

Hybrid LNPs for Cancer Immunotherapy



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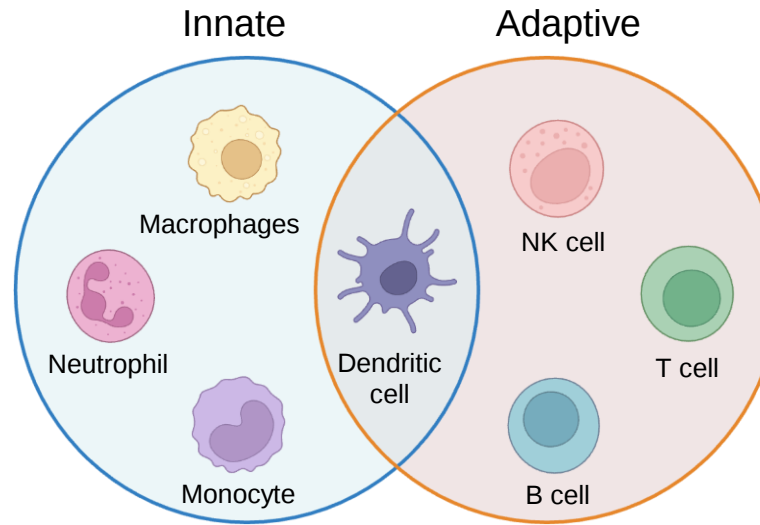


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Effective defense requires both innate and adaptive immunity

Innate arm:

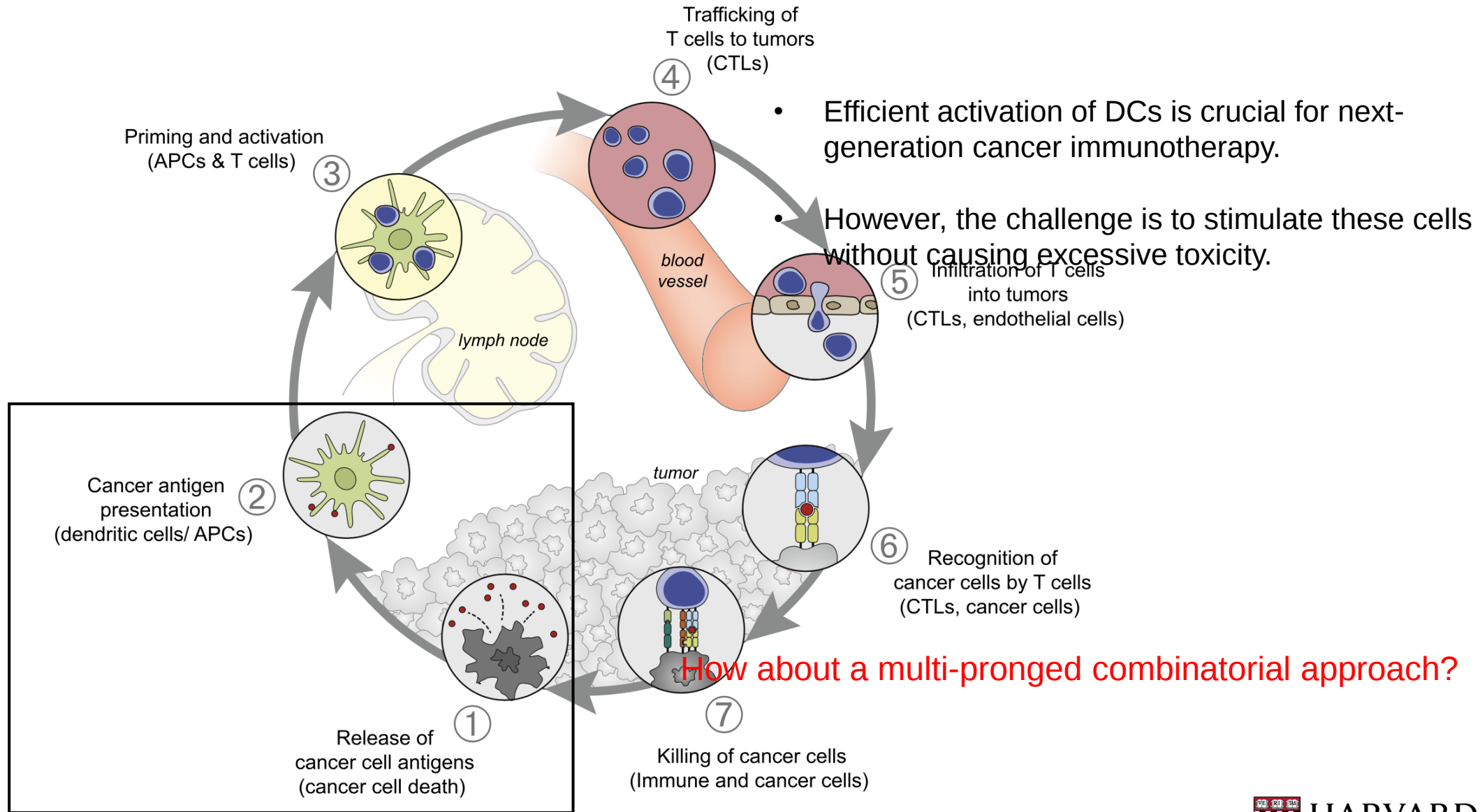
- Responds first and quickly (hours)
- Brings “the heat” (inflammation)



Adaptive arm:

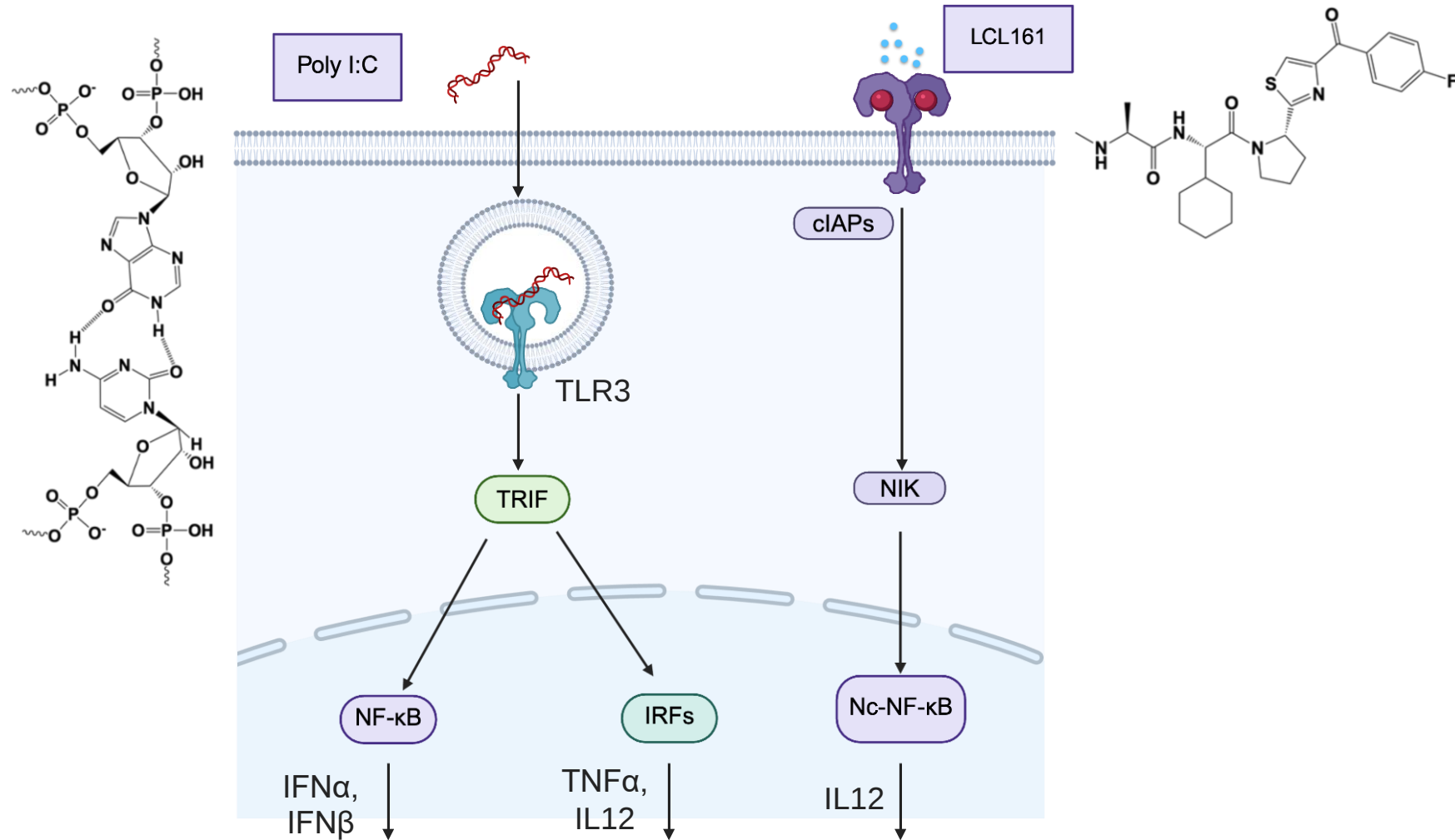
- Requires induction and time (days to weeks)
- Confers long-term “memory”

Dendritic cells bridge the innate and adaptive immune response



DS Chen et al. Immunity. 2013, 7, 1-10

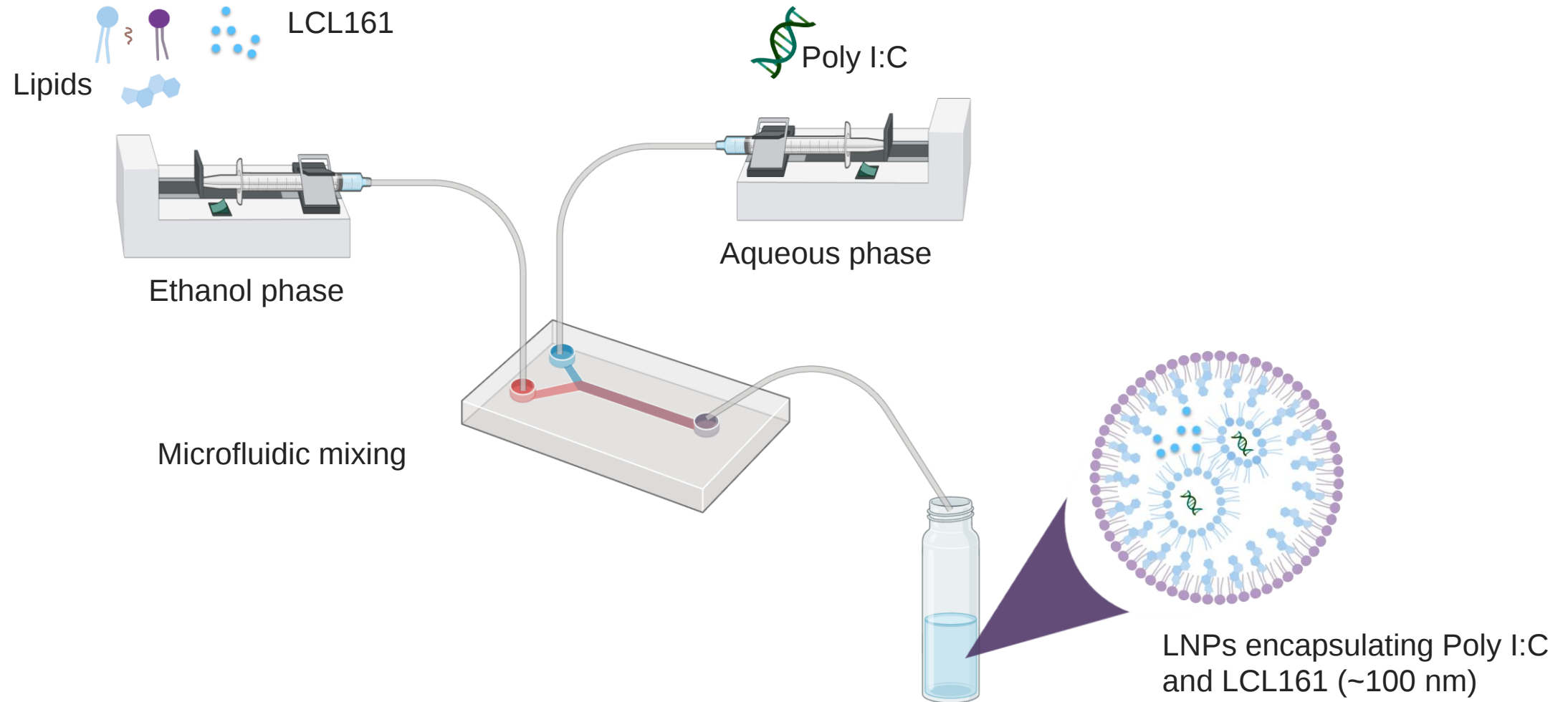
We primed dendritic cells by dual stimulating pathways



