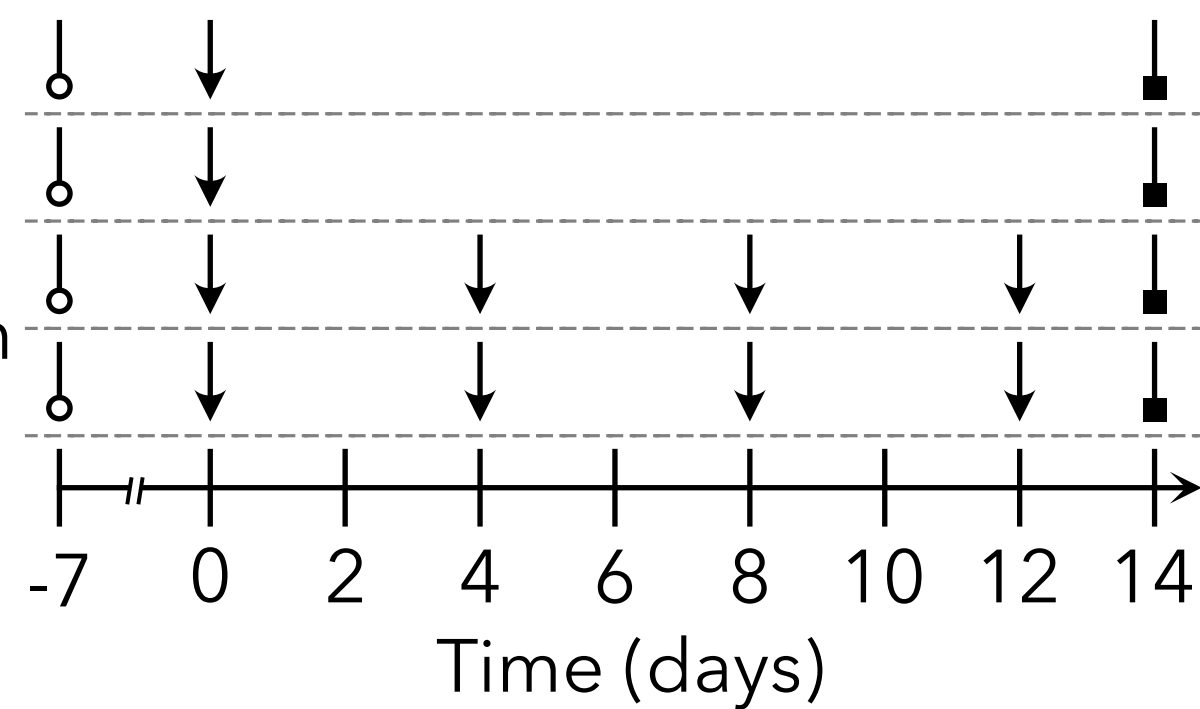
B16F10 melanoma cancer model



○ B16F10 inoculation (10⁵ cells)

