



# Development of LNP for mRNA Cancer Immunotherapy

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# LNP Technology:

## Clinically Validated



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

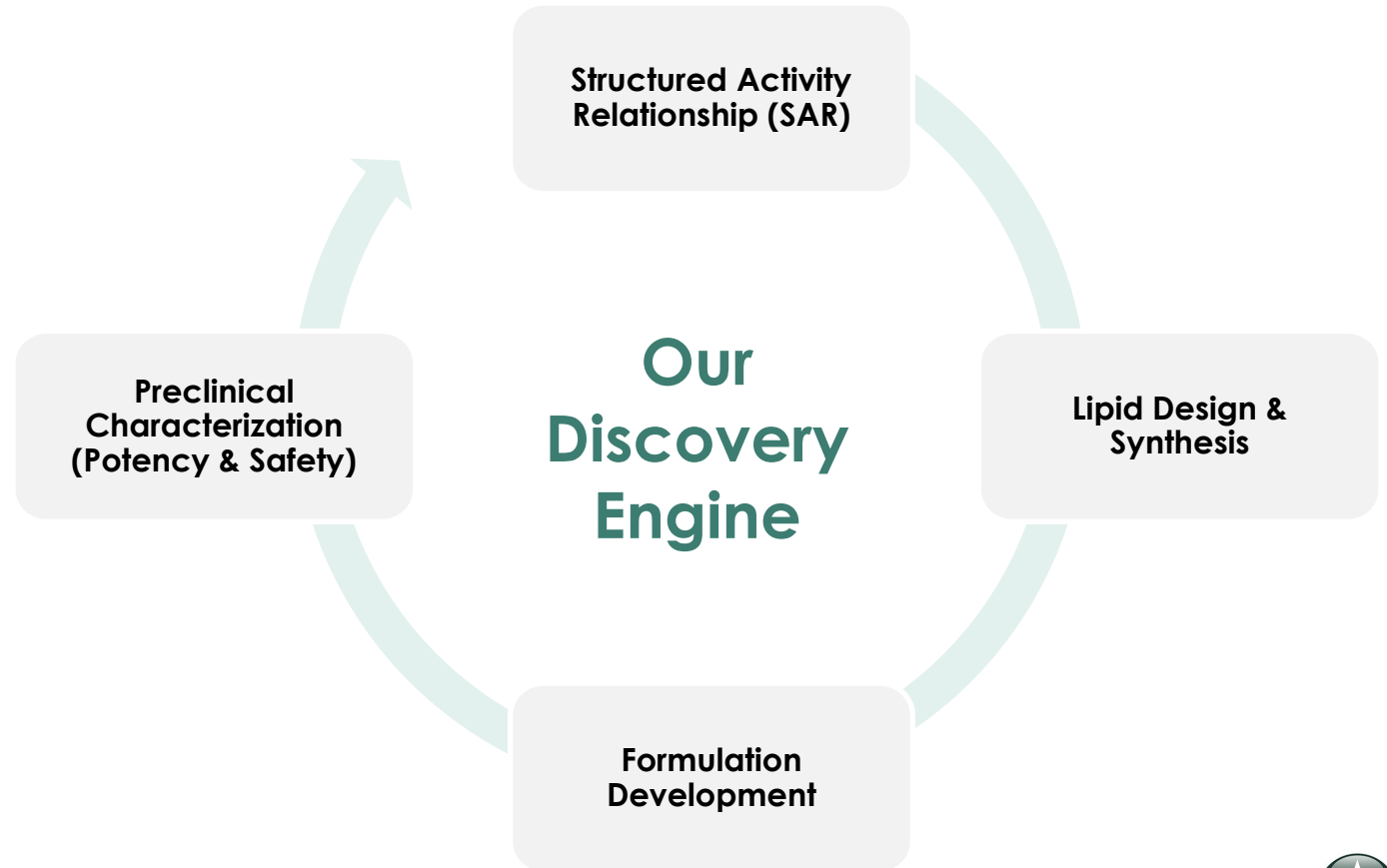
- Acuitas LNP formulation used in Comirnaty®  
(BioNTech/Pfizer partnership)

- Emergency authorization in Canada, US, EU, UK and elsewhere (2020)
- First approved mRNA therapeutic (2021)



