Tolerogenic mRNA-lipid nanoparticle vaccines for autoimmune disease

Jilian Melamed

Nanomedicine and Nanoscale Delivery: Gene Focus

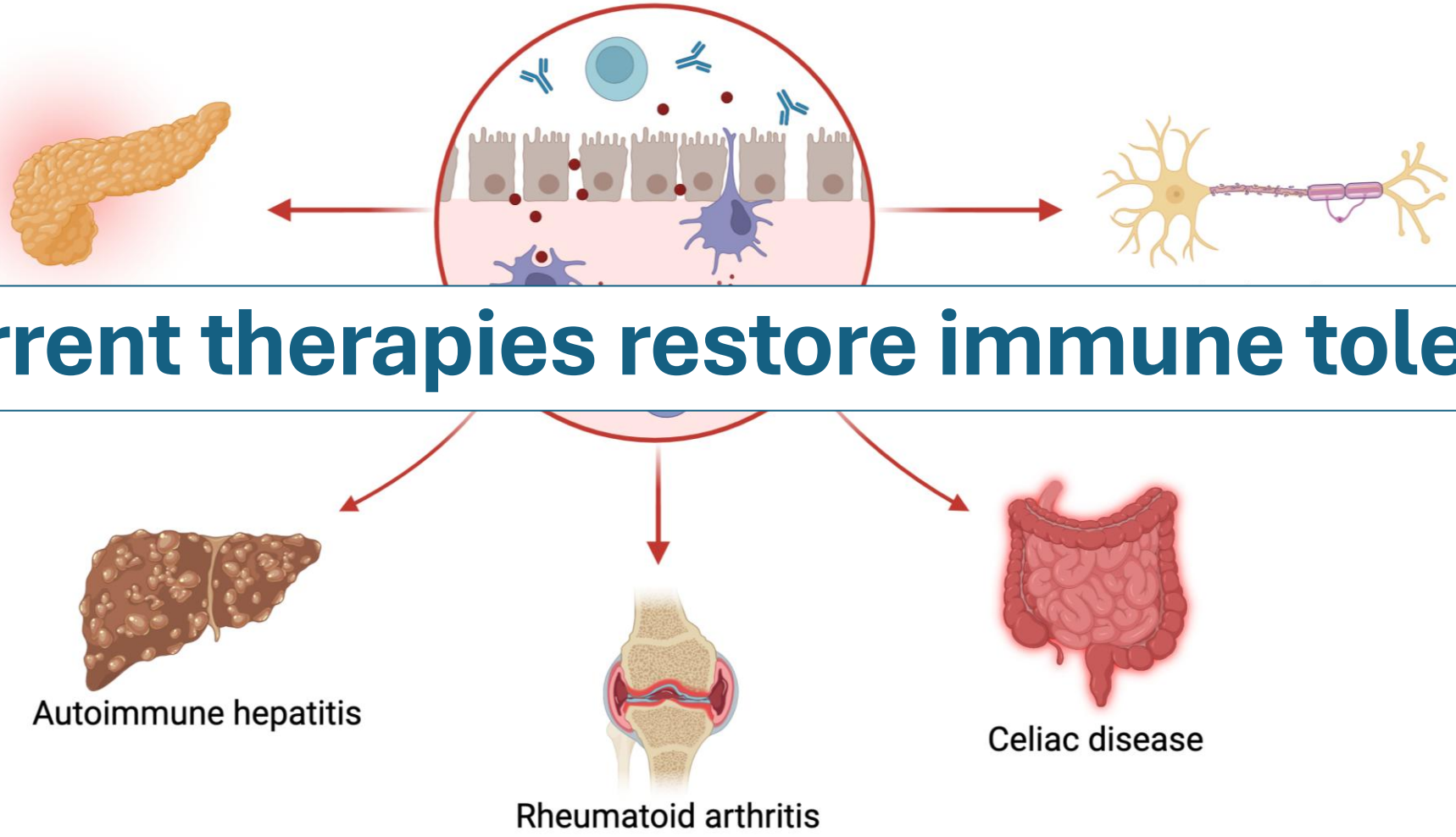
CRS 2025

July 17th, 2025

CRS 2025 ANNUAL MEETING & EXPOSITION
PHILADELPHIA, PA
JULY 13-18, 2025

NEXT-GENERATION DELIVERY INNOVATIONS

Autoimmune disease:
When the immune system mistakes self for threat

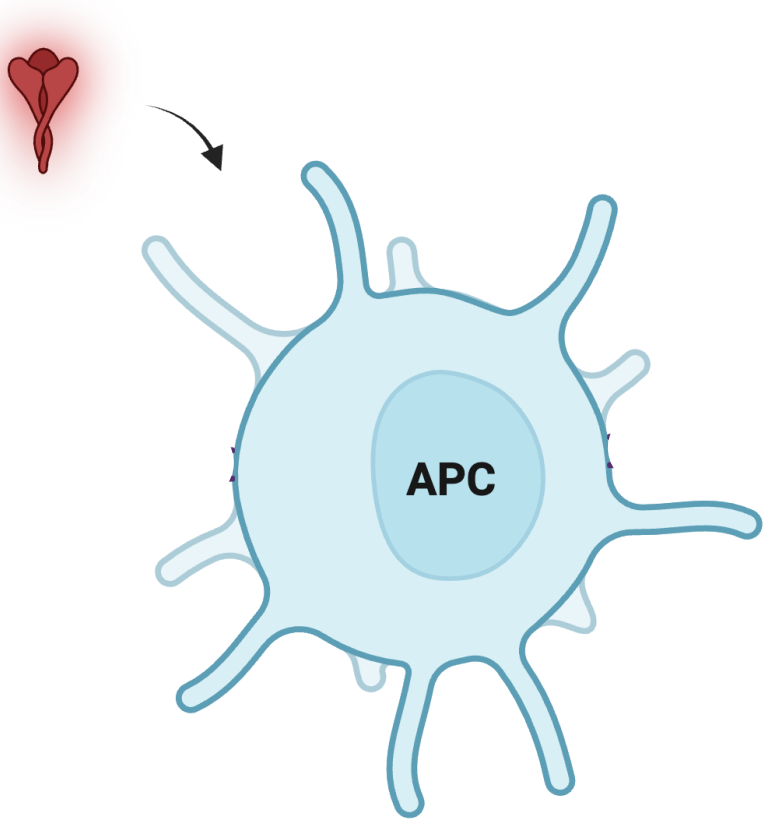


No current therapies restore immune tolerance

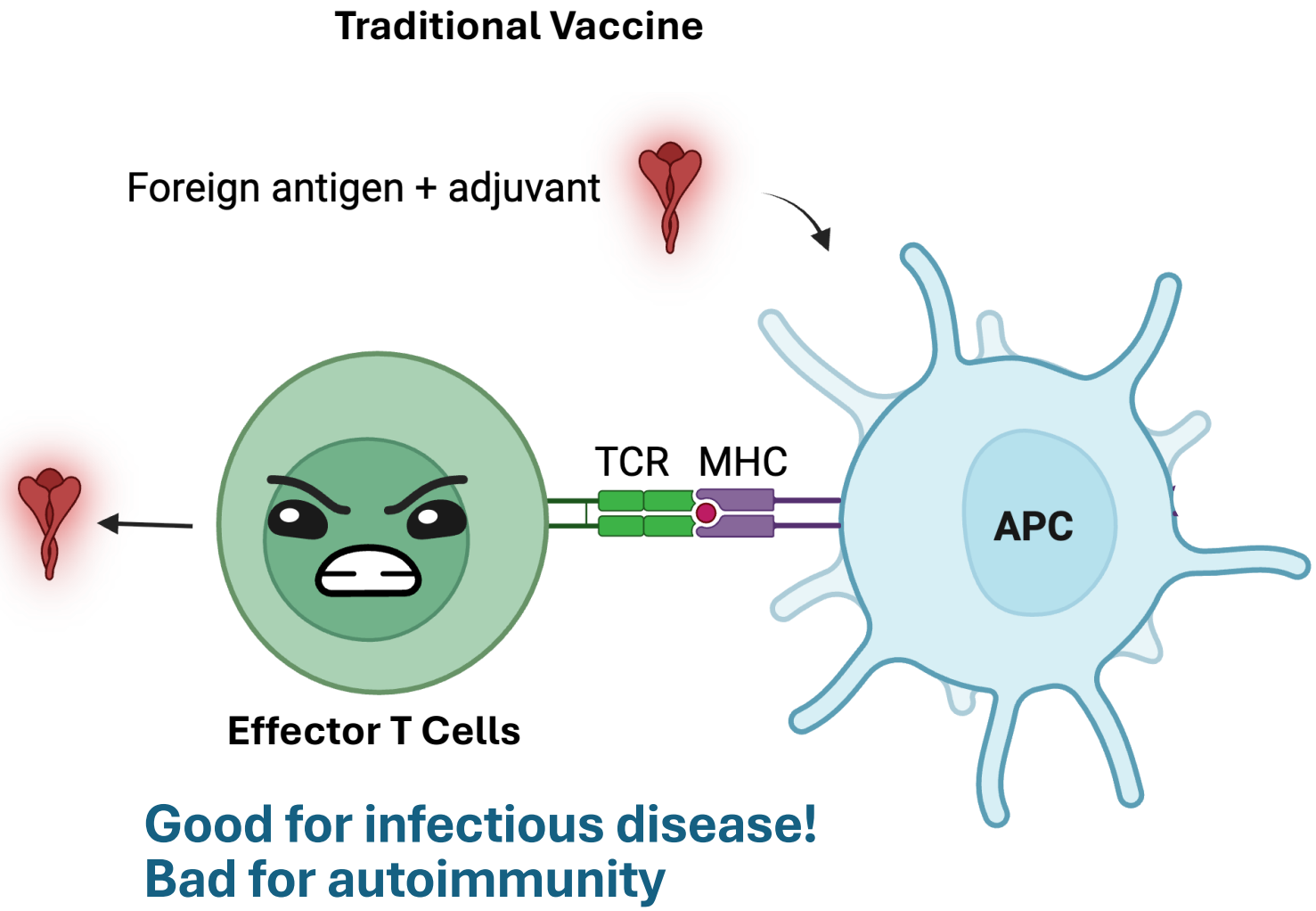
Tolerizing vaccines can restore immune tolerance