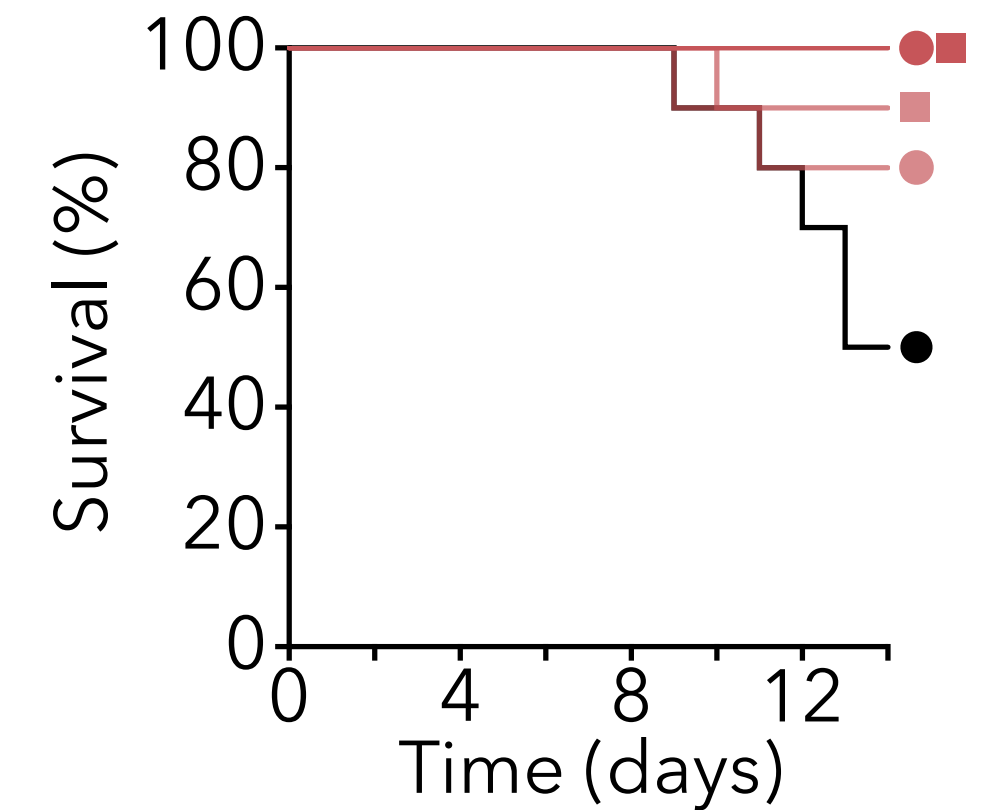
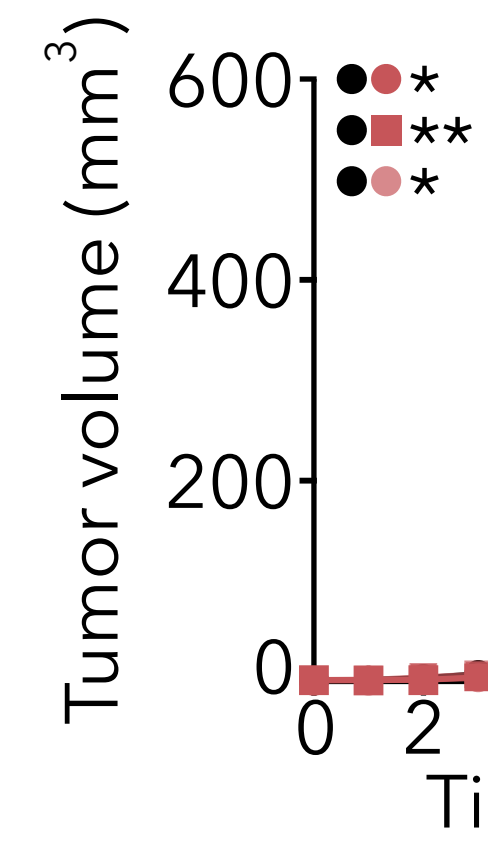
↓ aNP-mRNA injection

■ Euthanasia



aNP_{HMJ1}-mRNA_{IL-2}

- 1x0.5 mg kg⁻¹
- 4x0.125 mg kg⁻¹
- 1x0.16 mg kg⁻¹
- 4x0.04 mg kg⁻¹
- PBS



IFN- γ immunotherapy using aNP-mRNA

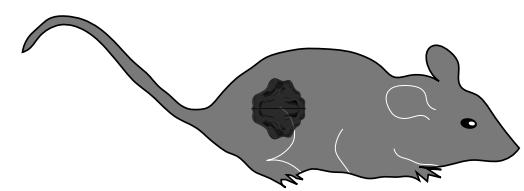
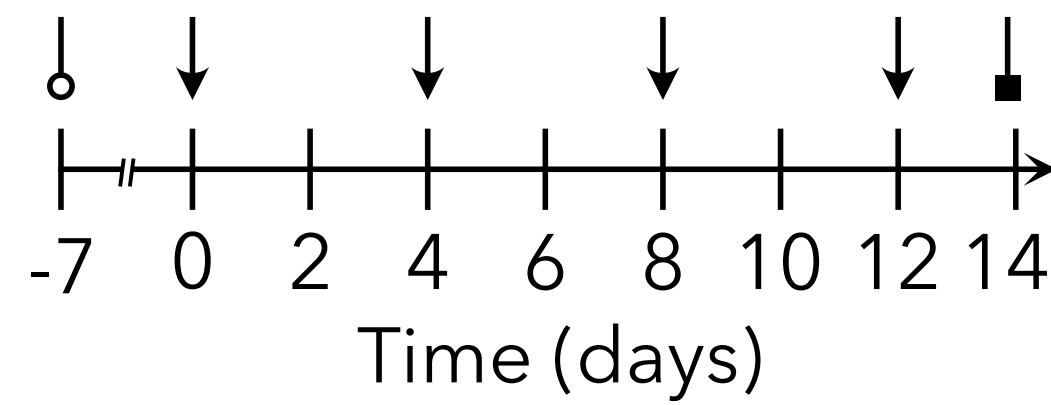
B16F10 melanoma cancer model