# 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





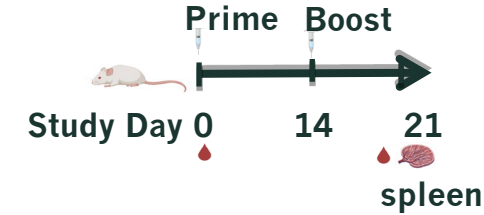
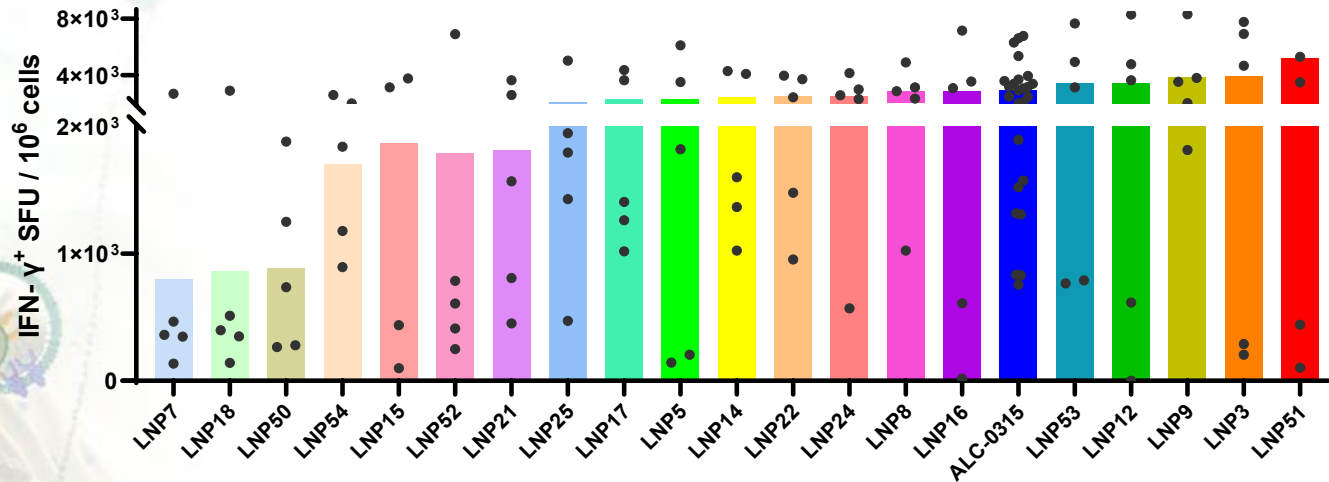
### Ionizable Cationic Lipid



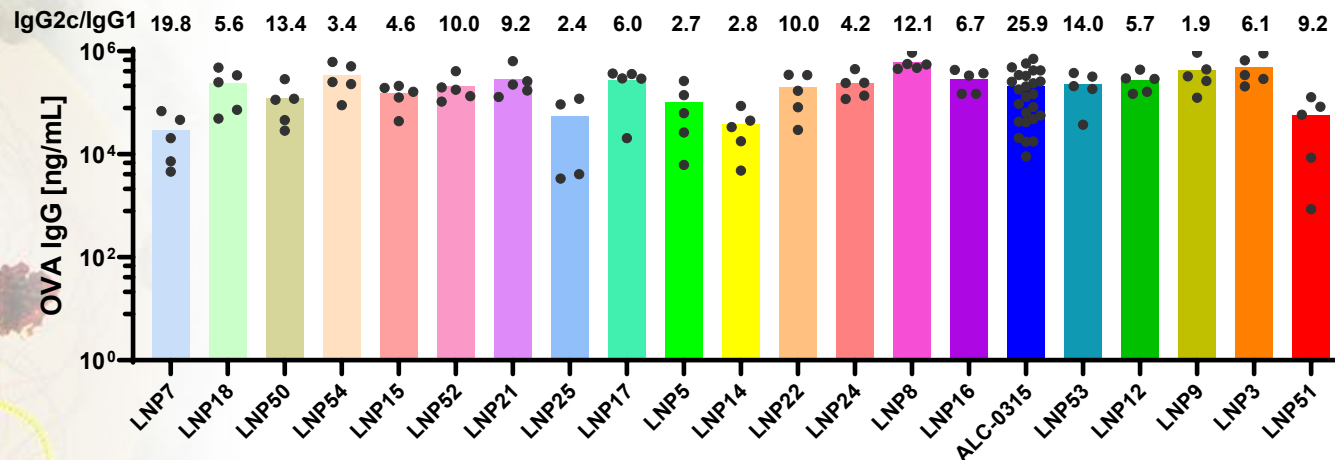
## Improved Lipids for Vaccine Applications (IM)

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# LNP screening for IM mRNA Cancer Immunotherapy