Traditional Vaccine

Foreign antigen + adjuvant

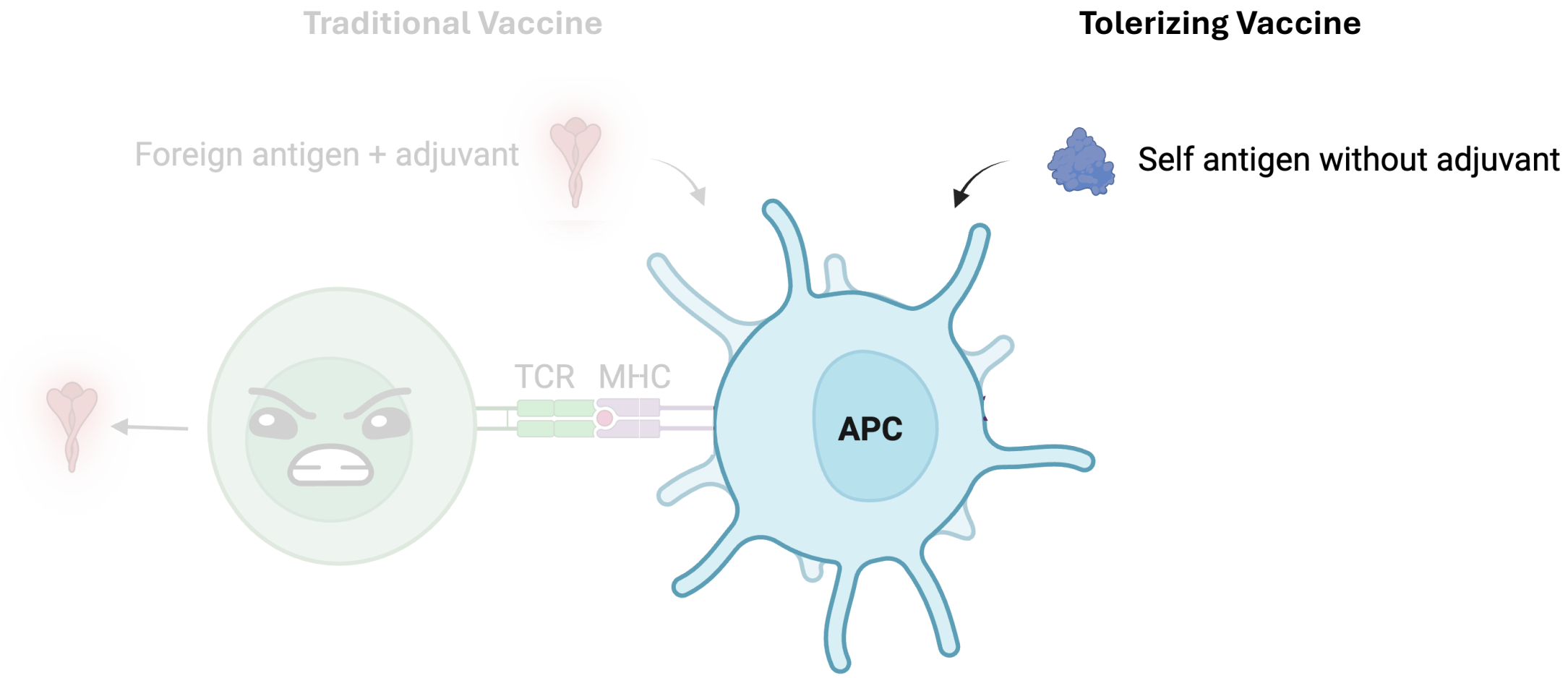


Tolerizing vaccines can restore immune tolerance



Good for infectious disease!
Bad for autoimmunity

Tolerizing vaccines can restore immune tolerance



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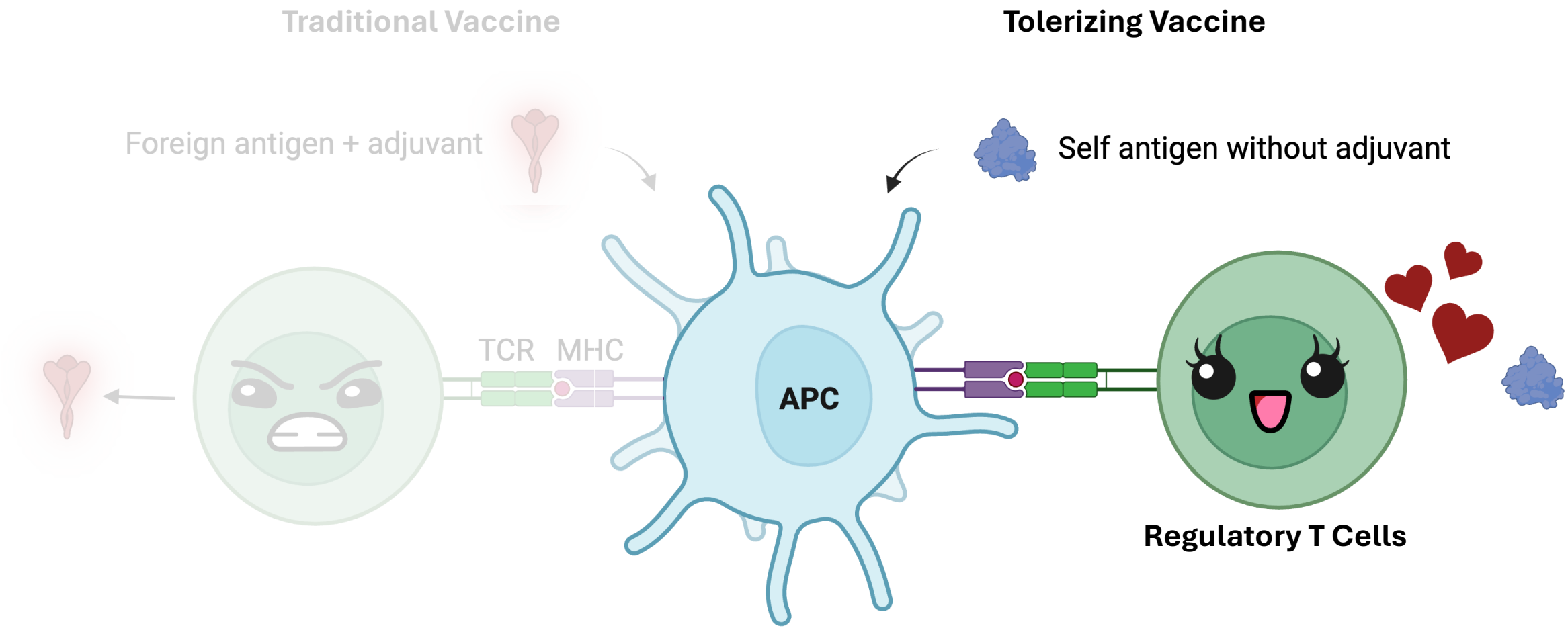


mRNA-LNP vaccines are highly effective for generating antigen-specific immune responses

SCCM

mRNA-LNP vaccines are highly effective for generating antigen-specific immune responses

Challenges for tolerizing vaccines

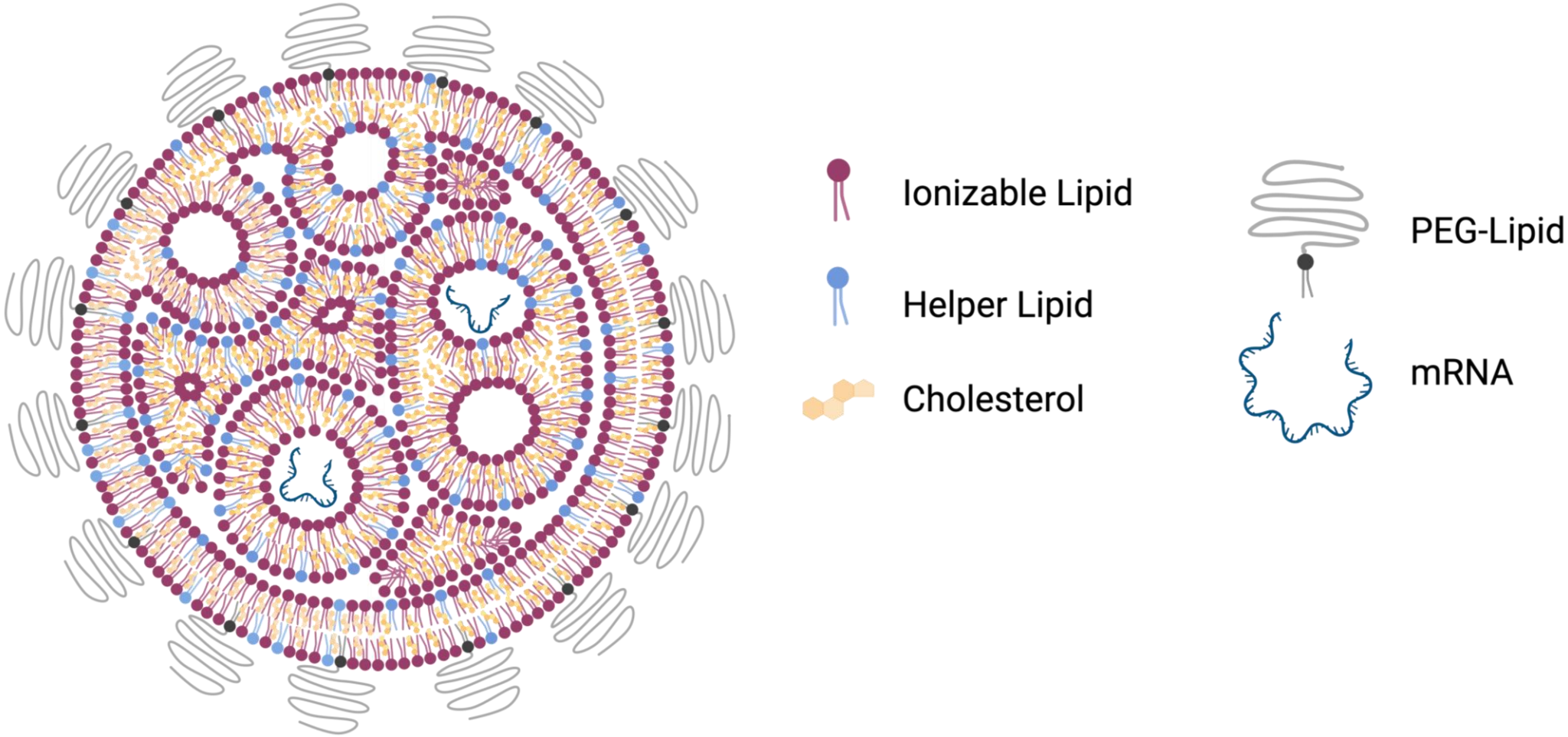
1. Systemic delivery to immune cells in relevant tissues

2. LNPs are highly inflammatory

SCCM

How can we engineer immune-tropic LNPs with reduced adjuvant activity?