IFN- γ

♂ B16F10 Inoculation

↓ aNP-mRNA injection

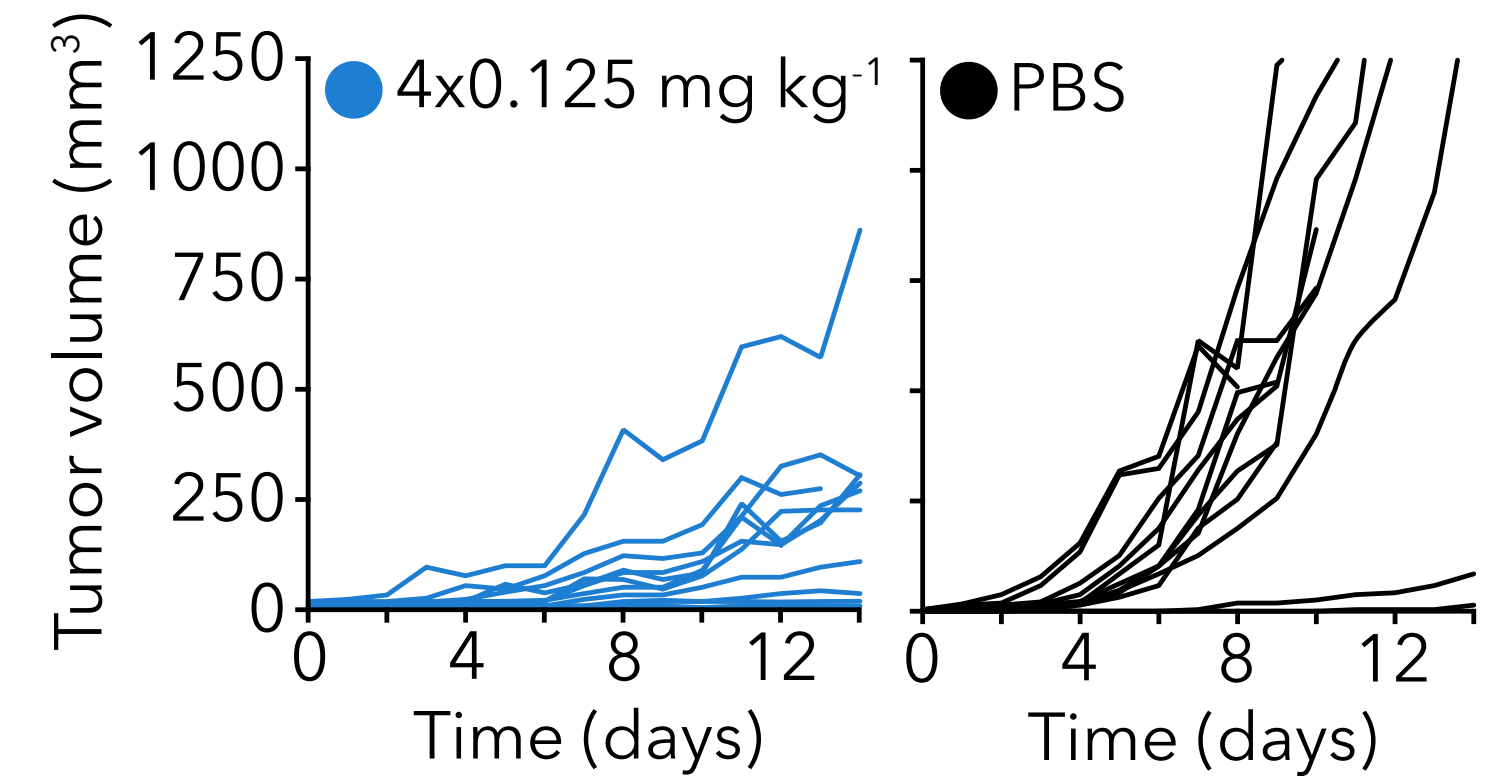
