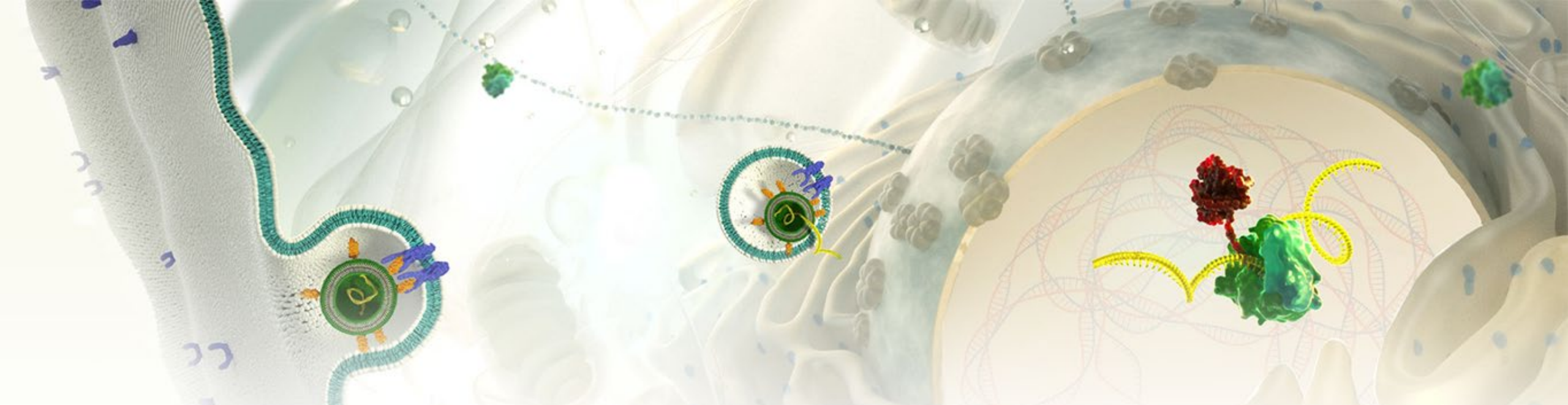


Development of LNP for mRNA Cancer Immunotherapy

Ghania Chikh

23 April 2025

WVC-2025

ACUITAS THERAPEUTICS

LNP Technology:

Clinically Validated