The delivery and adjuvanticity of LNPs are determined by their components



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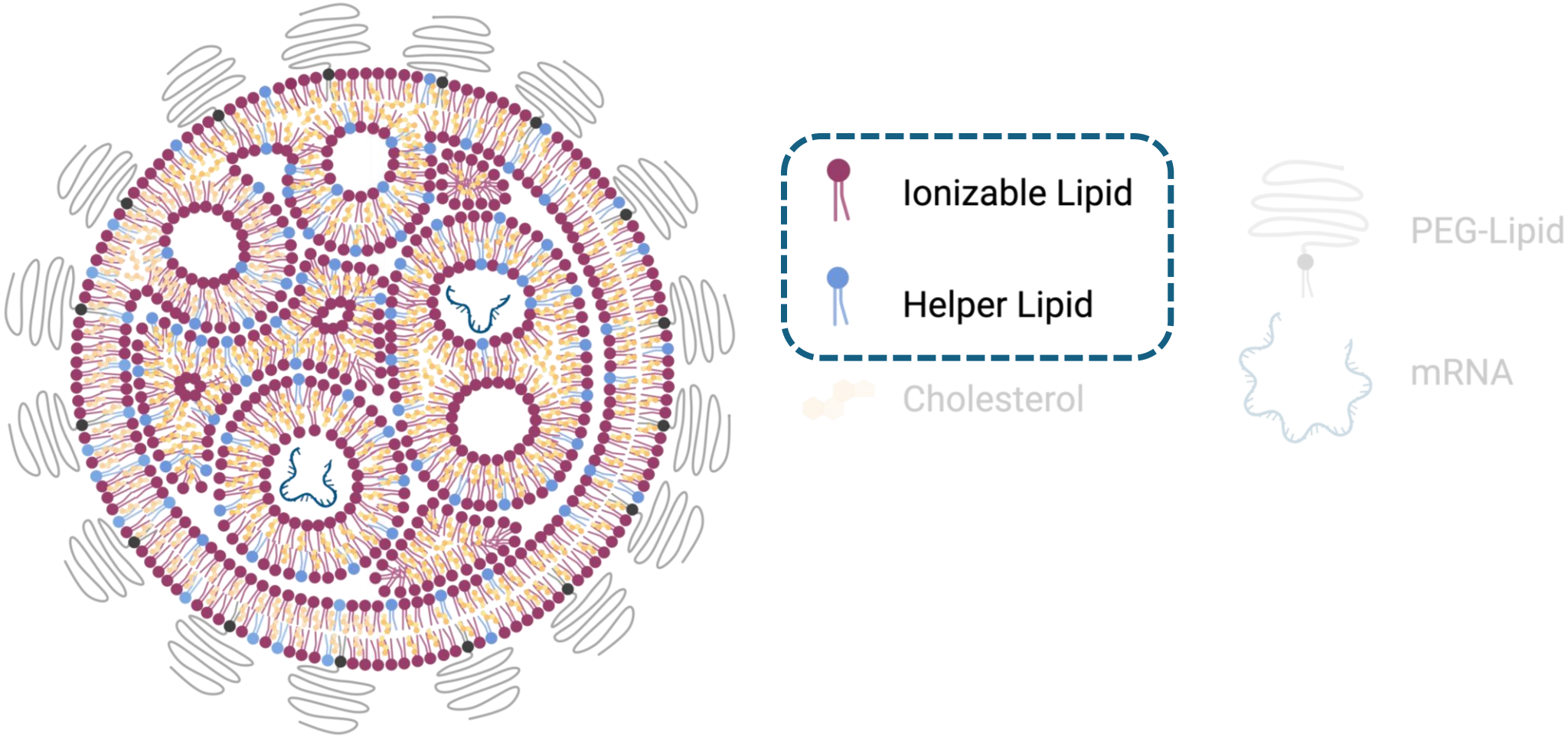
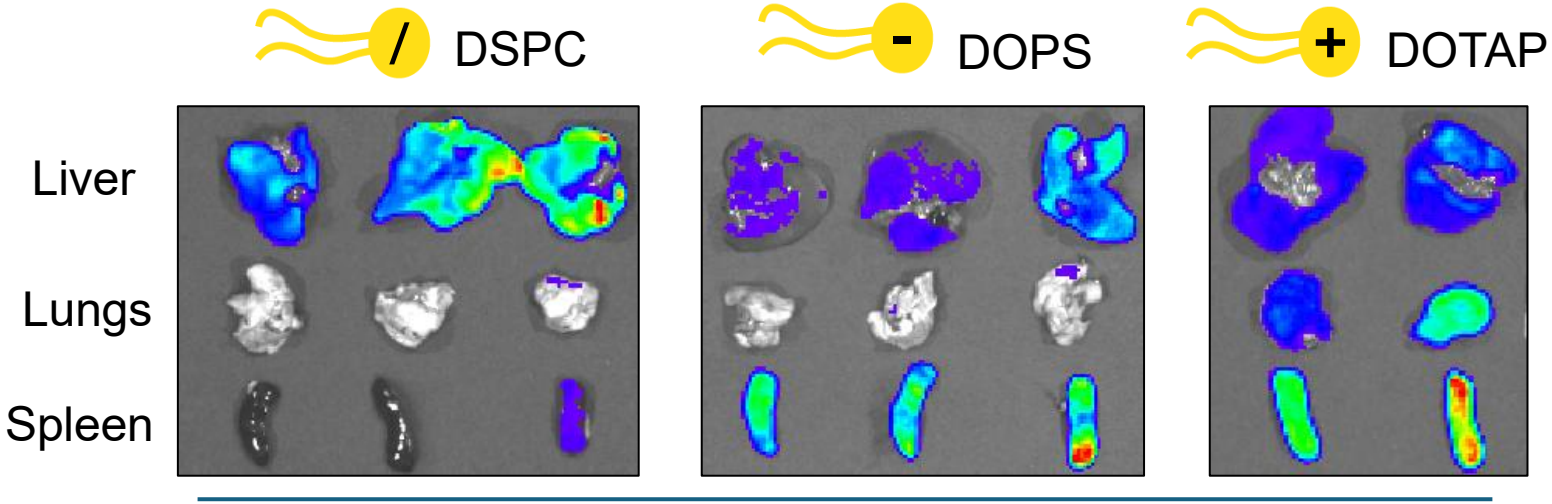


Charged helper lipids can re-route liver-tropic LNPs to other organs



LNPs contain ionizable lipid MC3

Dan Siegwart

- Cheng (2020) Nat Biotech
- Dilliard (2021) PNAS

Katie Whitehead

- LoPresti (2022) J Cont Rel
- Melamed (2023) Sci Adv

Selective ORgan Targeting "SORT"

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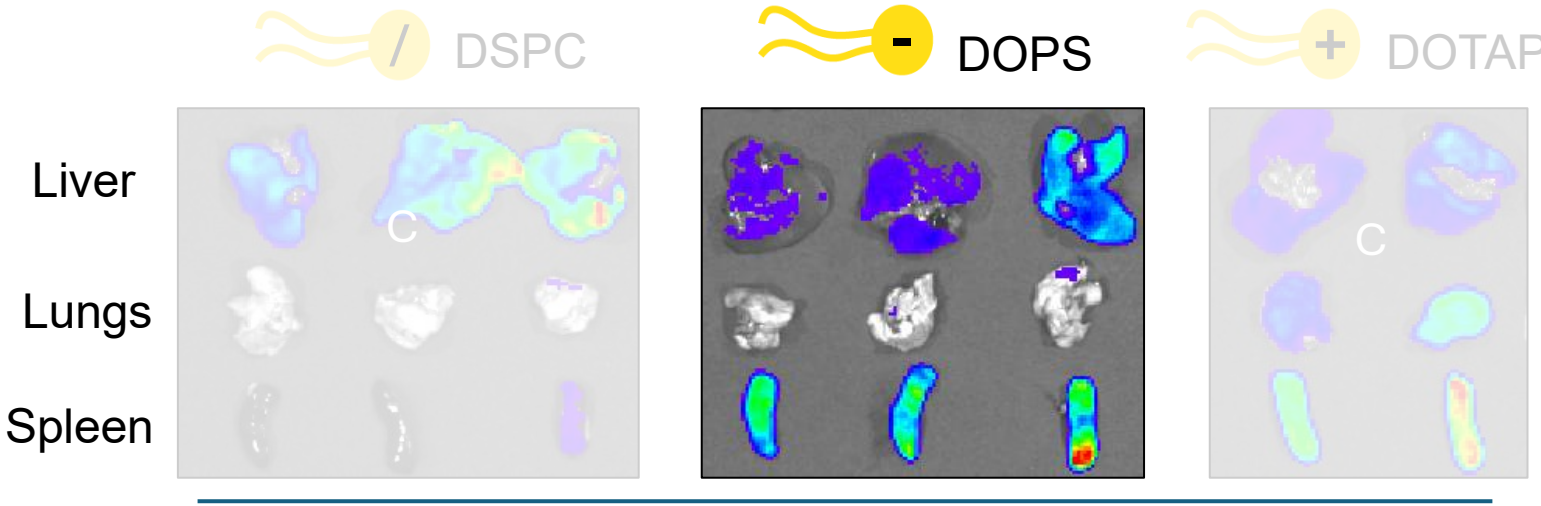

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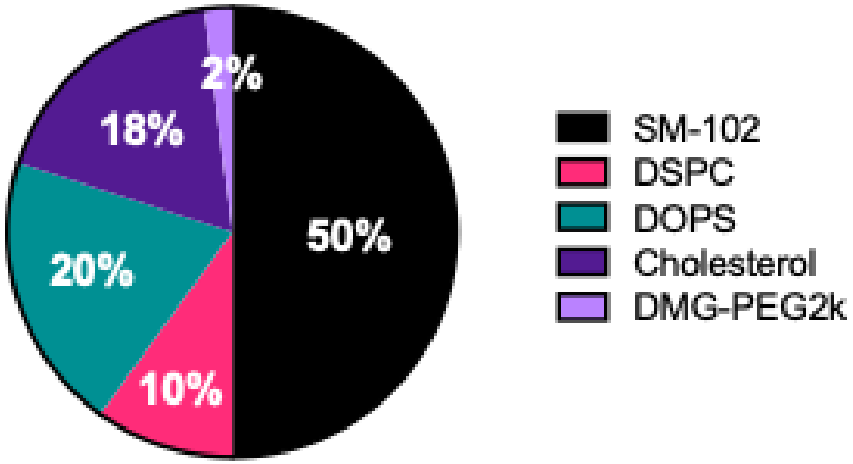
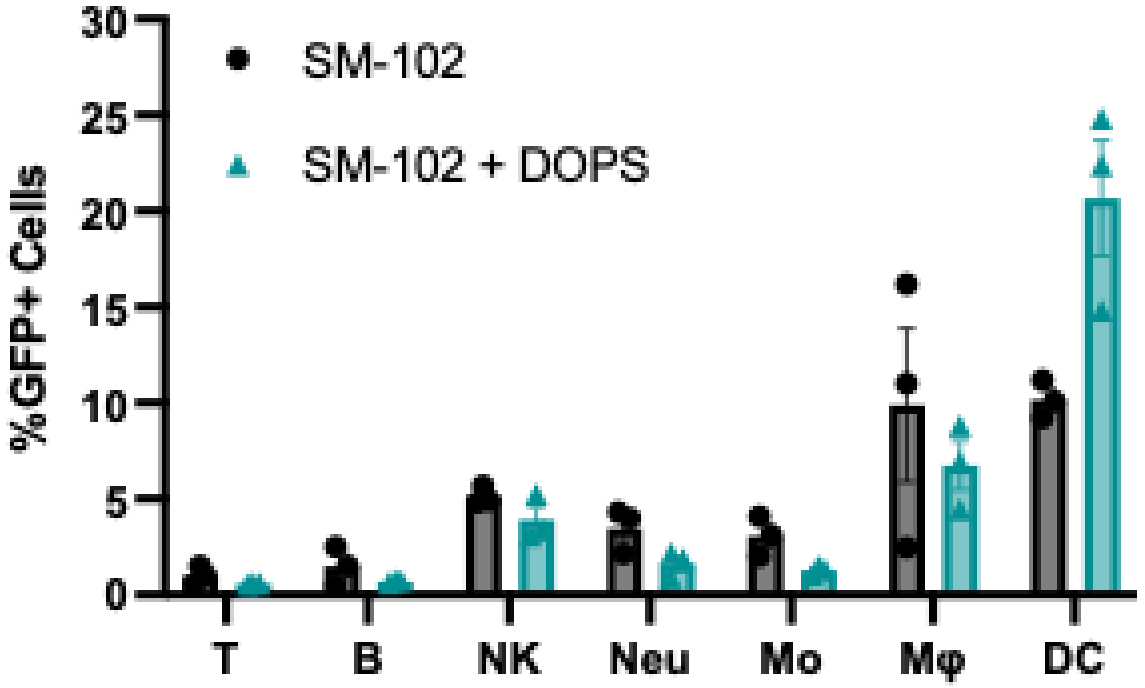
mRNA-LNPs containing anionic helper lipids transfect primarily splenic DCs