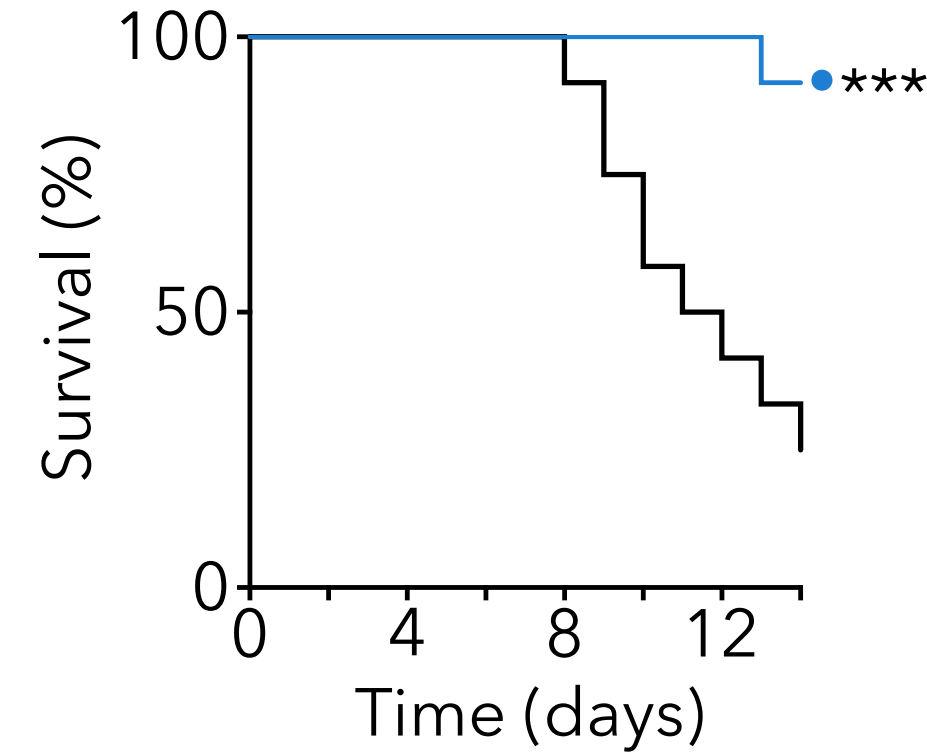
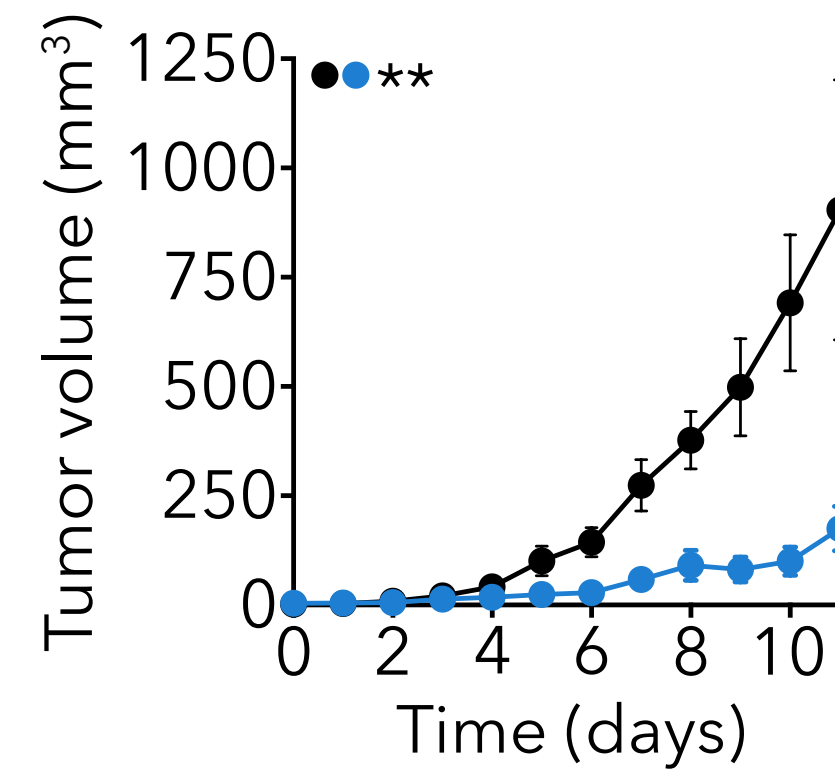
▣ Euthanasia