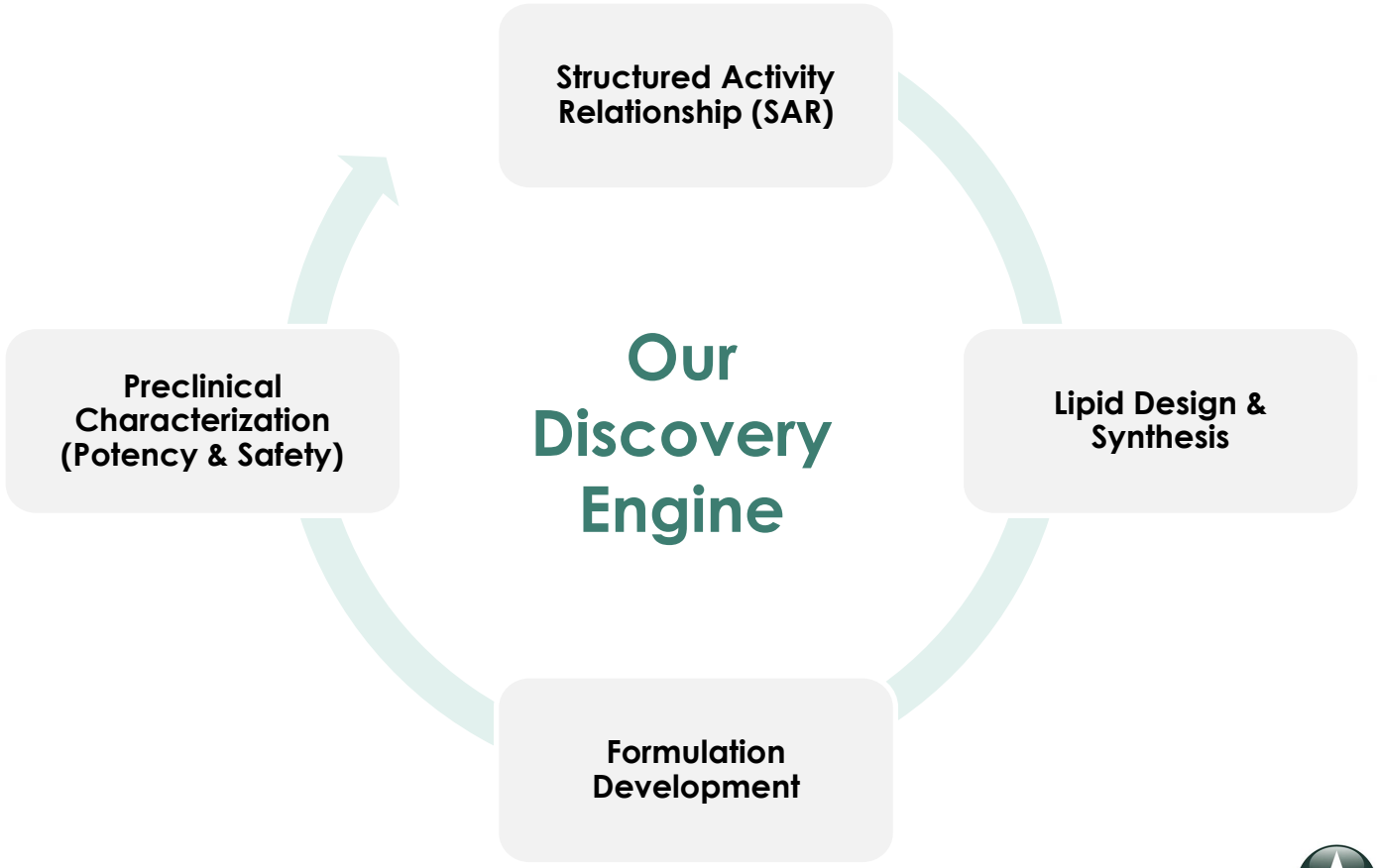
- Acuitas LNP formulation used in ONPATTRO® (Alnylam partnership)
  - First Approved RNAi product (2018)
  - Approved in Canada, US, EU, Japan & elsewhere