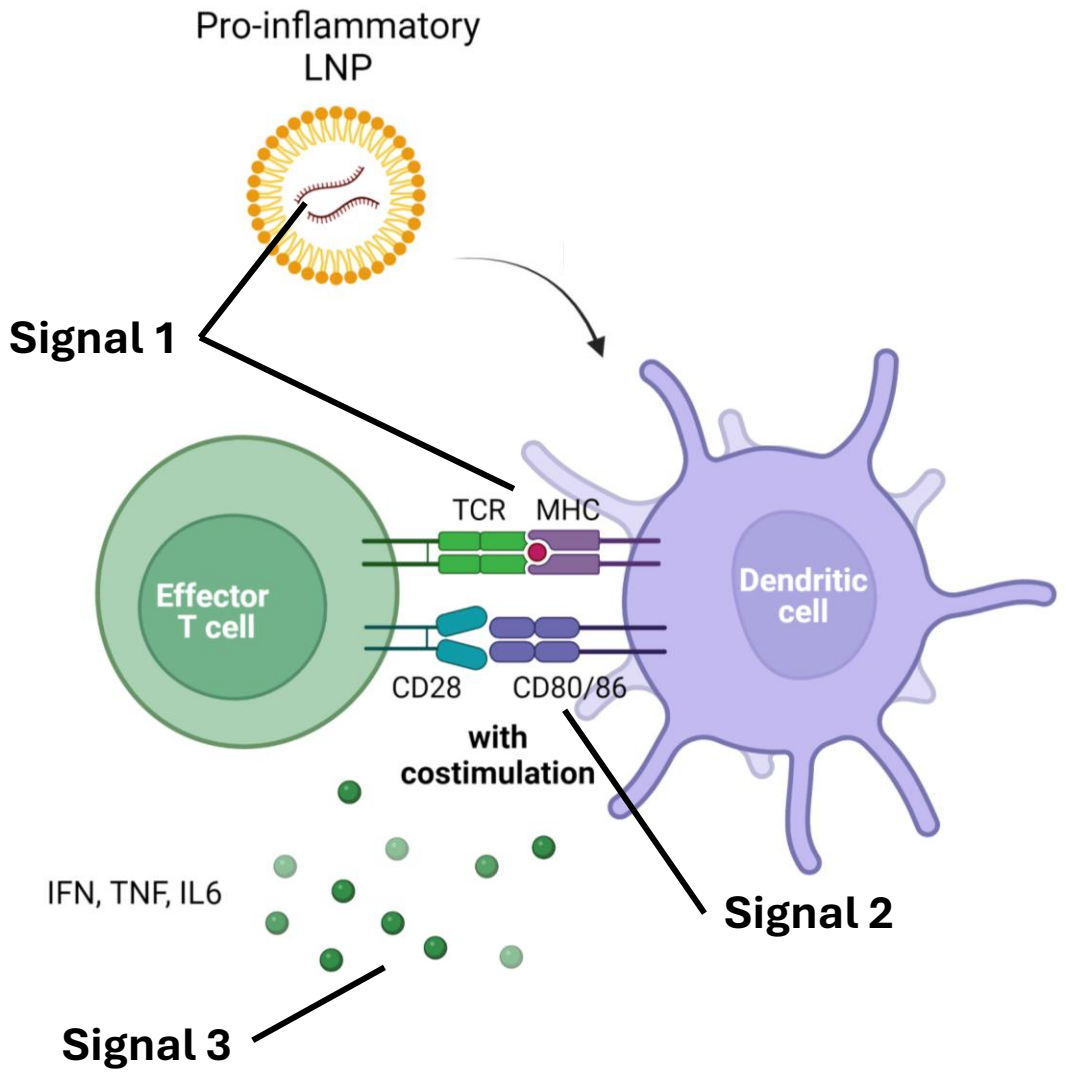


GFP mRNA-LNPs injected IV to BL/6 mice → 24 h → Spleens processed for flow cytometry

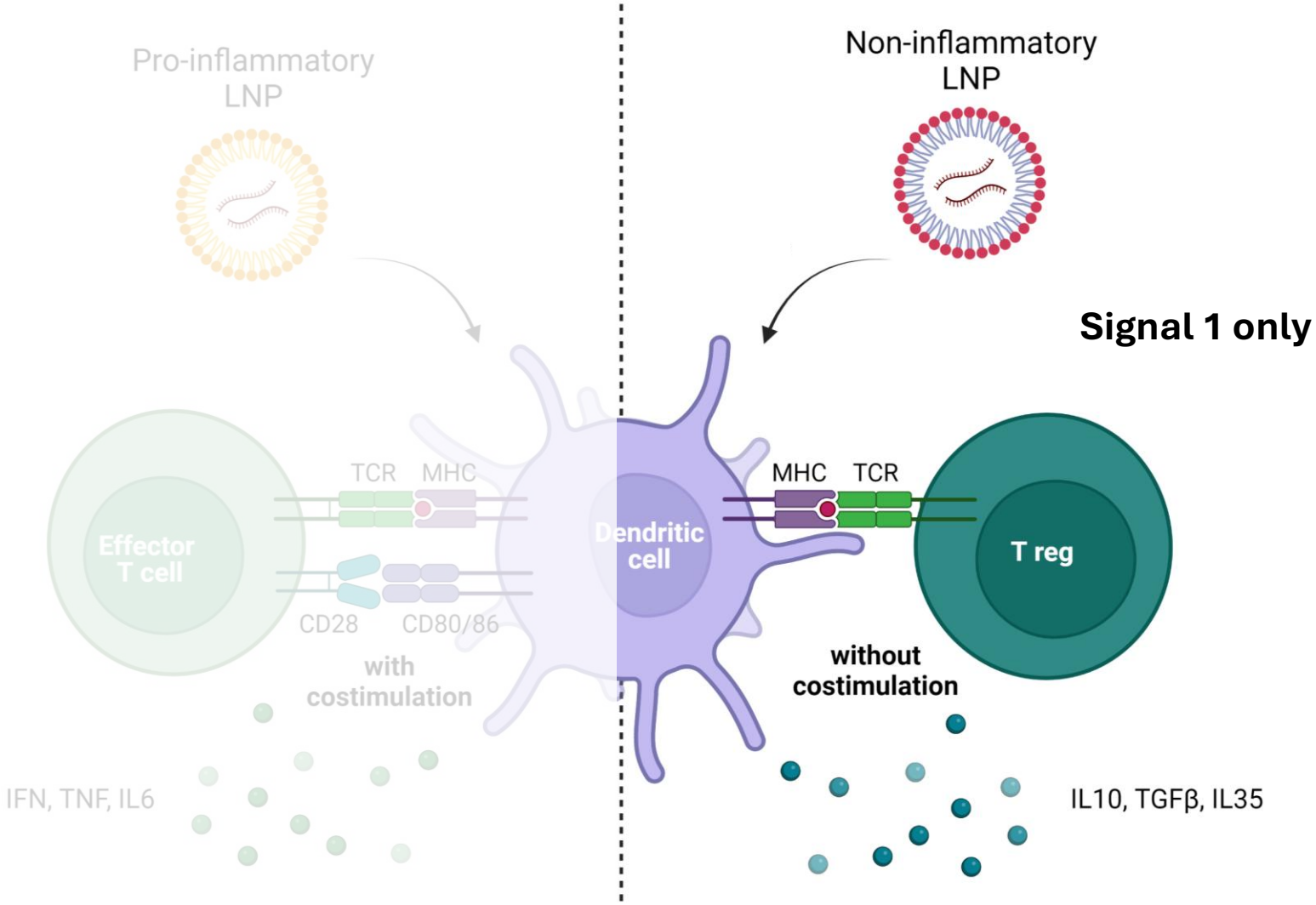


...but what is the impact on adjuvant activity?

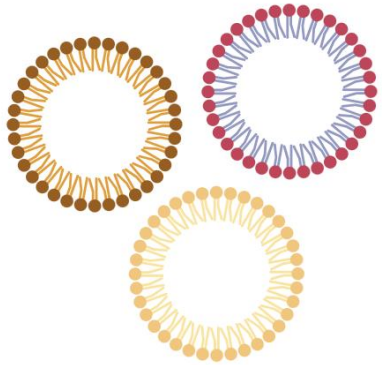
3 signals are needed to mediate adjuvant activity



The absence of inflammatory cues (signals 2 + 3) promotes immune tolerance



Evaluating mRNA-LNP delivery to immune cells and resultant adjuvant activity



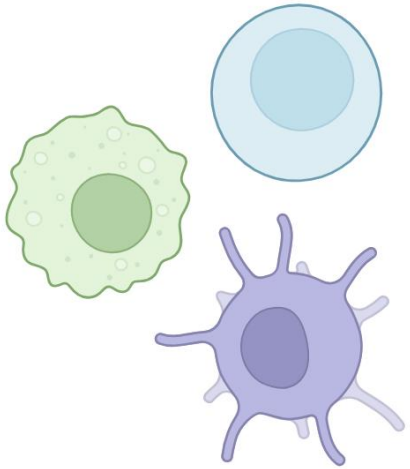
Combinatorial library of 40 LNPs, GFP mRNA

- Ionizable lipids
- Anionic lipids
- Lipid ratios

Delivered IV to C57BL/6 mice

4 h | 18 h

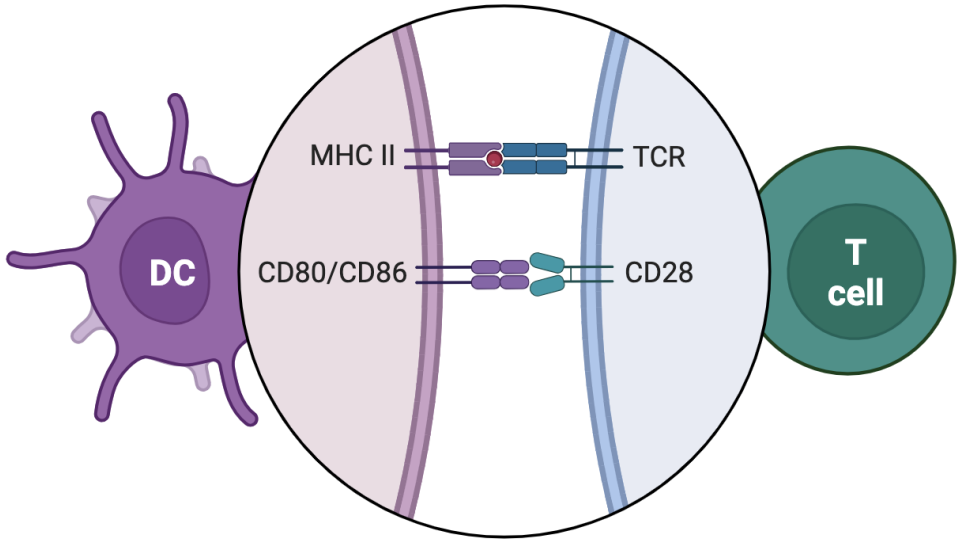
serum cytokine analysis **(Signal 3)**

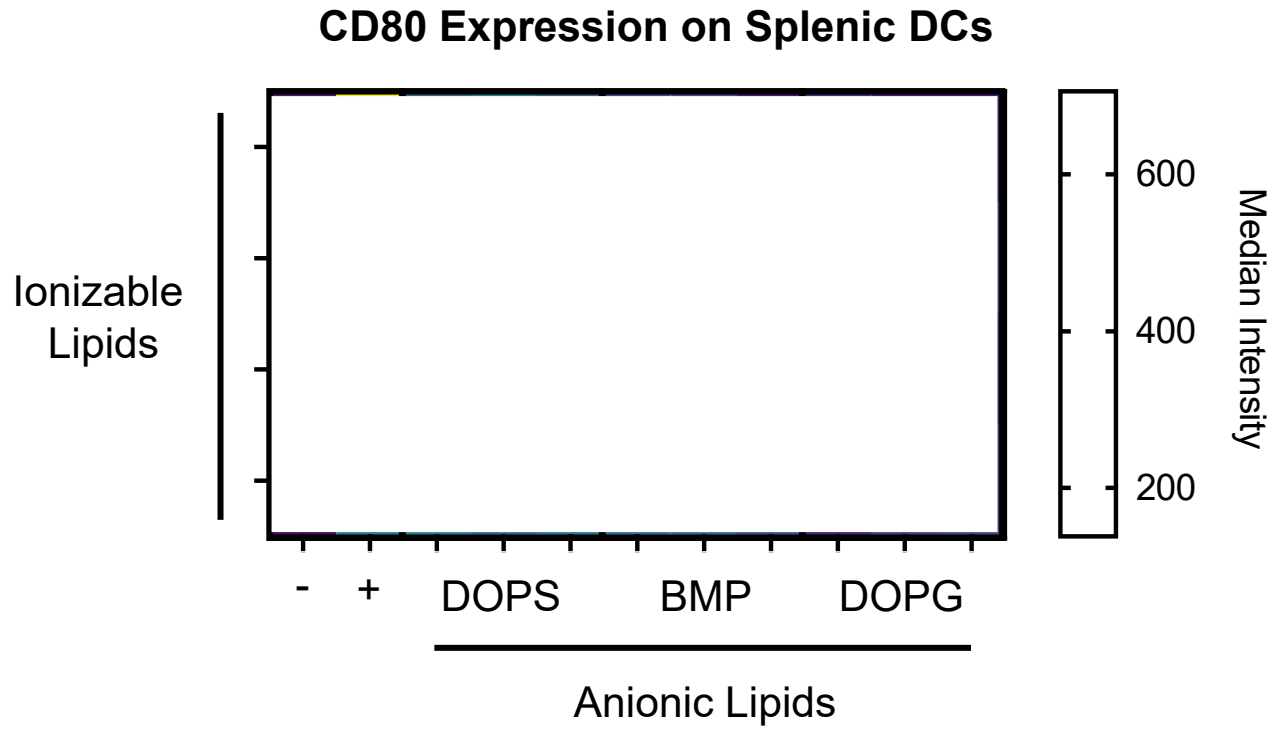


Analyze splenocytes

DC activation **(Signal 2)**

Anionic helper lipids reduce DC costimulation (Signal 2)