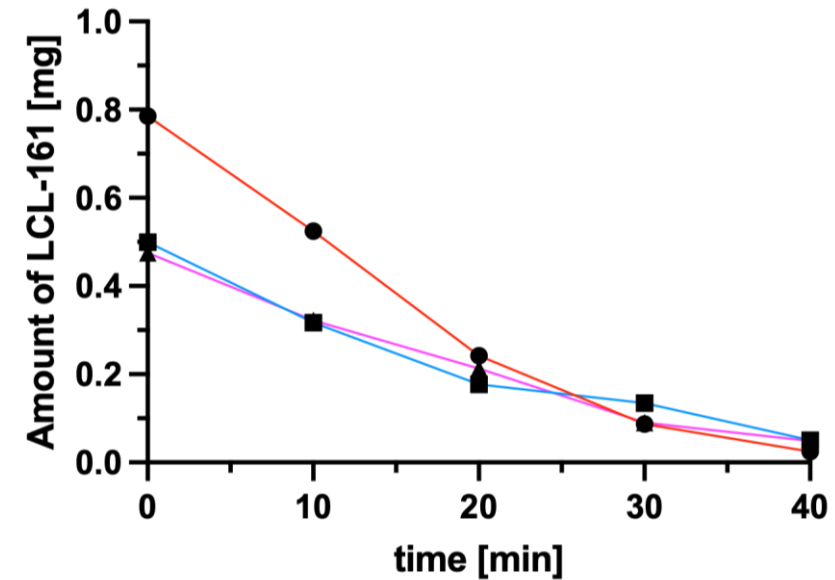
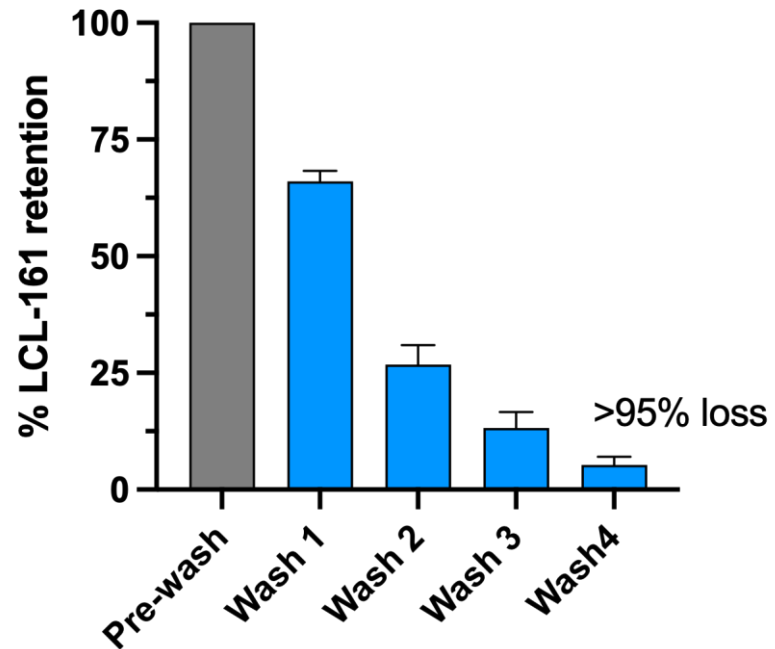
Dendritic cell maturation for anti-tumor response

R. Das *et al.* Adv. Sci. 2023, 10, 2303576.

Our platform: LNPs for priming dendritic cells



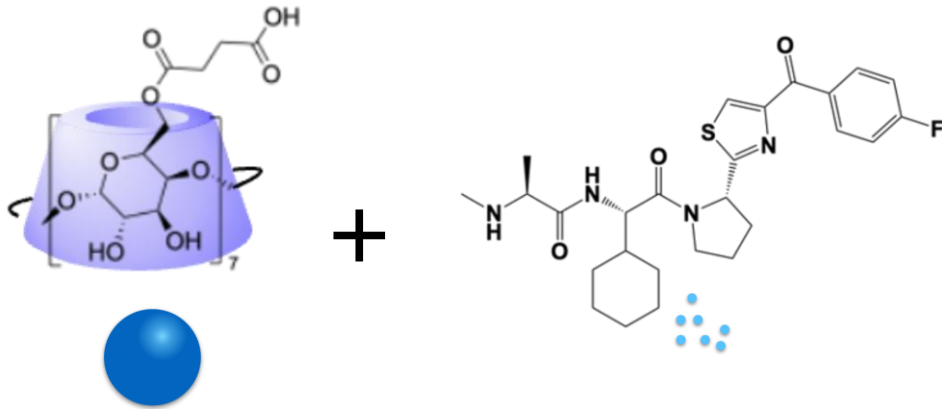
Direct LCL161 incorporation into LNPs led to rapid leakage



Can we use a second nanoparticle as a “sponge” for LCL161?