aNP_{HMJ1}-mRNA_{IFN- γ}

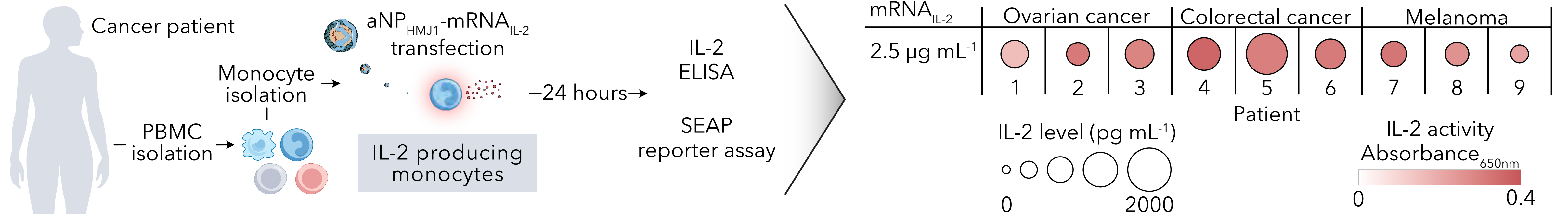
● 4x0.125 mg kg⁻¹

● PBS



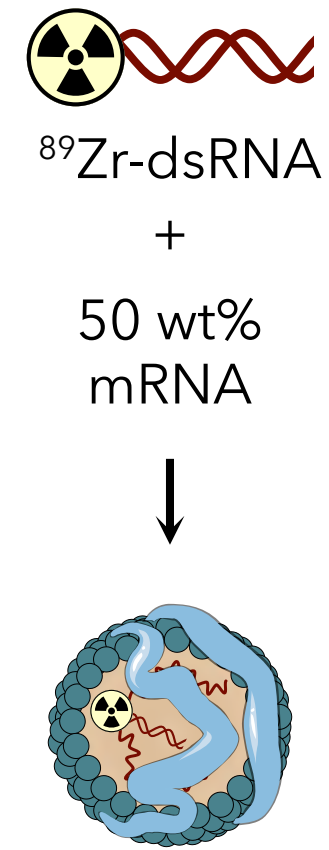
IL-2 immunotherapy using aNP-mRNA

Cancer patient cells *ex vivo*



aNP-mRNA in non-human primates

● ^{89}Zr -aNP_{HMJ1}-mRNA_{mCherry}