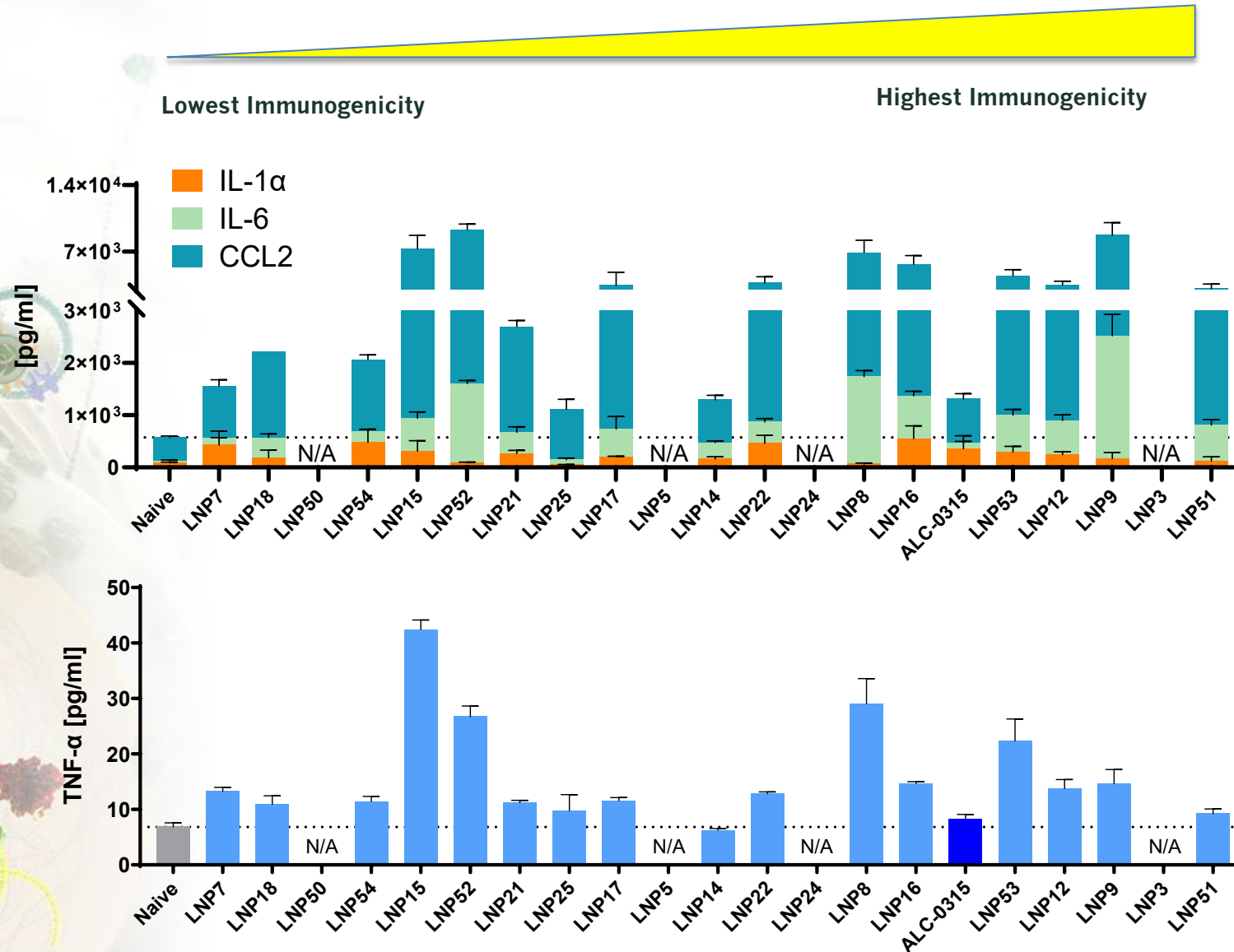


- Several rationally selected ionizable lipids induced potent cellular response, including ALC-0315 used in COMIRNATY®.
- A strong Th1 bias humoral response was induced.