Cyclodextrin nanoparticles were used as a "sponge" for LCL161

Ultra small nanoparticle as a "sponge" for small molecule therapeutics

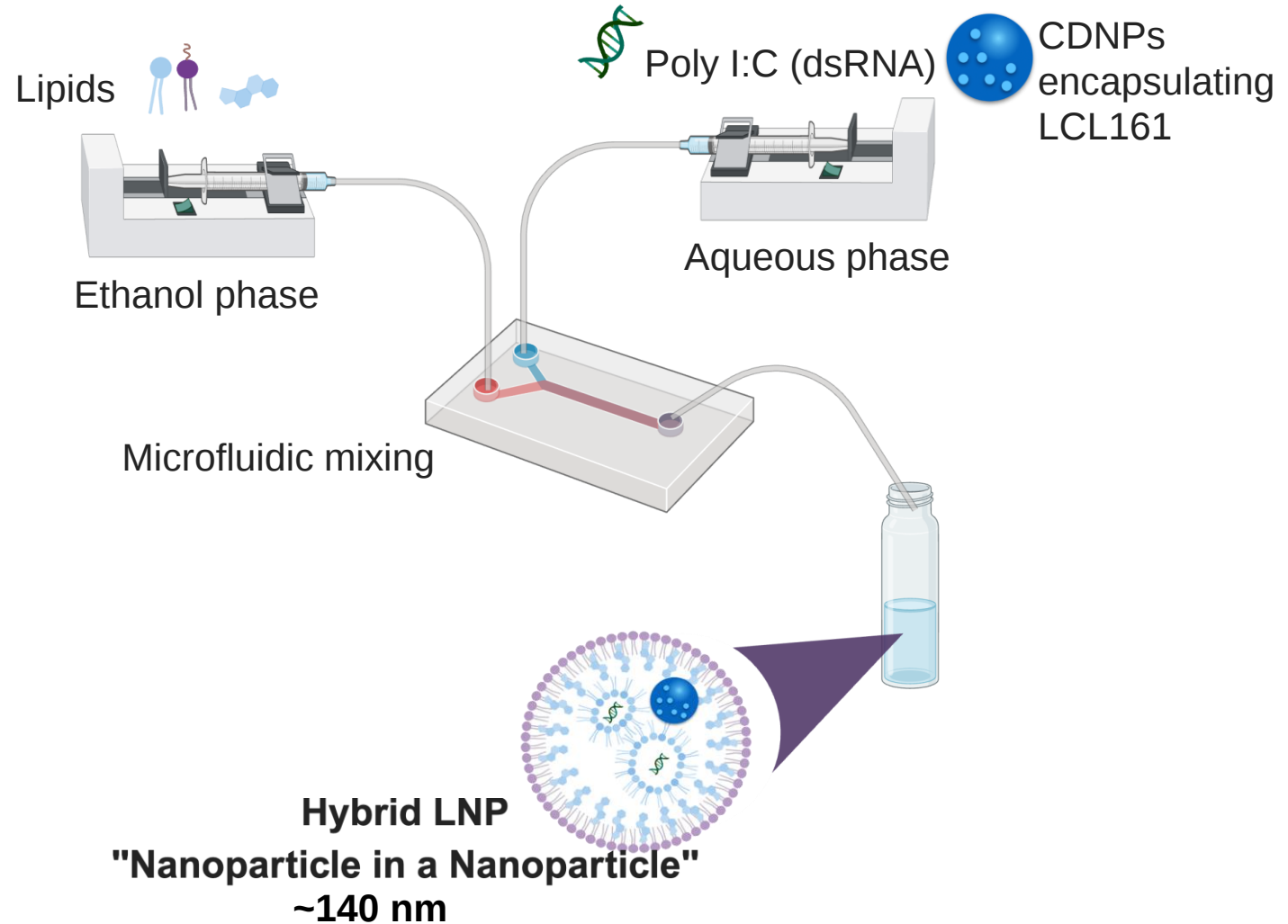


Cyclodextrin nanoparticle (CDNPs)