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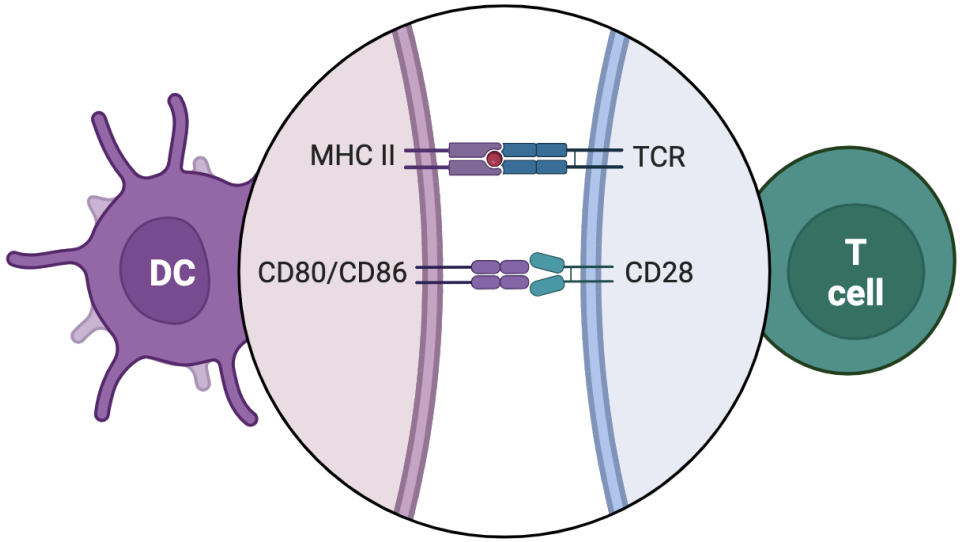

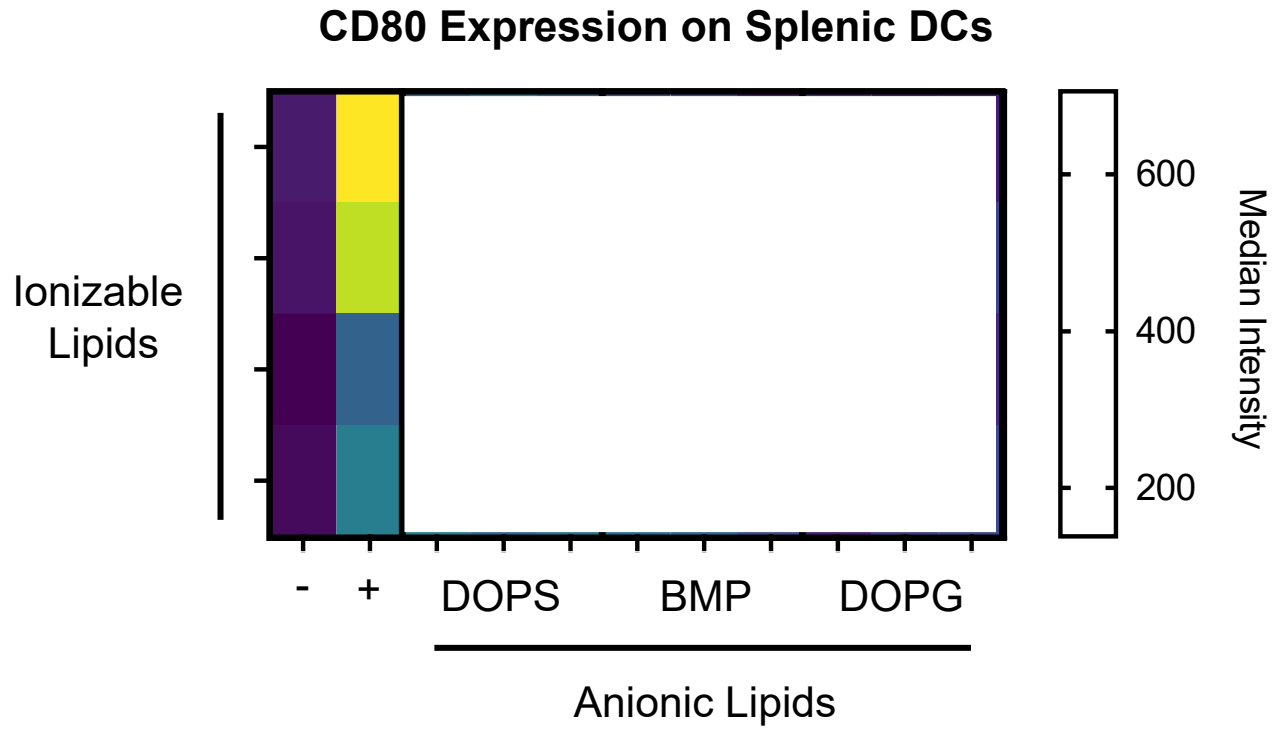

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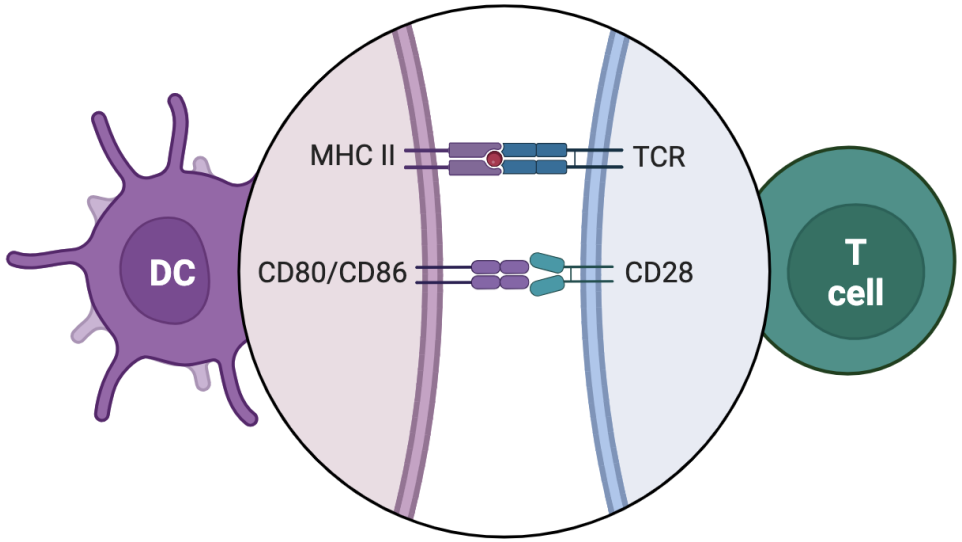
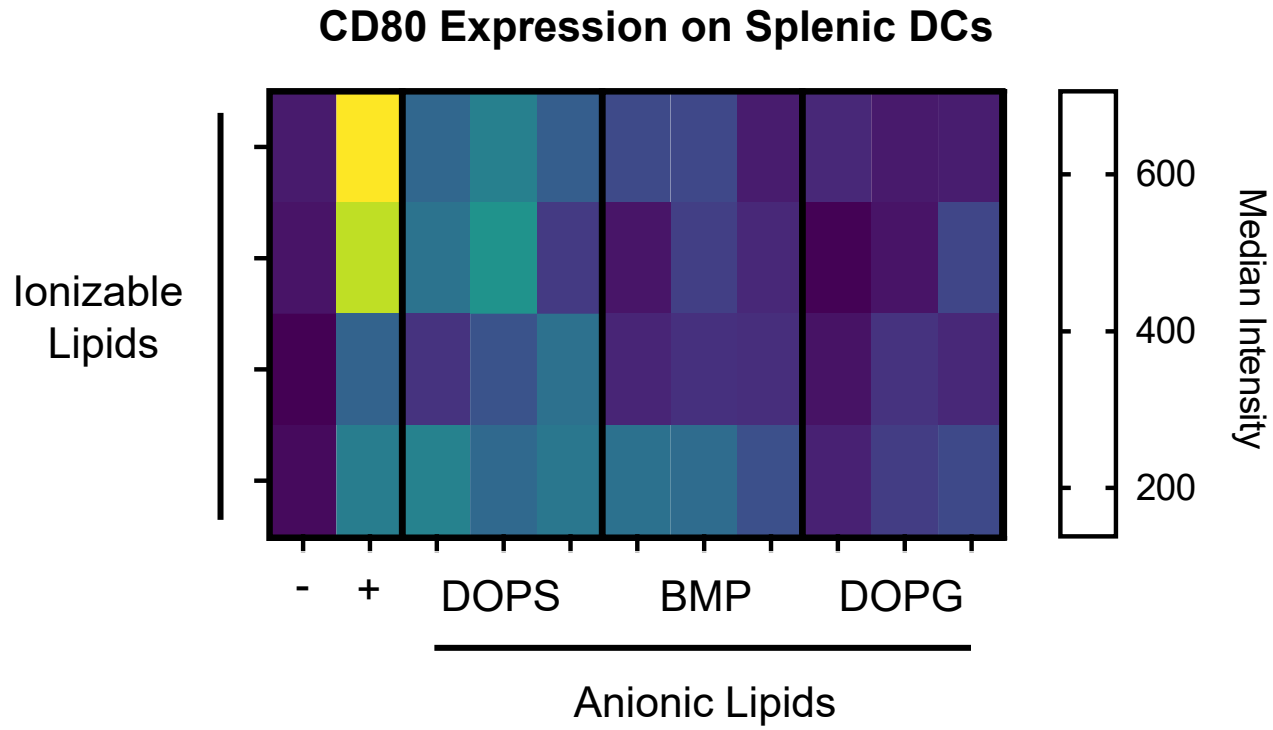
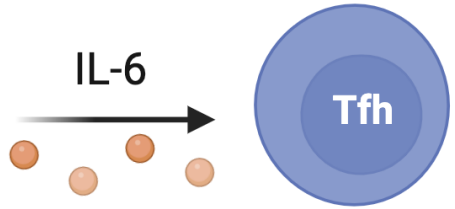
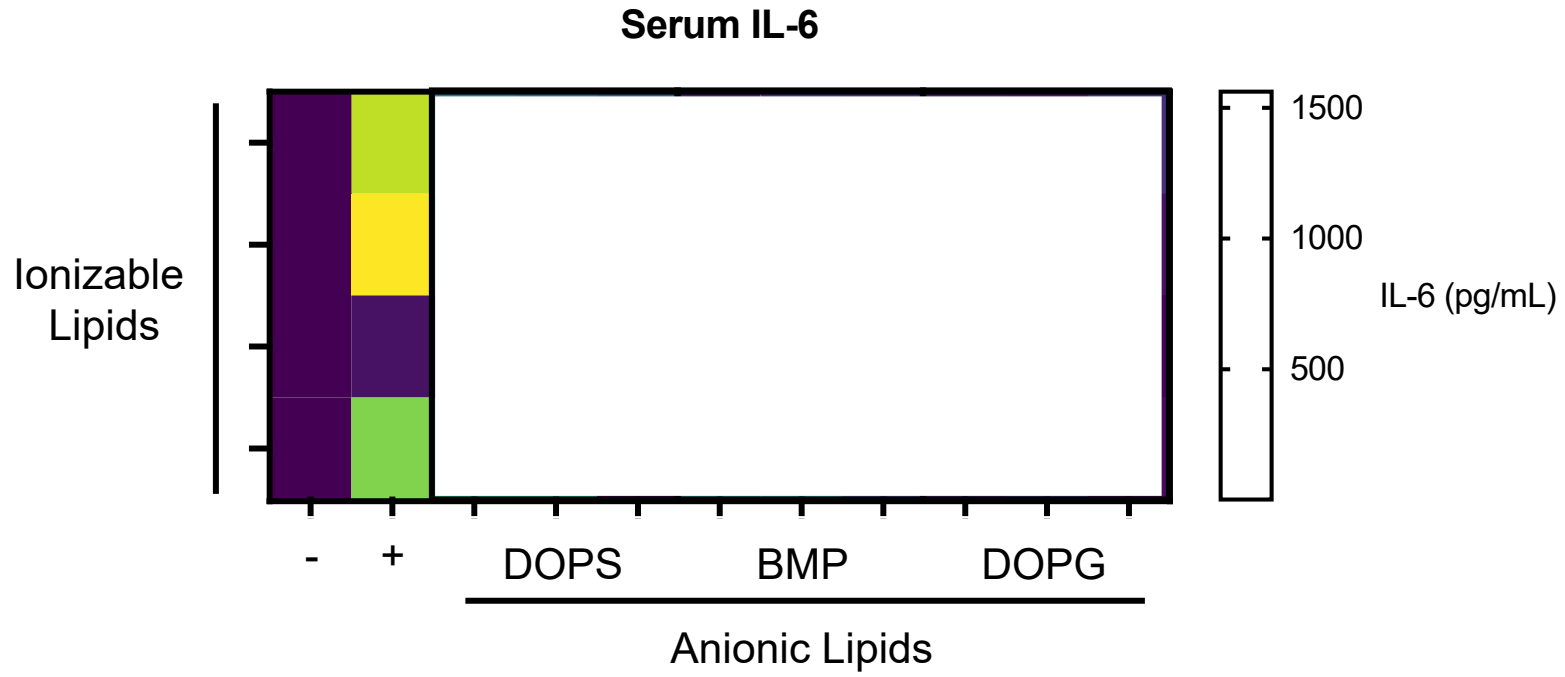