- Acuitas LNP formulation used in Comirnaty® (BioNTech/Pfizer partnership)
  - Emergency authorization in Canada, US, EU, UK and elsewhere (2020)
    - First approved mRNA therapeutic (2021)

ACUITAS THERAPEUTICS

Our Approach to Innovation

- Iterative approach to identify novel lipids and favorable LNP properties
- Enhance potency and safety profile for LNP carriers
- Enable broad range of mRNA therapeutic applications



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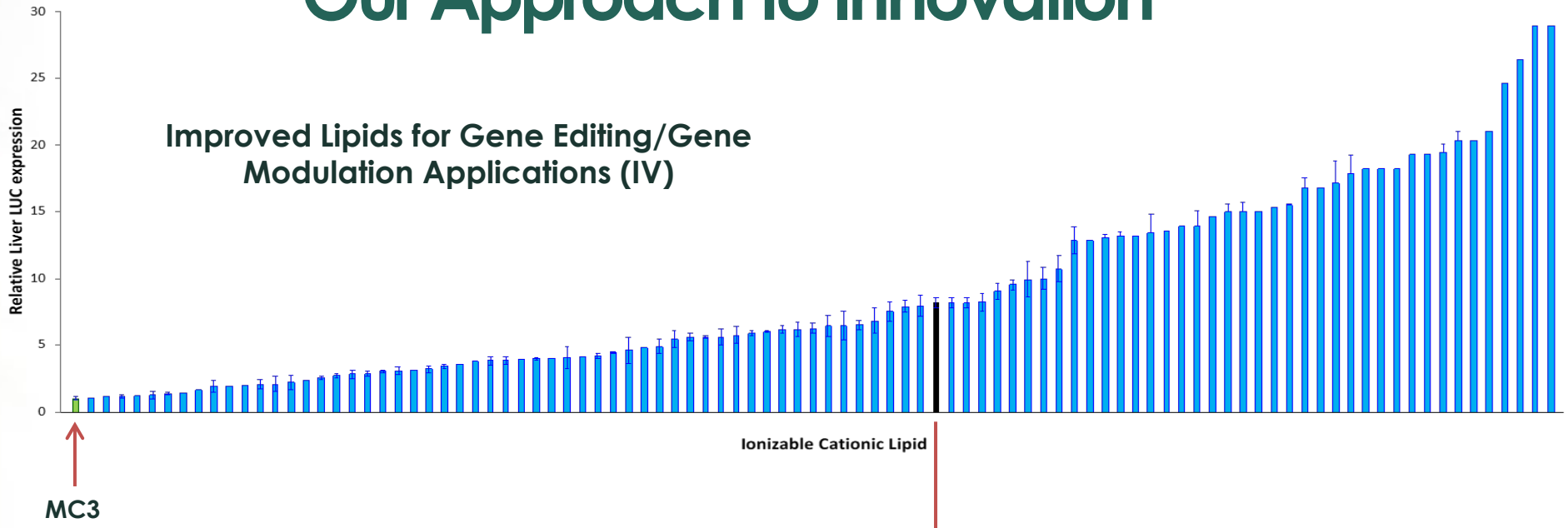
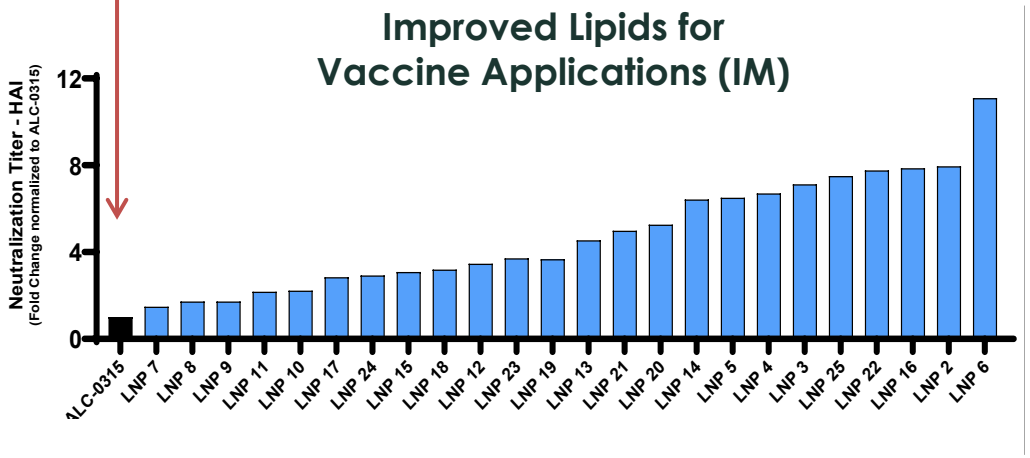
Our Approach to Innovation



Enhanced potency enables partner programs across a broad range of therapeutic applications



- Screening program combined with key SAR relationship analysis results in substantial improvement in LNP potency.