LCL161

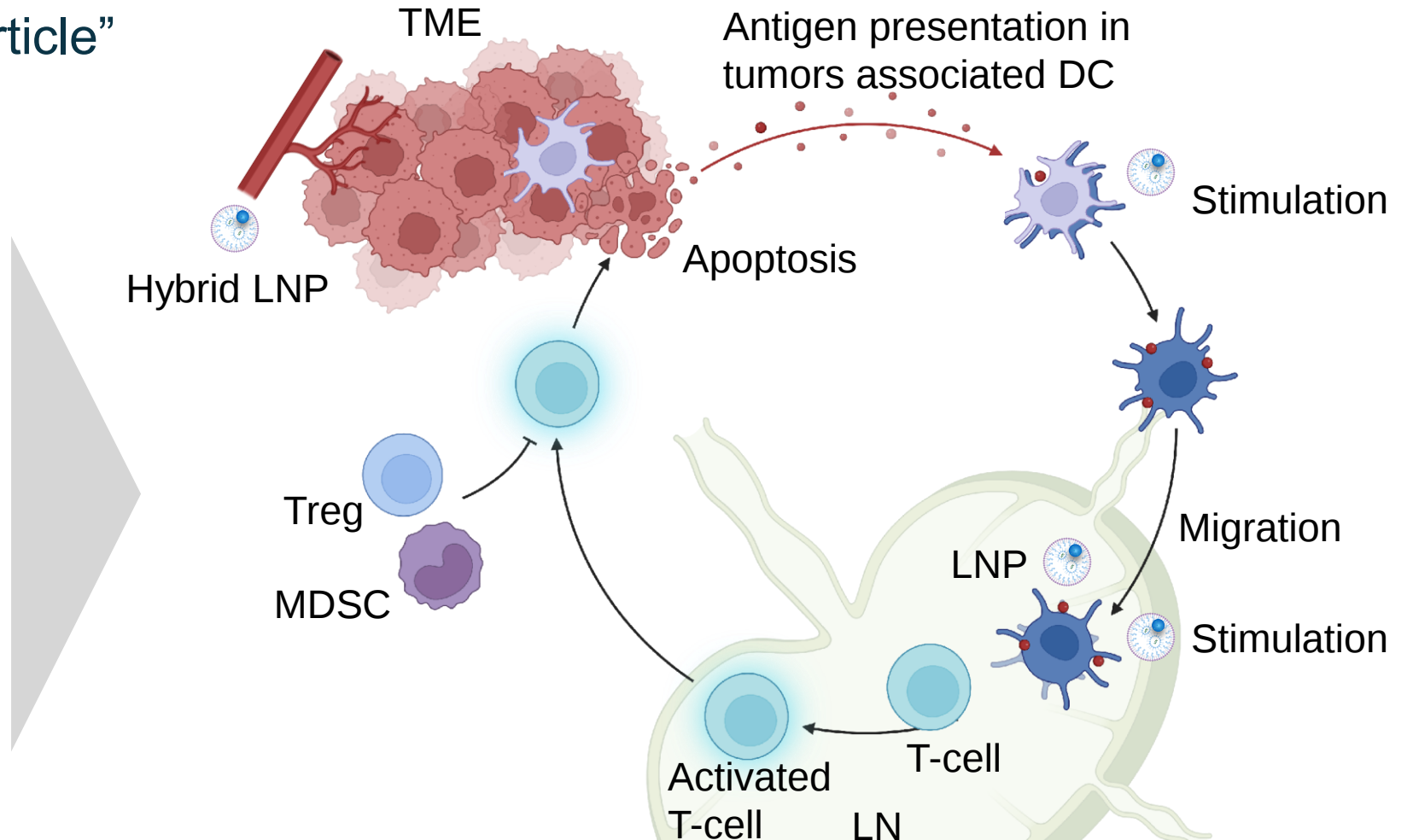
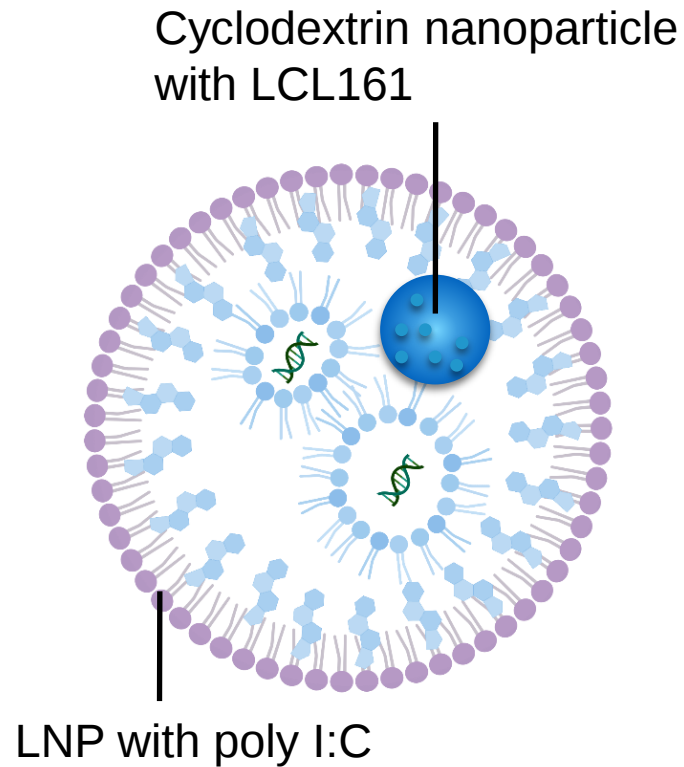
CDNPs encapsulating LCL161
(30 nm)

S. Lugani *et al.* Adv. Mater. 2022, 3, 210394.



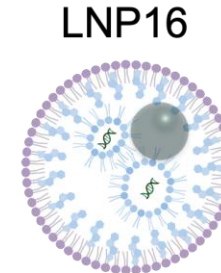
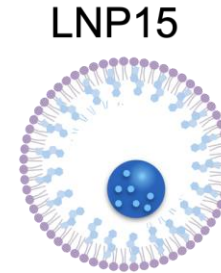
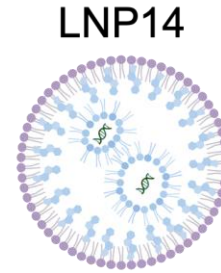
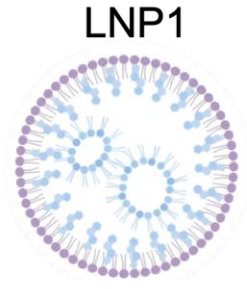
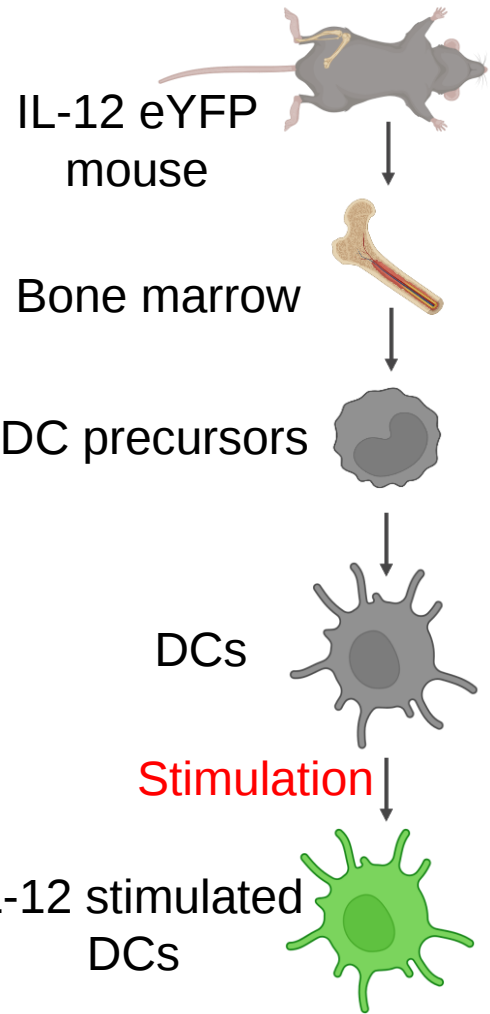
Hybrid LNPs circulates and gains access to myeloid DCs