Anionic helper lipids reduce inflammatory cytokine production (Signal 3)





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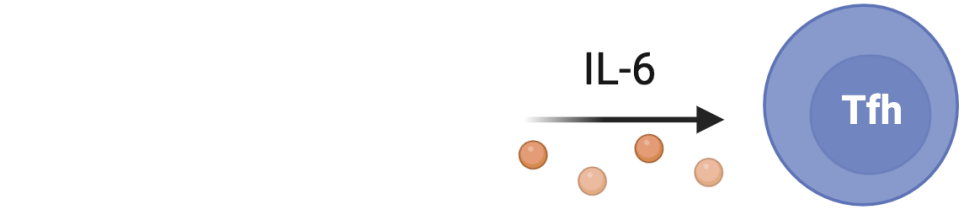
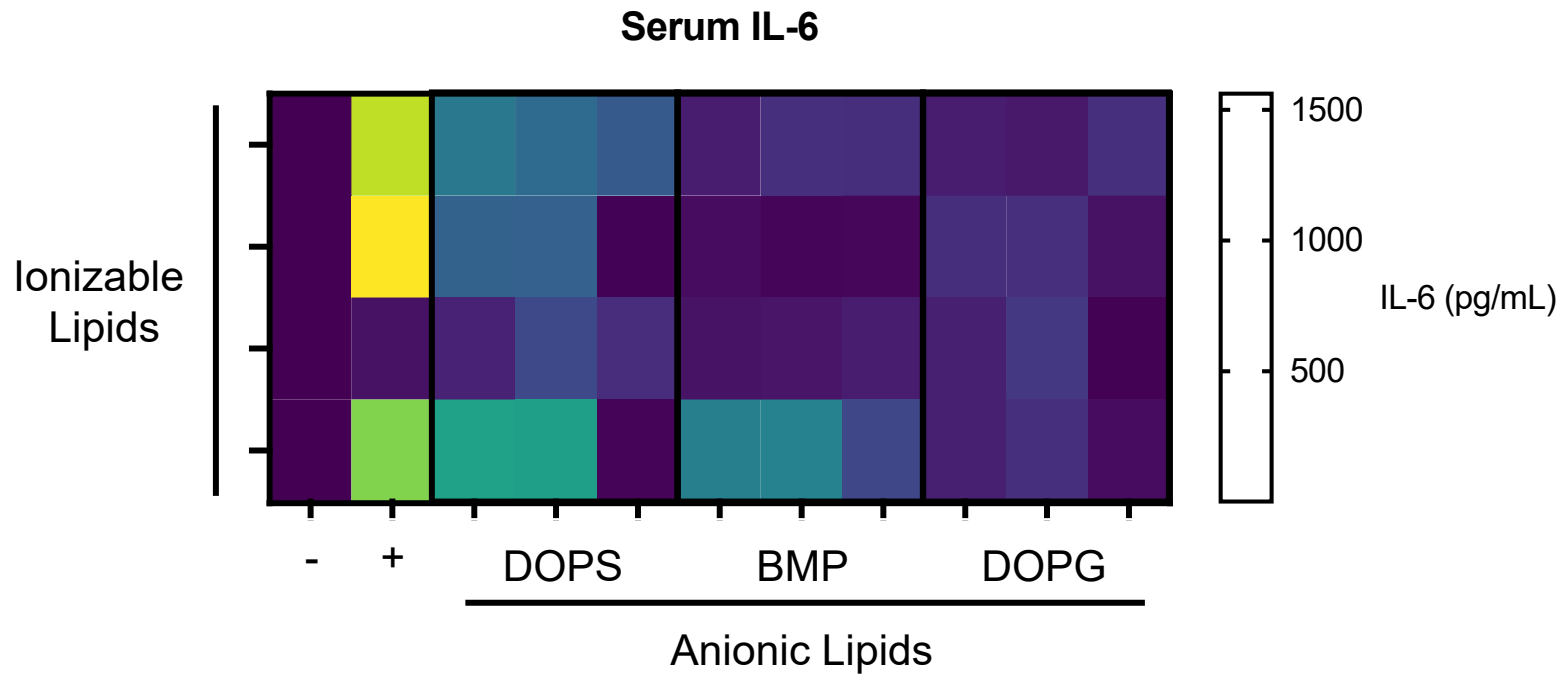
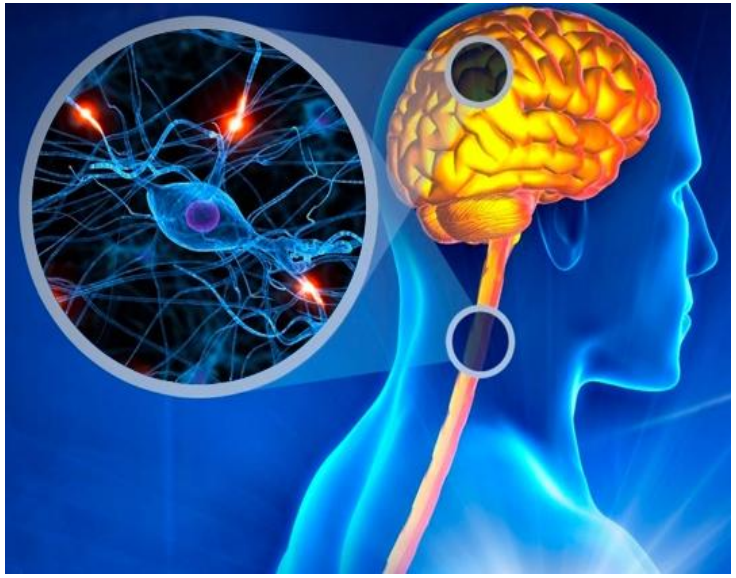


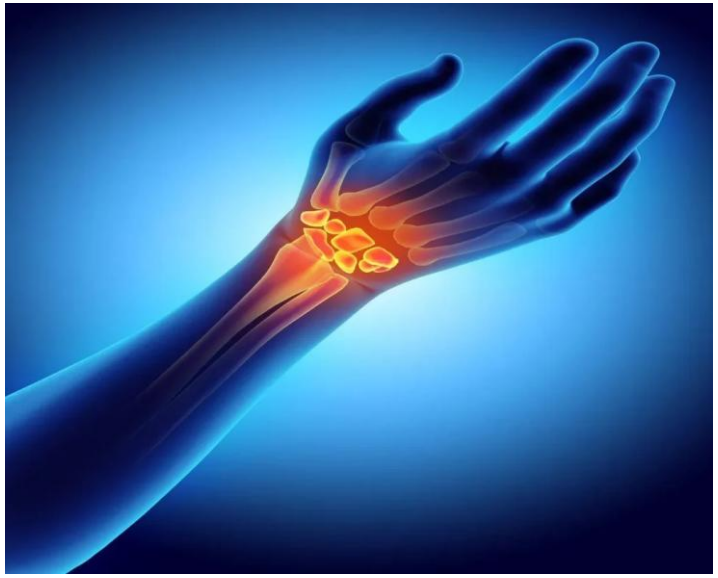


Is this sufficient to elicit tolerogenic immune responses in autoimmune disease?