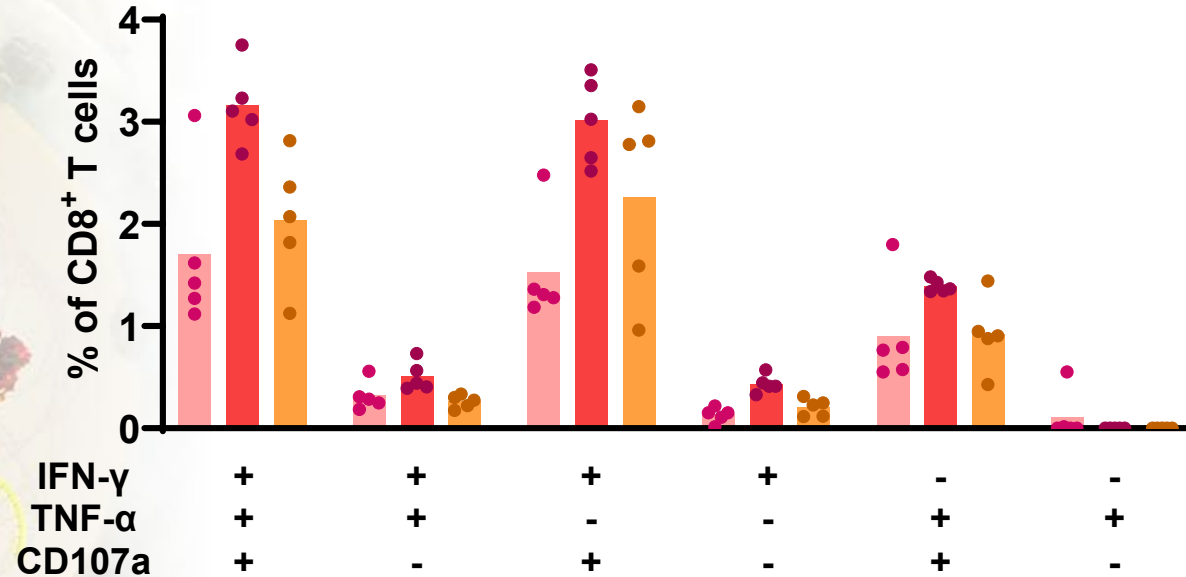
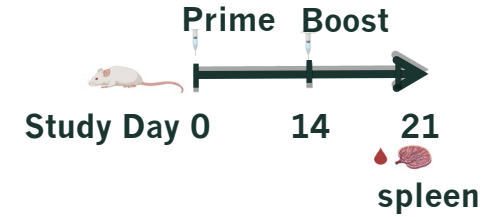
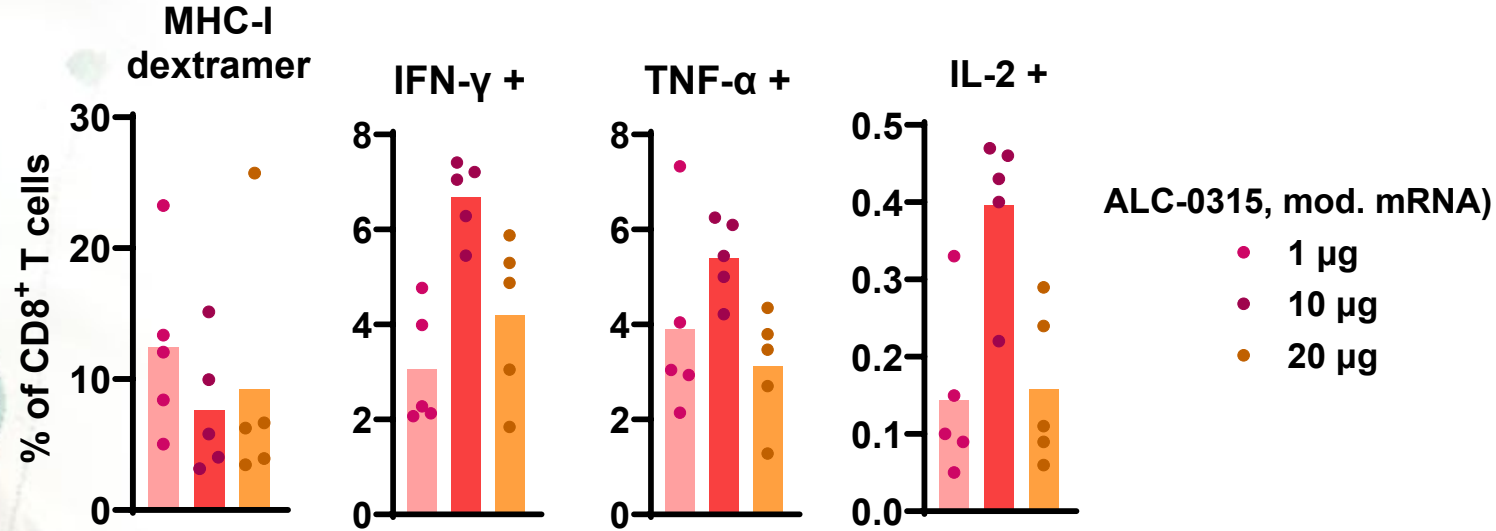
# Innate Immune stimulation by LNP-mRNA Cancer Immunotherapy