“Nanoparticle-in-a-nanoparticle”

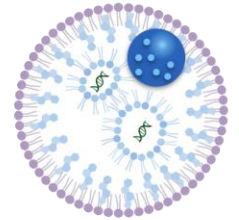


R. Das *et al.* Adv. Sci. 2023, 10, 2303576.

Dual stimulation leads to the highest IL12 production in DCs



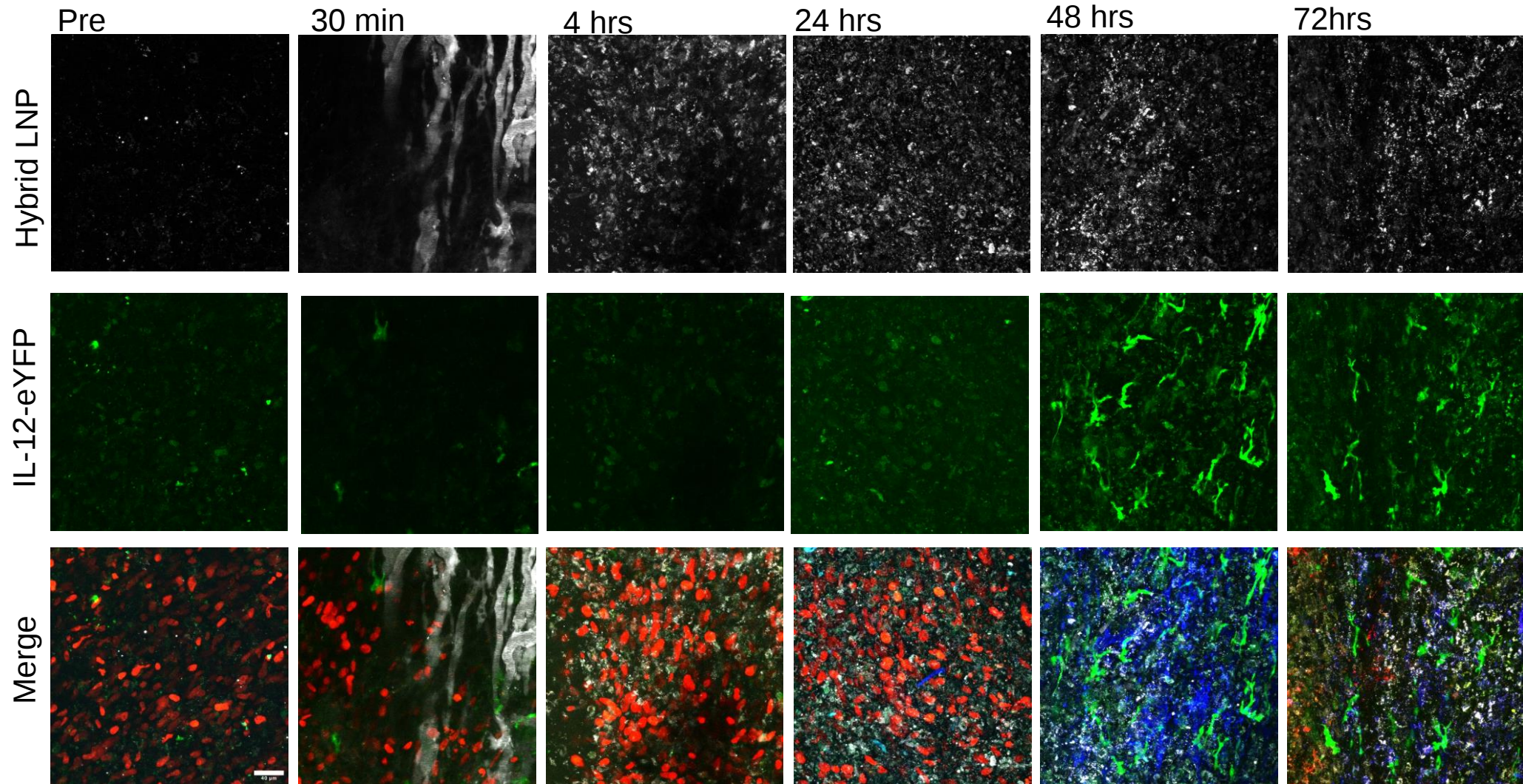
Hybrid LNP
LNP17



Scale bar = 50 μ m

R. Das *et al.* Adv. Sci. 2023, 10, 2303576.

Intravital microscopy imaging to determine pharmacokinetics and dynamics