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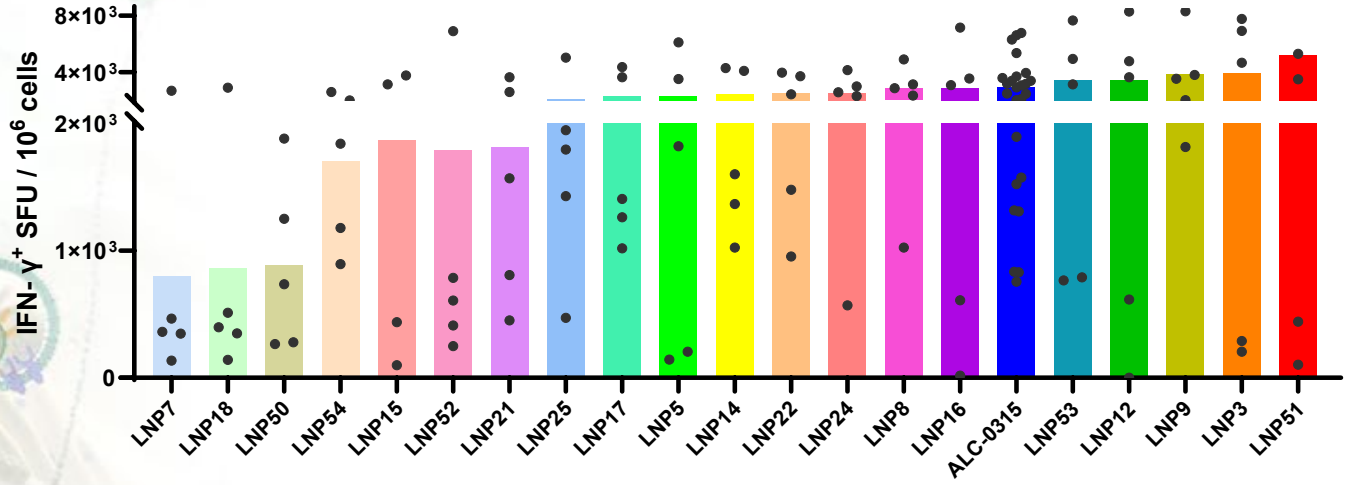
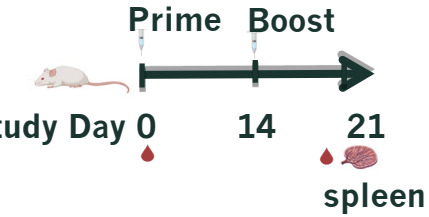
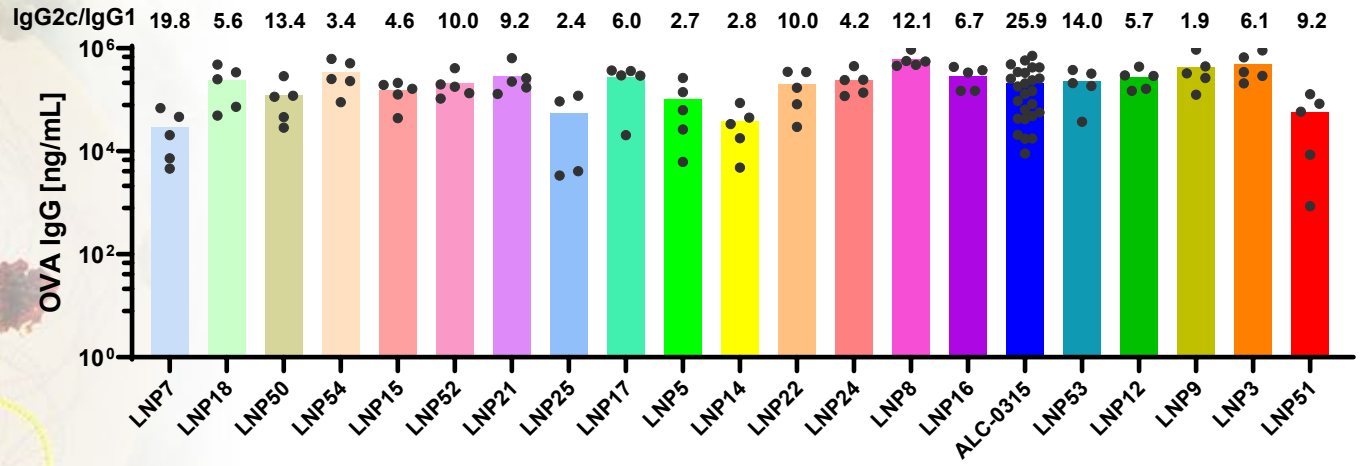
LNP screening for IM mRNA Cancer Immunotherapy







- Several rationally selected ionizable lipids induced potent cellular response, including ALC-0315 used in COMIRNATY®.
- A strong Th1 bias humoral response was induced.