Multiple Sclerosis



Rheumatoid Arthritis



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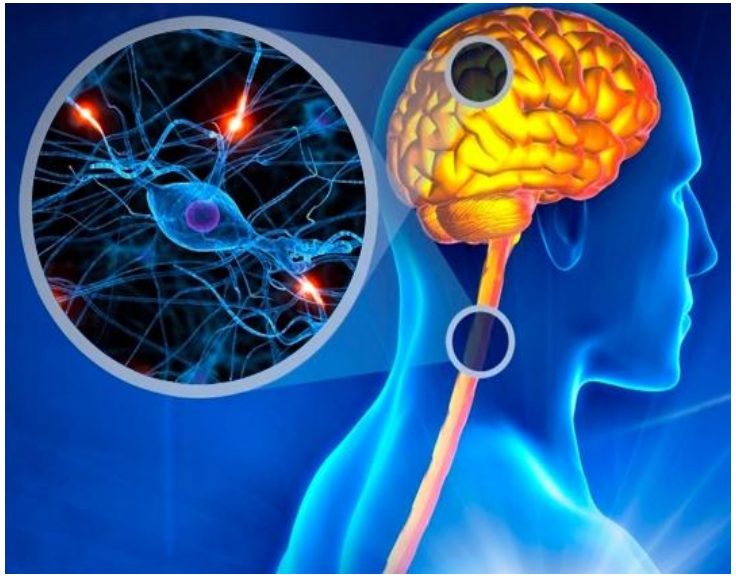
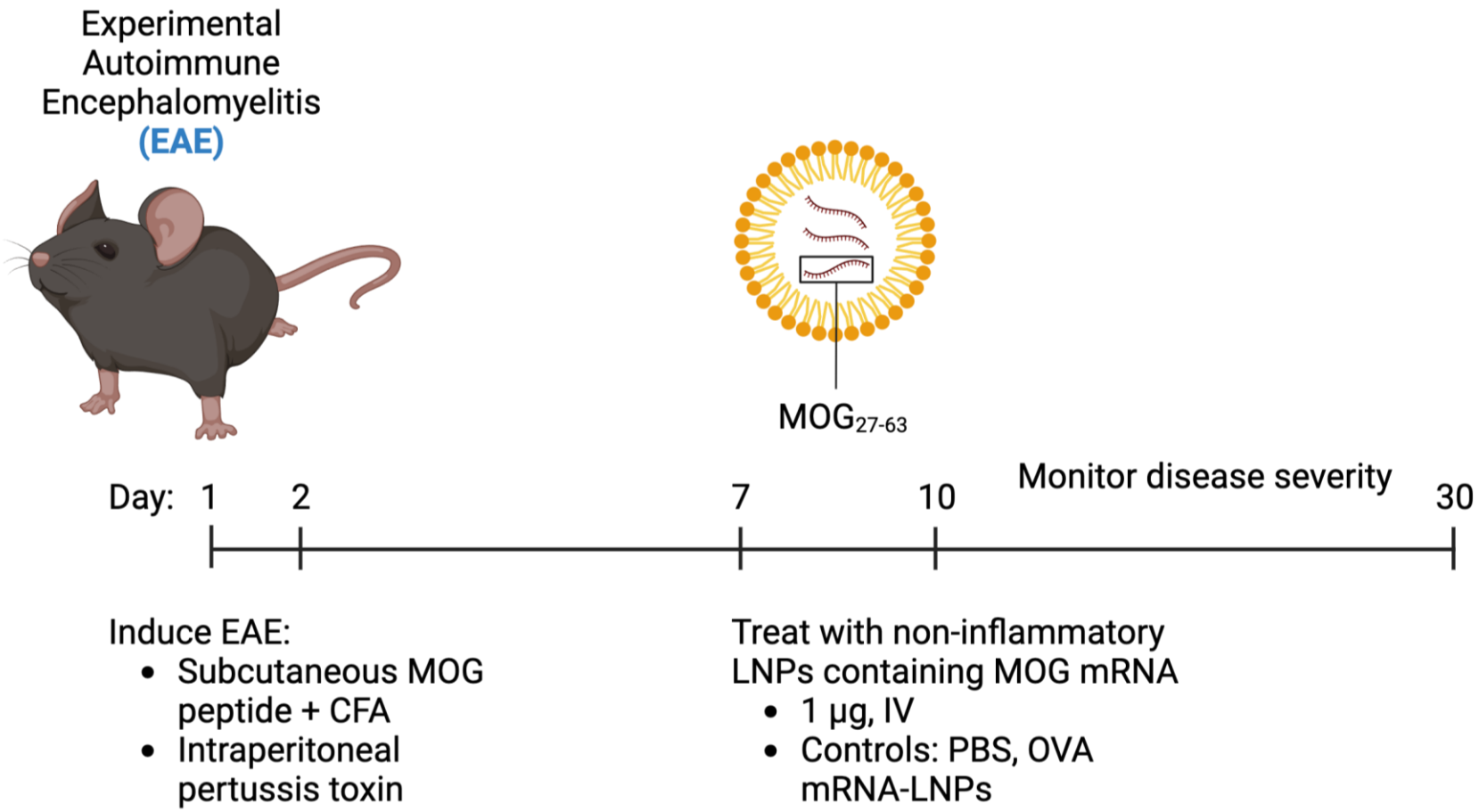


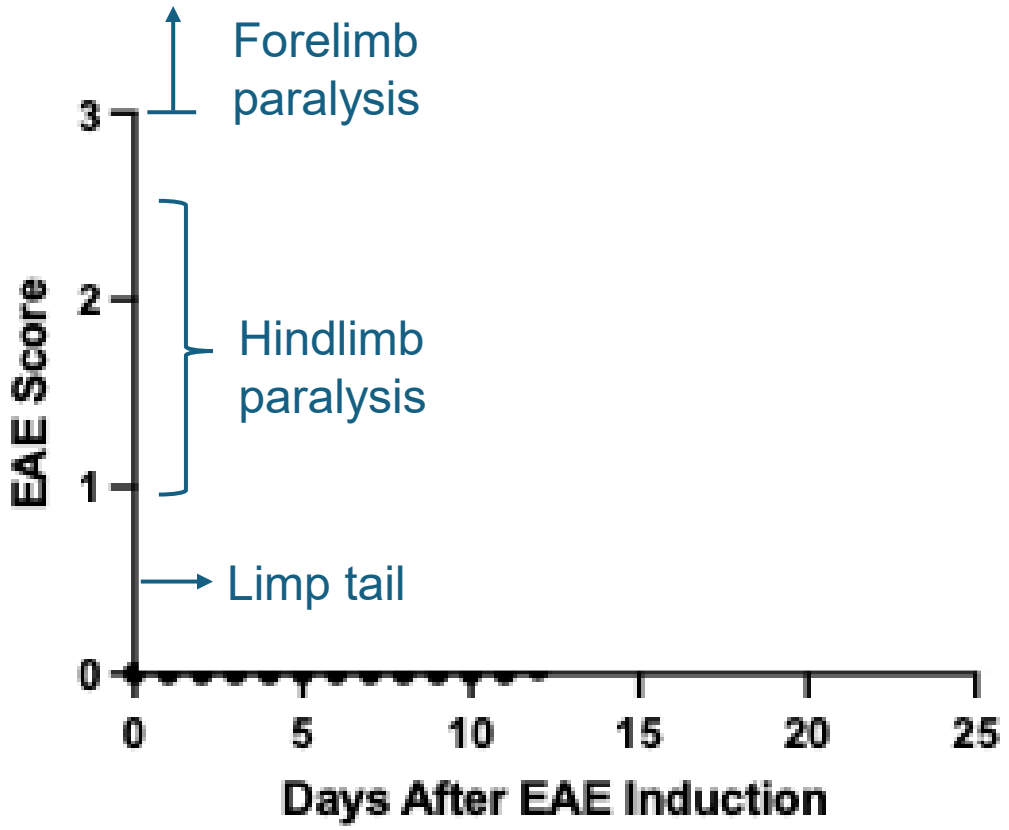
Rheumatoid Arthritis

Can non-inflammatory LNPs delivering MOG mRNA reduce severity in a mouse model of MS?



EAE mice show progressive paralysis and recovery

Scoring is performed by blinded observers



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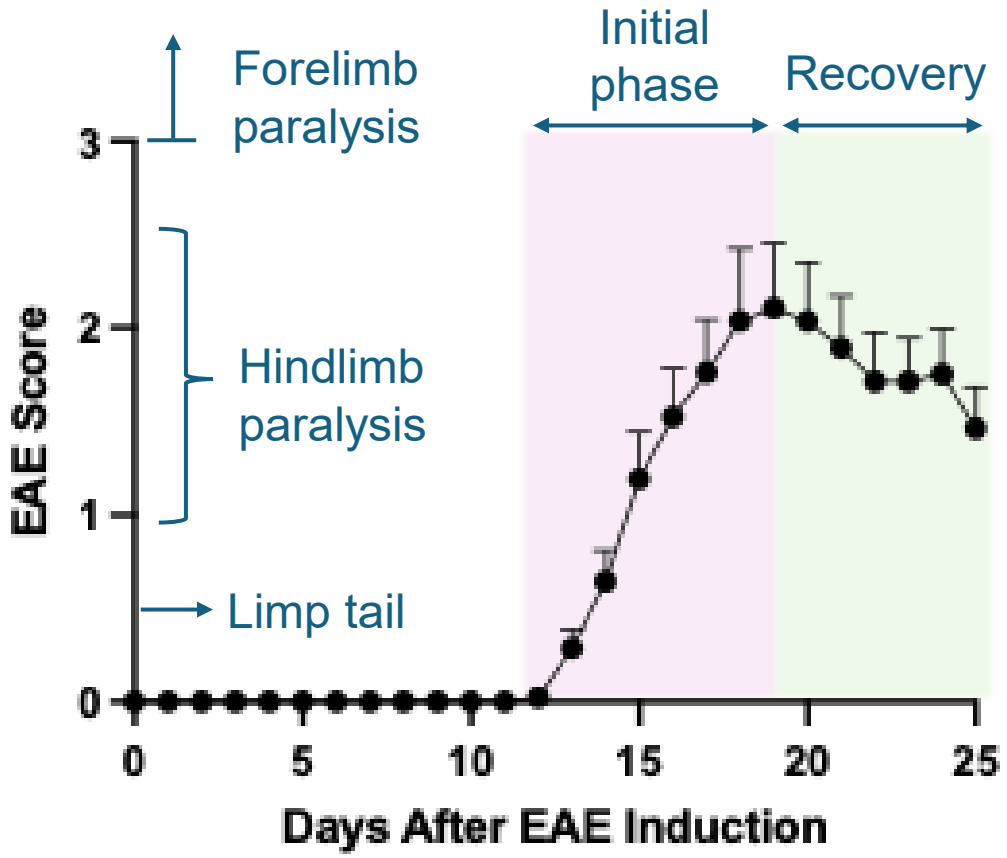
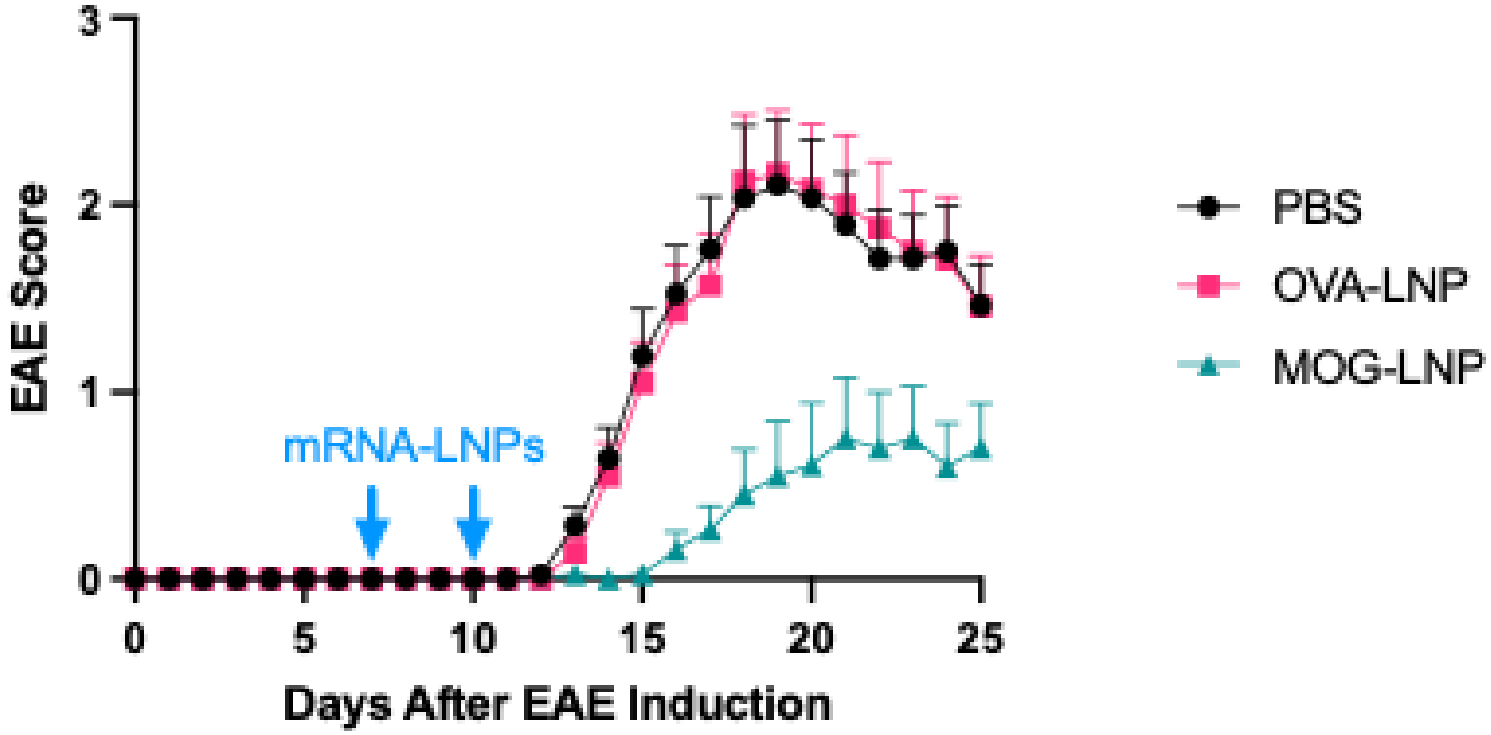


Tolerogenic MOG-LNPs reduce EAE severity



Can tolerogenic mRNA-LNPs induce protection against autoimmune disease?