● ^{89}Zr -aNP_{HMJ1}-mRNA_{IL-2}



↑ 0.02 mg mRNA kg⁻¹ injection

⌋ PET/MRI scan

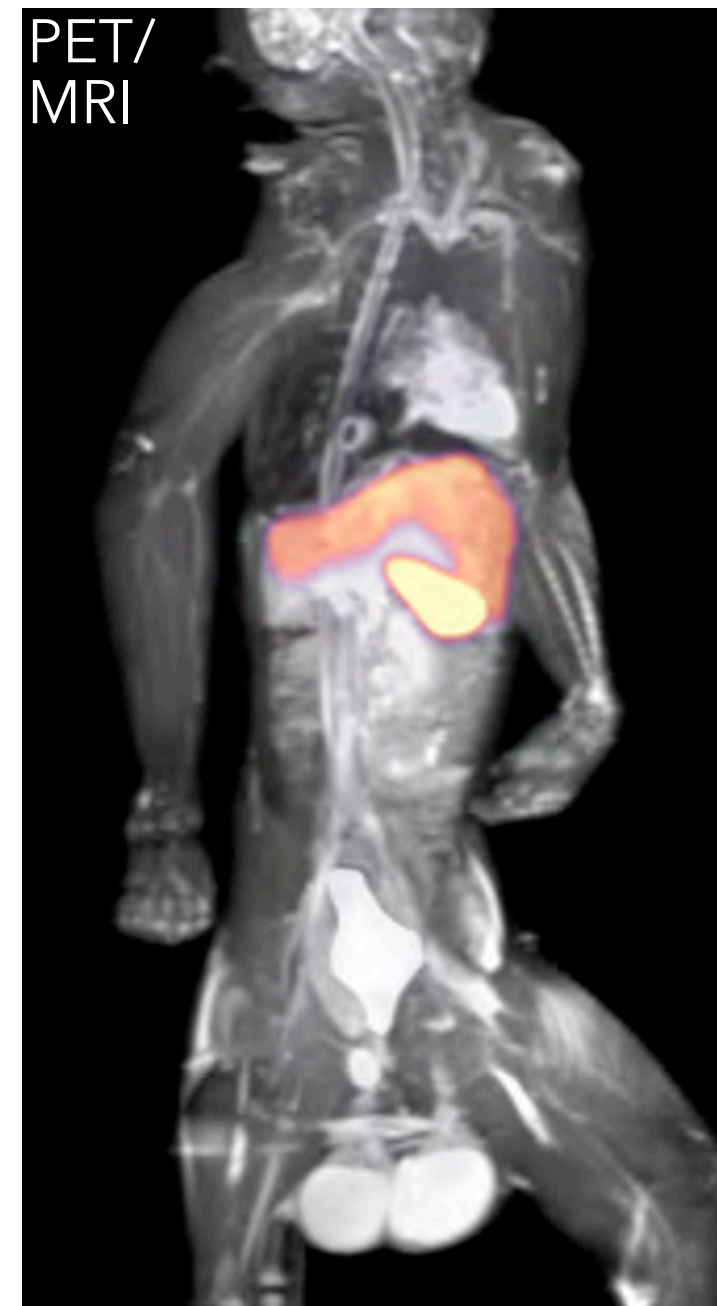
⌋ Blood collection

PET



● 2 hours
NHP₁
mRNA_{mCherry}

PET/
MRI

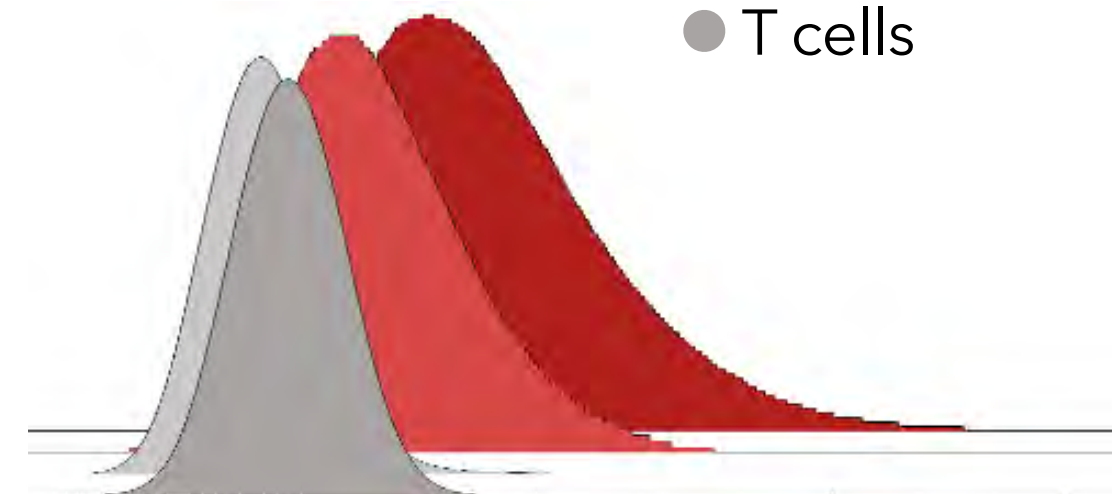


0 25
SUV