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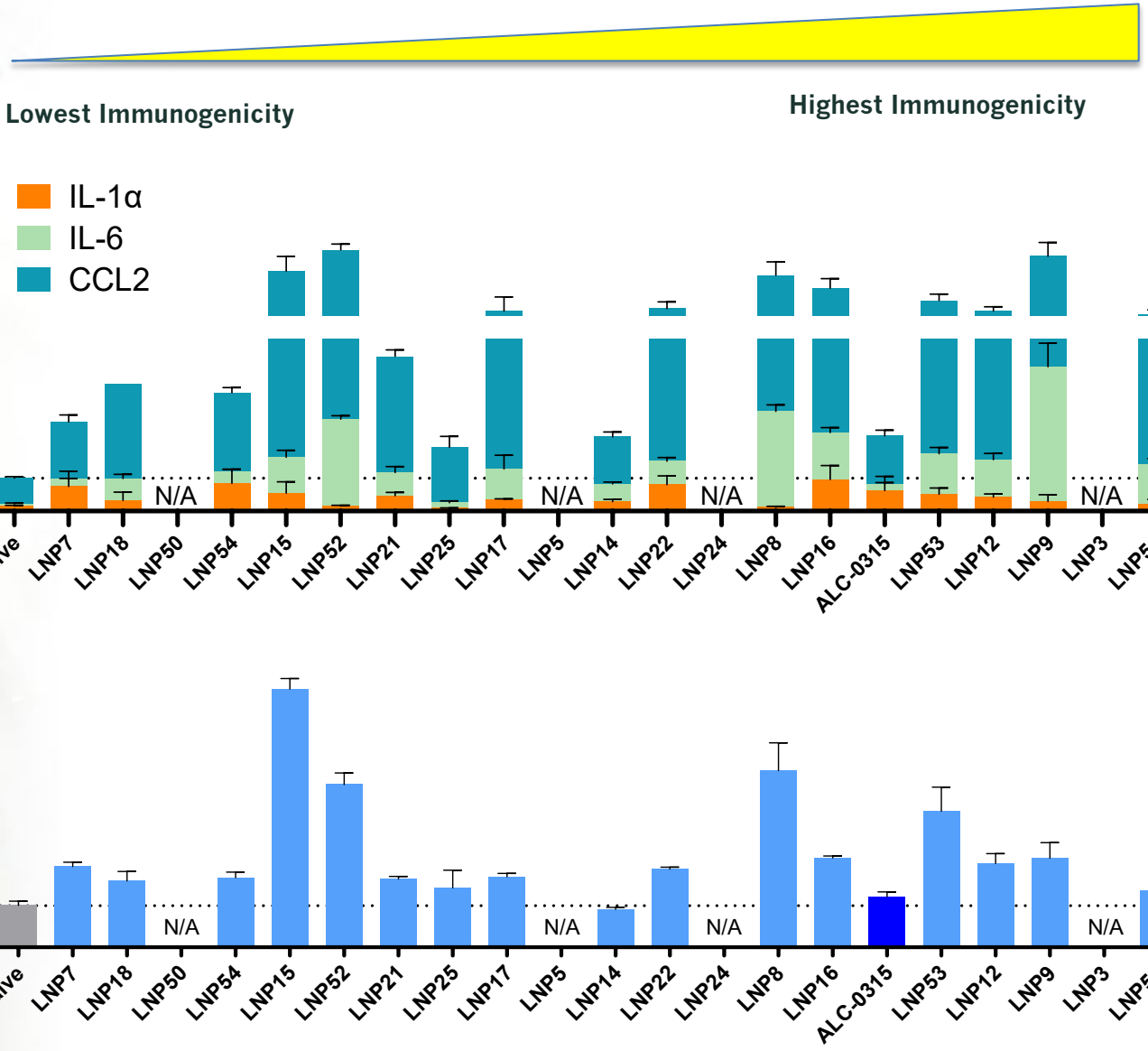
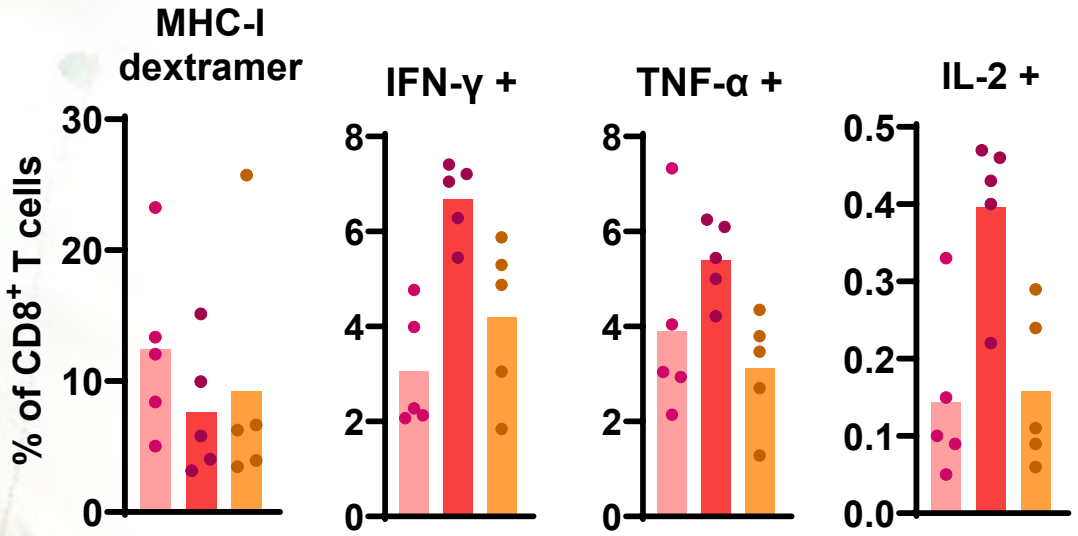
Innate Immune stimulation by LNP-mRNA Cancer Immunotherapy