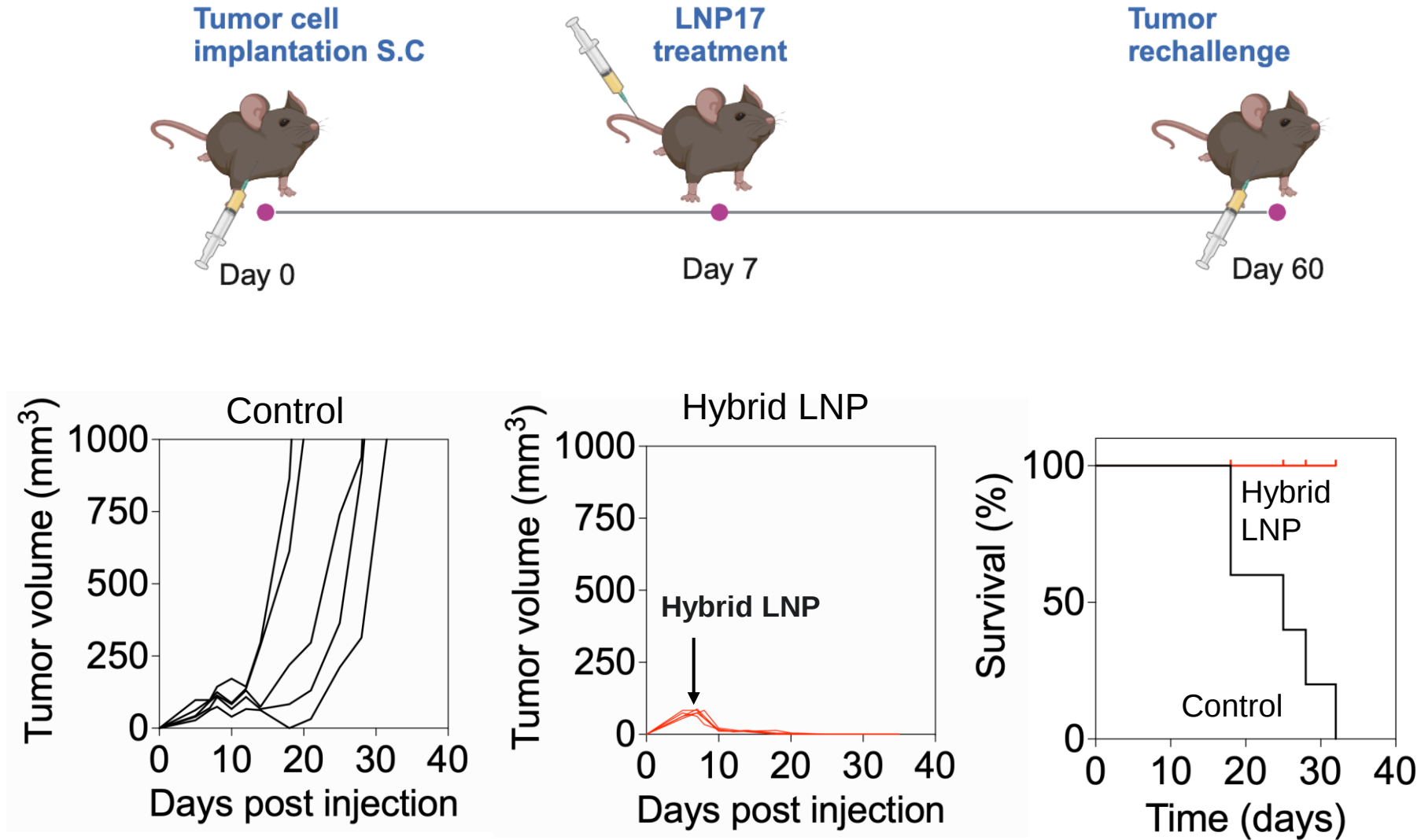


LNP17, MC38-H2B-apple, IL-12-YFP, Dextran-PB

Scale bar = 100 μm

R. Das *et al.* Adv. Sci. 2023, 10, 2303576.

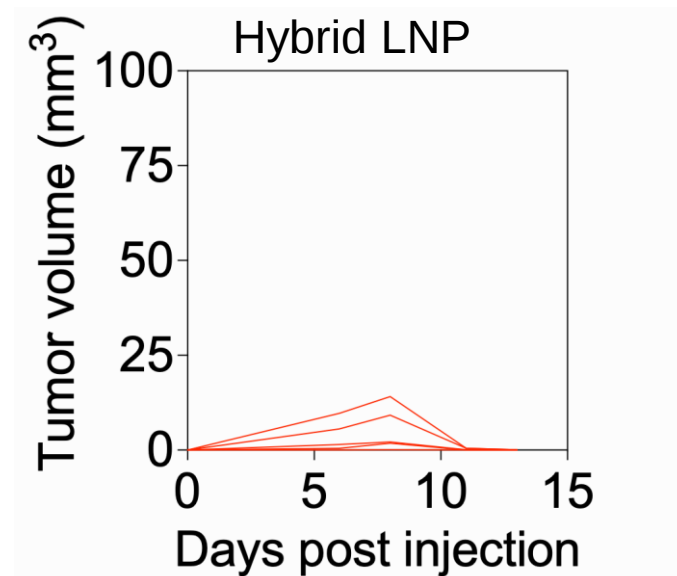
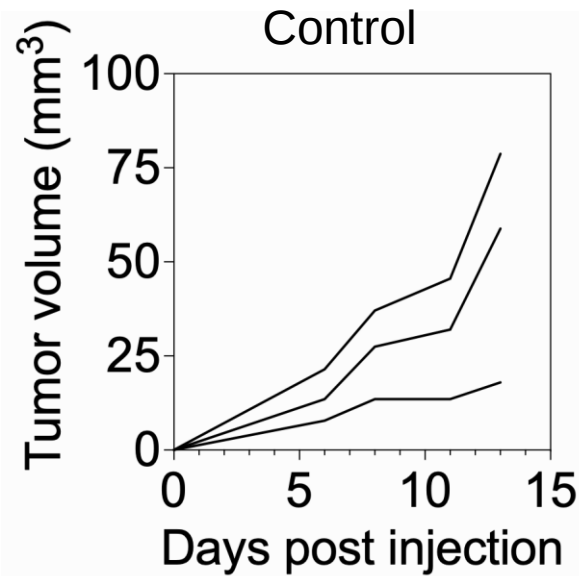
A single dose of hybrid LNPs (LNP17) led to 100% survival in MC38 tumor model