Multiple Sclerosis

- Tolerogenic mRNA-LNPs show protective effects in EAE
- Simple, single antigen model

Can tolerogenic mRNA-LNPs induce protection against autoimmune disease?

Multiple Sclerosis

- Tolerogenic mRNA-LNPs show protective effects in EAE
- Simple, single antigen model

Rheumatoid Arthritis

Universiteit Utrecht

Dr. Femke Broere

Dr. Naomi Benne

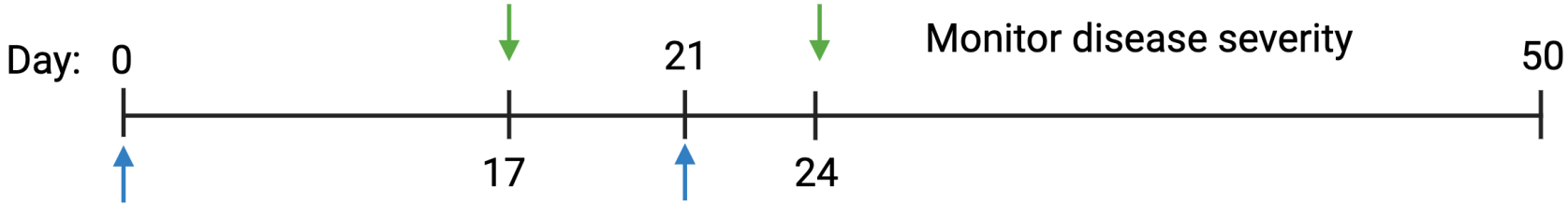
Can non-inflammatory LNPs delivering mB29a mRNA reduce severity in a mouse model of RA?

Proteoglycan-induced arthritis **(PGIA)**

Treat with non-inflammatory LNPs containing mB29a mRNA

- 0.5 µg, IV
- Controls: saline, OVA mRNA-LNPs

mB29a = HSP70-derived peptide

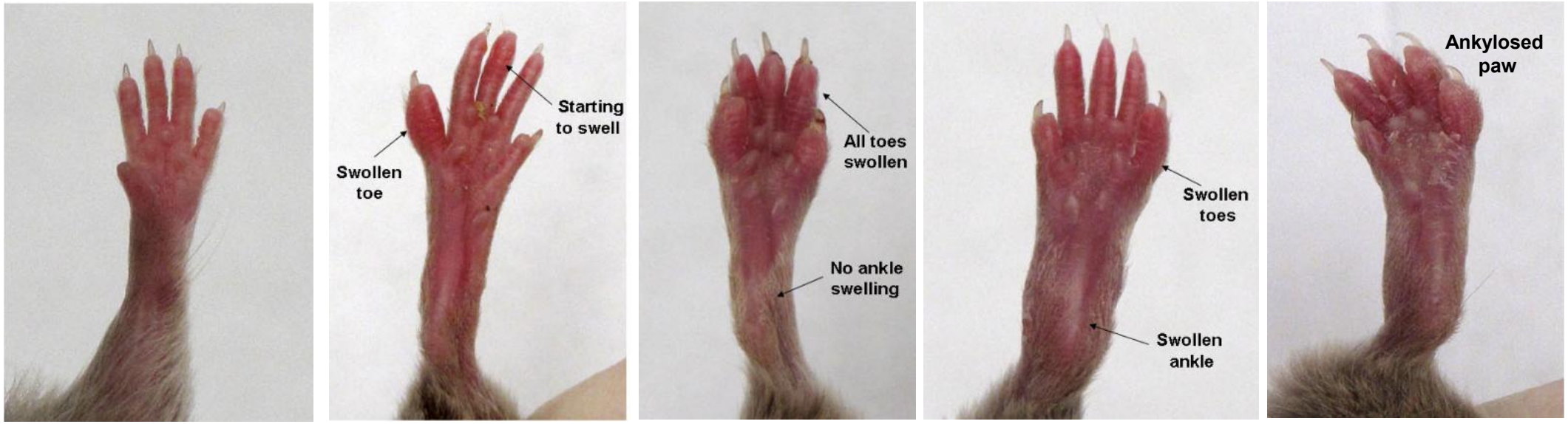


Induce PGIA:

- Intraperitoneal proteoglycan/DDA

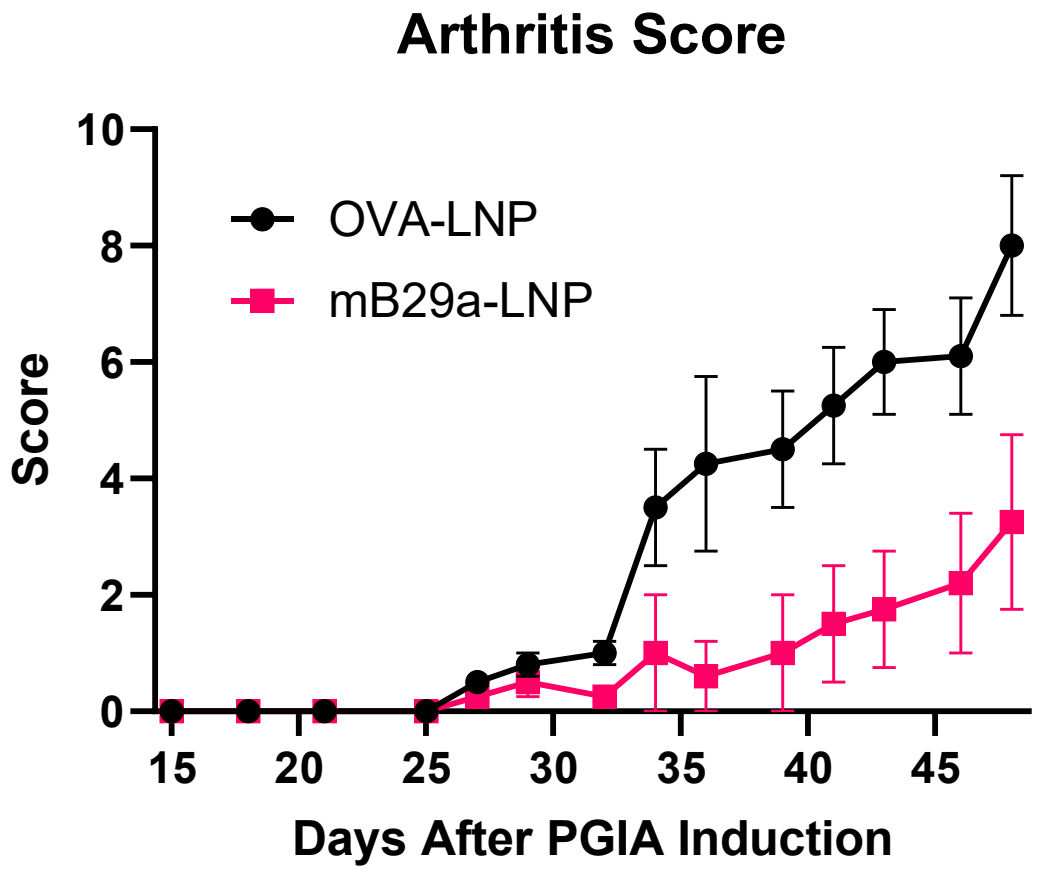
PGIA severity is scored based on paw appearance

Score: 0 1 2 3 4



Scores for all 4 paws are added
Max score = 16

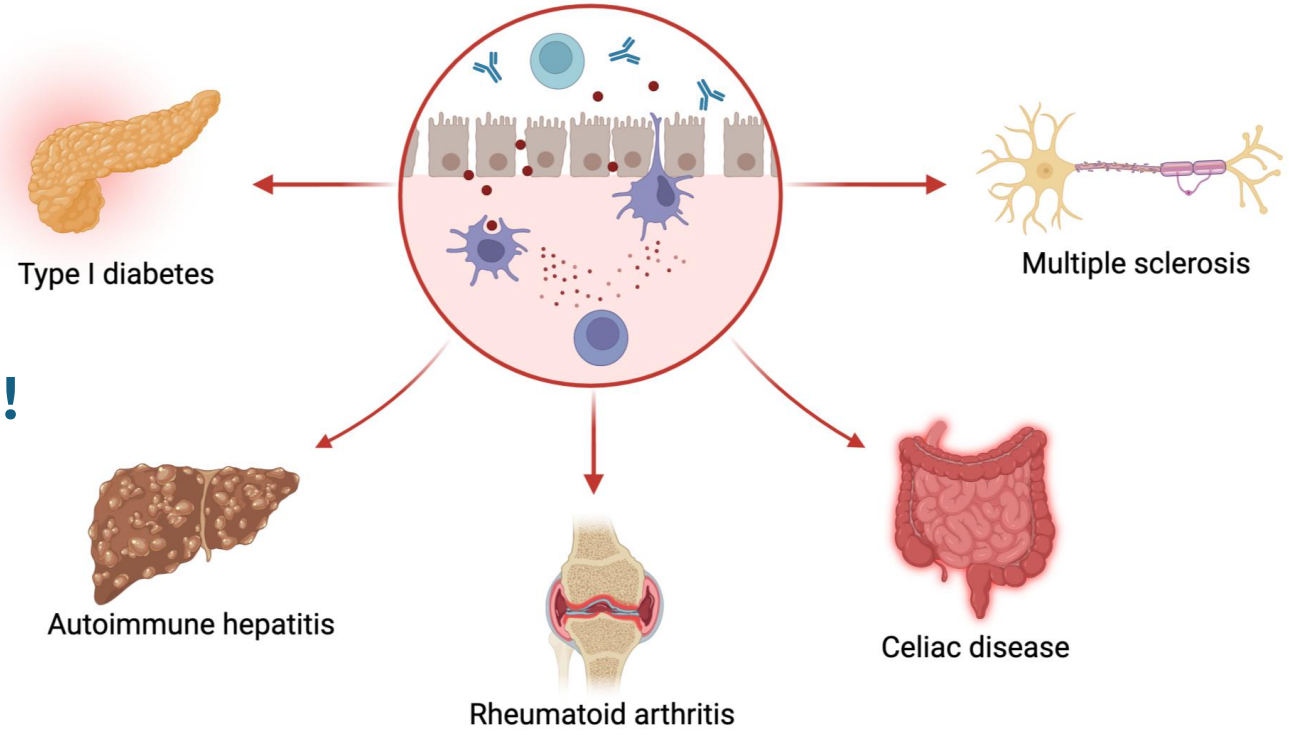
Tolerogenic mB29a-LNPs reduce PGIA severity



Anionic SORT LNPs can reduce disease severity in models of autoimmune disease

- Depends on lipid composition
  - Ionizable lipid
  - Anionic lipid

- Additional considerations and lessons learned: **everything matters!**
  - LNP formulation strategy, size
  - Dose
  - Injection route
  - **What works for one disease isn't necessarily the best for others**



Acknowledgements

Weissman Lab

Jenna Muscat-Rivera
Michael Kegel
Rose Razavi
Si-Han Wu
Lesley Chaboub
Roxanne Perez Tremble
Drew Weissman

Honghong Sun

Utrecht University

Deja Porenta
Naomi Benne
Arjan Stoppelenburg
Femke Broere

Cincinnati Children's Hospital

Yrina Rochman
Marc Rothenberg

Penn Medicine | Institute for RNA Innovation

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