- No correlation between adaptive immune response to vaccine and innate immune stimulation

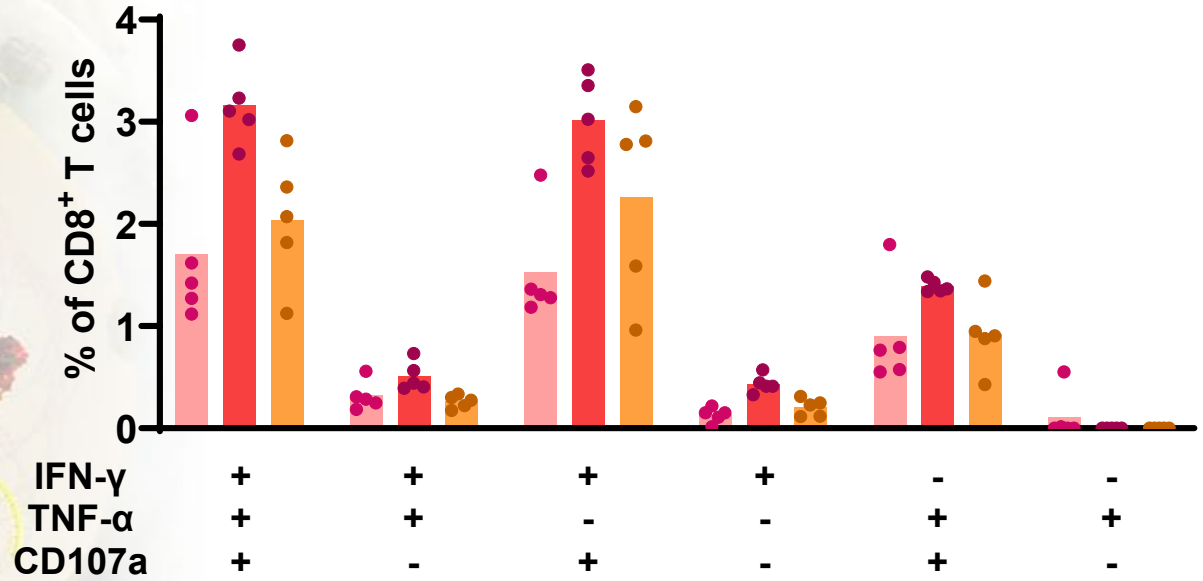
LNP Development for mRNA Cancer Immunotherapy

Dose Response



ALC-0315, mod. mRNA)

- 1 µg
- 10 µg
- 20 µg



- Equivalent magnitude of CD8 T cells quantified by dextramer staining
- 10 µg dose induced the highest polyfunctional cells as measured by IFN-γ, TNF-α, and lytic potential