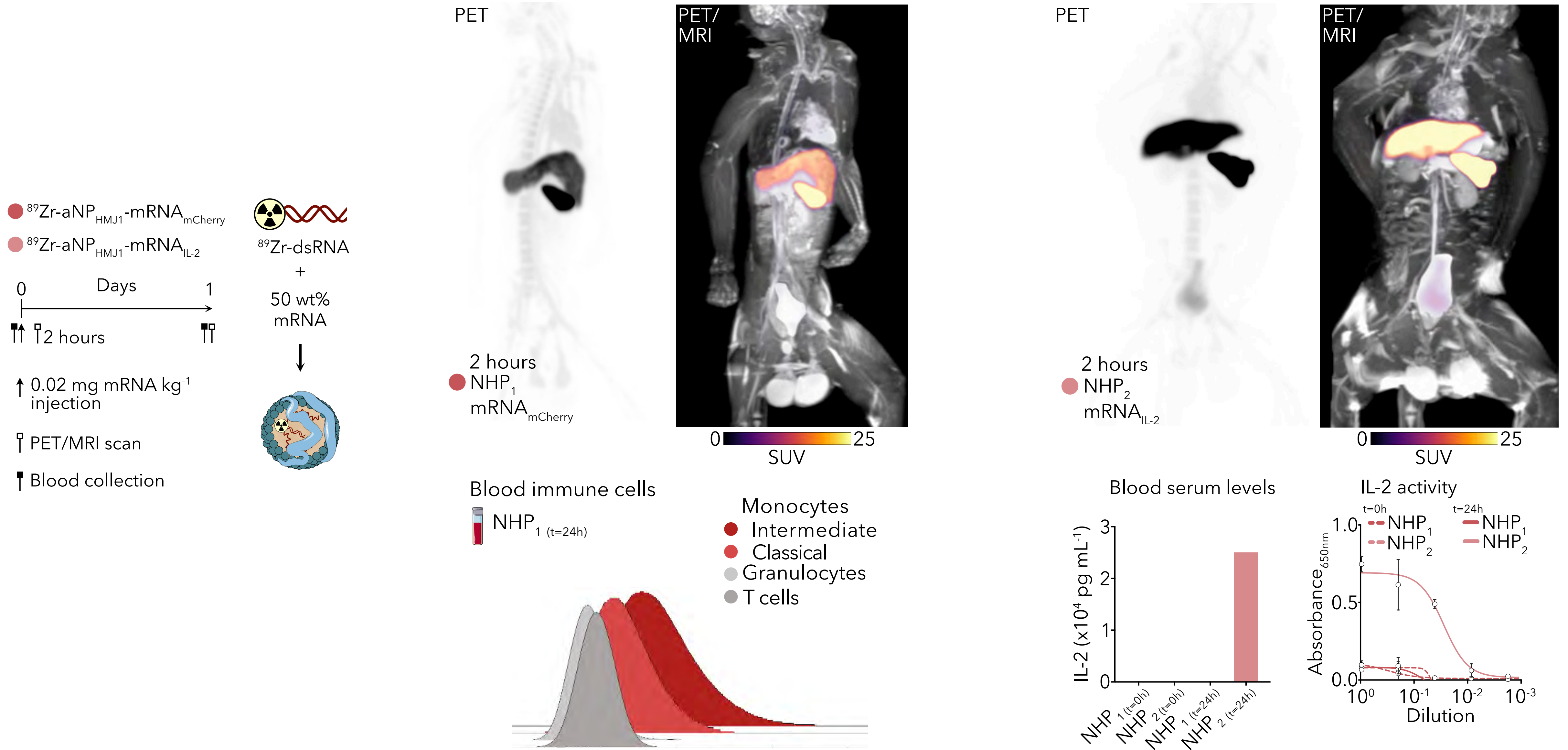
Blood immune cells

● NHP₁ (t=24h)

- Monocytes
 - Intermediate
 - Classical
- Granulocytes
- T cells



aNP-mRNA in non-human primates





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Henk Janssen *in memoriam*