R. Das *et al.* Adv. Sci. 2023, 10, 2303576.

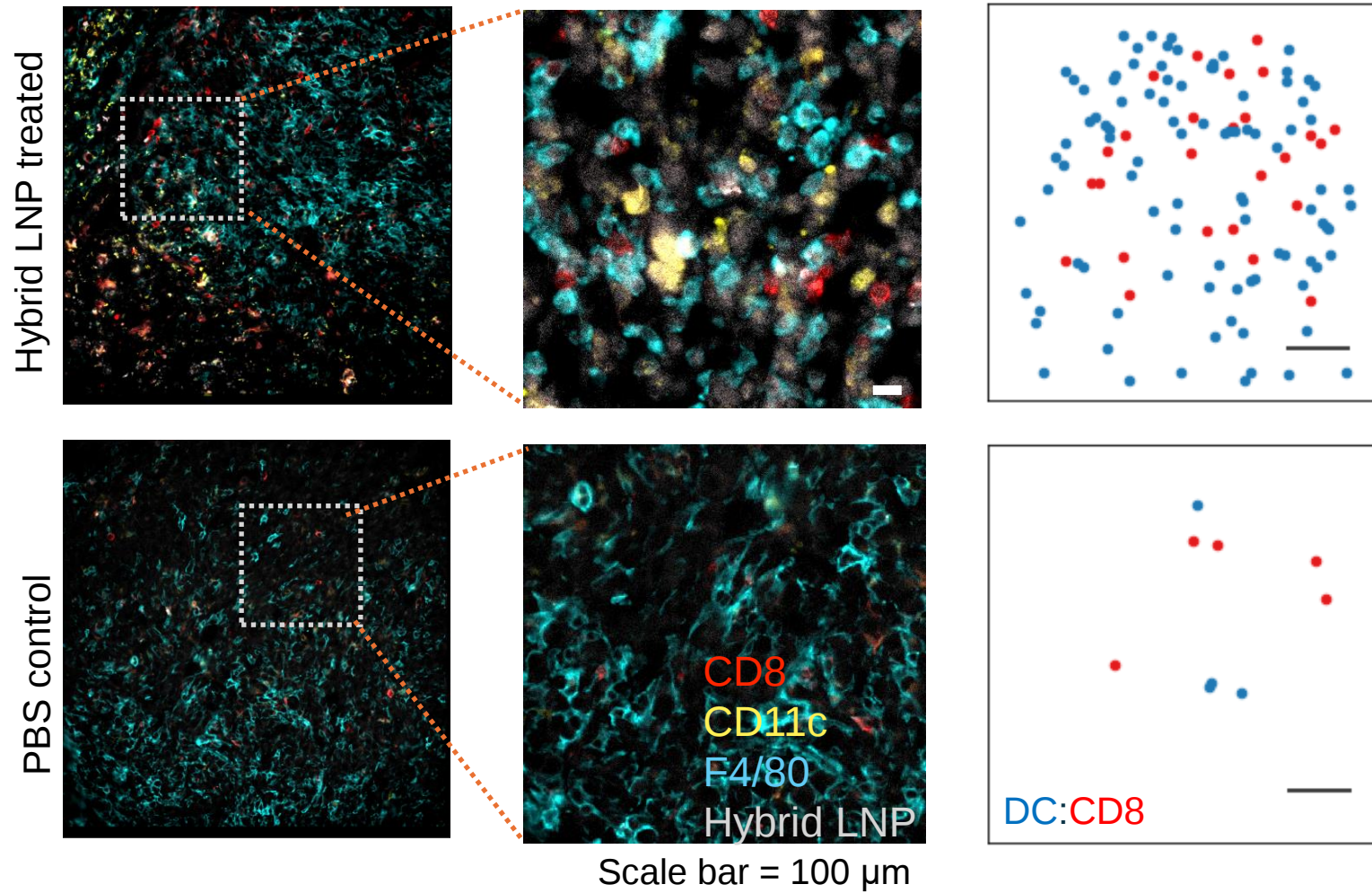
Tumor rejection in rechallenge experiment demonstrates adaptive immune response

Rechallenge with MC38 tumor cells was done after 2 months...



Complete responders from Previously treated mice group

Hybrid LNP therapy showed substantial increase in tumor DCs and CD8 T cells

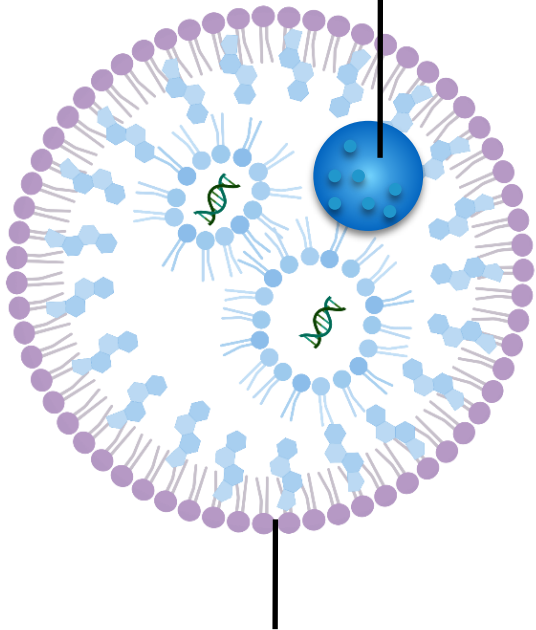


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Summary

“Nanoparticle-in-a-nanoparticle”

Cyclodextrin nanoparticle
with LCL161



LNP with poly I:C

- Efficient DC activation led to long-term memory response (at least 2 months)
- DC stimulation by dual pathways has the potential to reduce dosing without compromising efficacy

Ongoing work:

Reprogram DC with novel mRNA-adjuvants to enable controlled and more efficient immuno-stimulation

- being tested in multiple cancer models and infectious diseases

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