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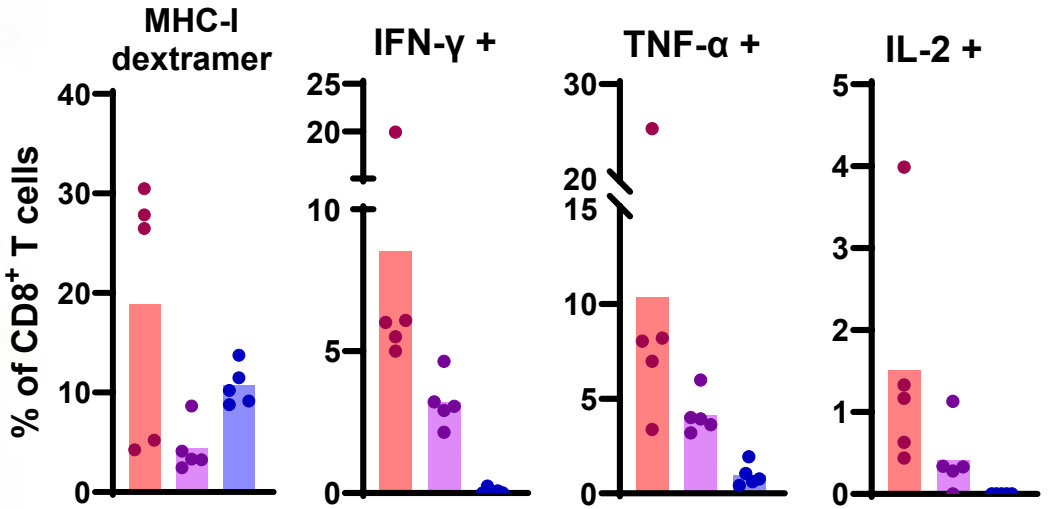
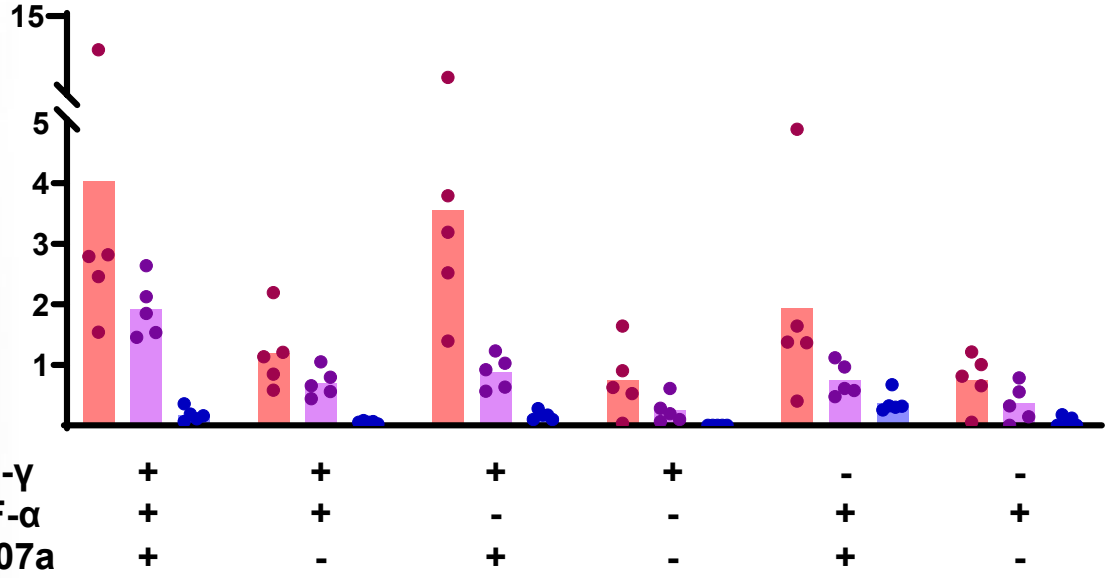
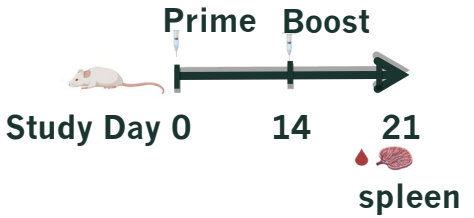
LNP Development for mRNA Cancer Immunotherapy

Uridine-based mRNA & comparison to lipoplex







- ALC-0315 + unmod. RNA (10μg, im)
- ALC-0315 + mod. RNA (10μg, im)
- LPX + unmod. RNA (30μg, iv)

- Unmod. mRNA induced higher frequency and functional antigen specific CD8 T cells than mod. mRNA.
- Despite high CD8 T cell frequency, lipoplex failed to induce active T cell response based on cytokine secretion and lytic activity marker.

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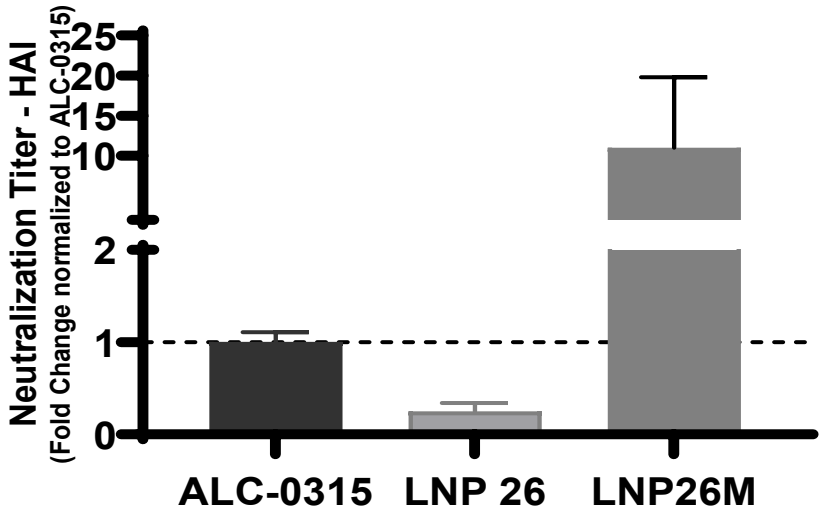
LNP Development for mRNA Cancer Immunotherapy

Optimisation of LNP Physical & chemical Characteristics for Improved Potency



- Optimizing biophysical & biochemical characteristics of LNP led to significantly higher immunogenicity

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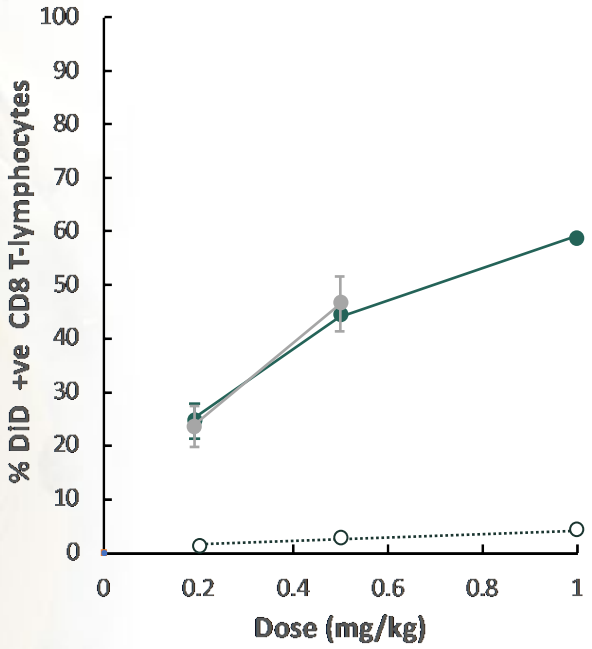
LNP Development for mRNA Cancer Immunotherapy

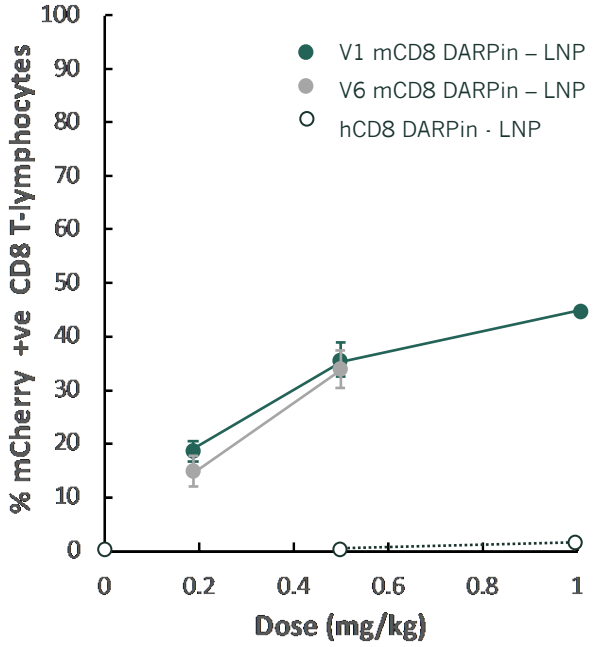
APCs Targeting for Improved Potency

Active targeting Proof of concept: Target cell binding and reporter gene expression

LNP binding



Reporter gene expression



- CD8 DARPin targeted mRNA LNP show dose depending, target specific binding and transgene expression in CD8 lymphocytes

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Summary

- Acuitas' LNP are promising candidates for cancer immunotherapy development:
  - Several lipids were identified to induce potent CD8 T cell response with a strong Th1 bias humoral response, including ALC-0315 used in COMIRNATY®.
- Significantly higher CD8 T cell response was obtained with unmodified mRNA compared to modified mRNA.
- Compared to lipoplex, LNP @ 1/3rd of the dose elicited comparable or better cellular response.
- LNP induced differential innate immune stimulation profiles which were not correlated with adaptive immune response to vaccine.
- Future development includes:
  - Identify Acuitas LNP that can break tolerance and inhibit tumor growth using syngeneic neoantigen model
  - Optimize LNP biophysical & biochemical characteristics; develop LNP targeted to APCs for increased cancer vaccine potency.
  - Further SAR modeling to identify lipid structures favorable for therapeutic cancer vaccine.

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