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

# LNP Development for mRNA Cancer Immunotherapy

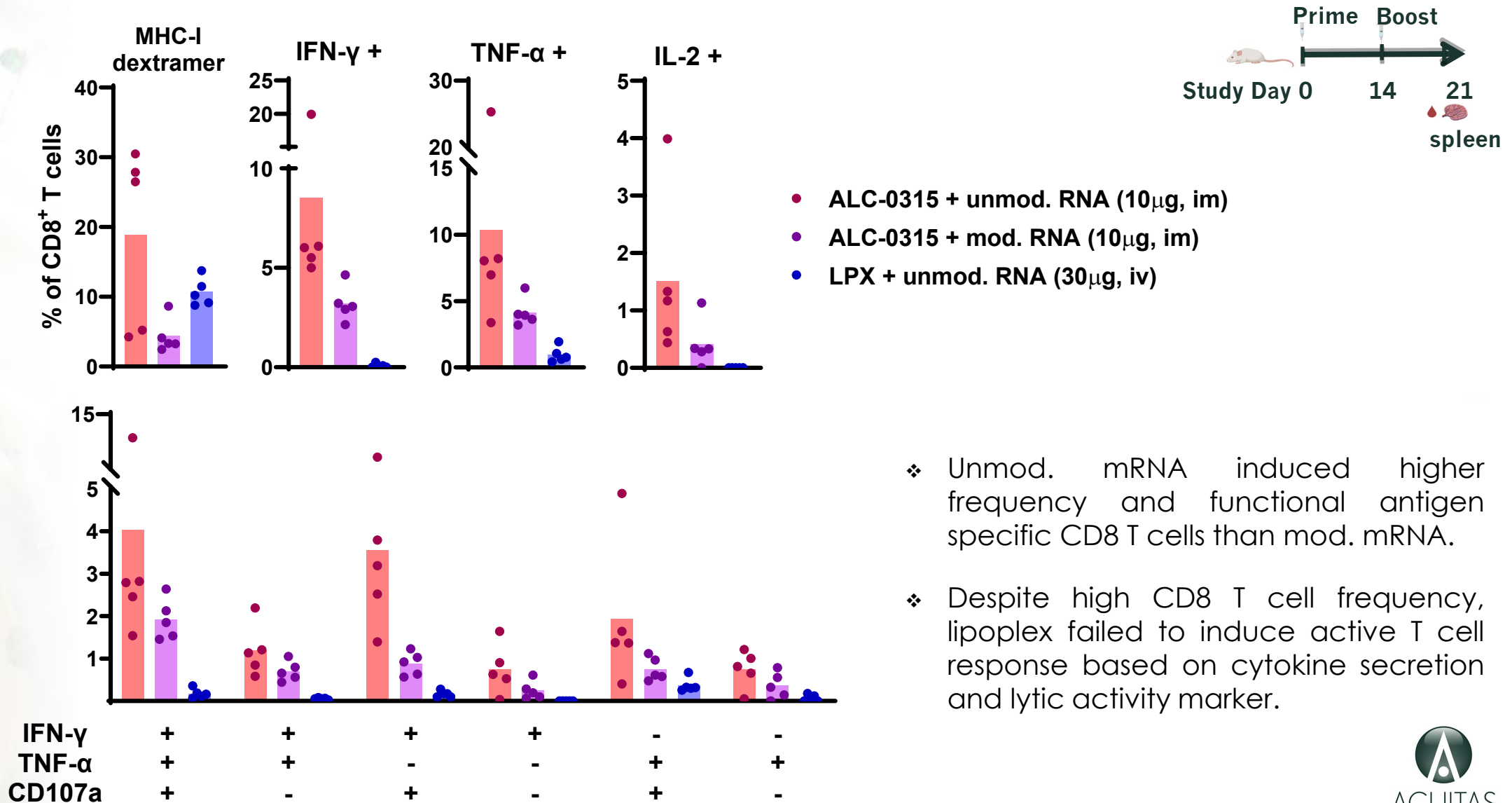
## Dose Response



- 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

# LNP Development for mRNA Cancer Immunotherapy

## Uridine-based mRNA & comparison to lipoplex

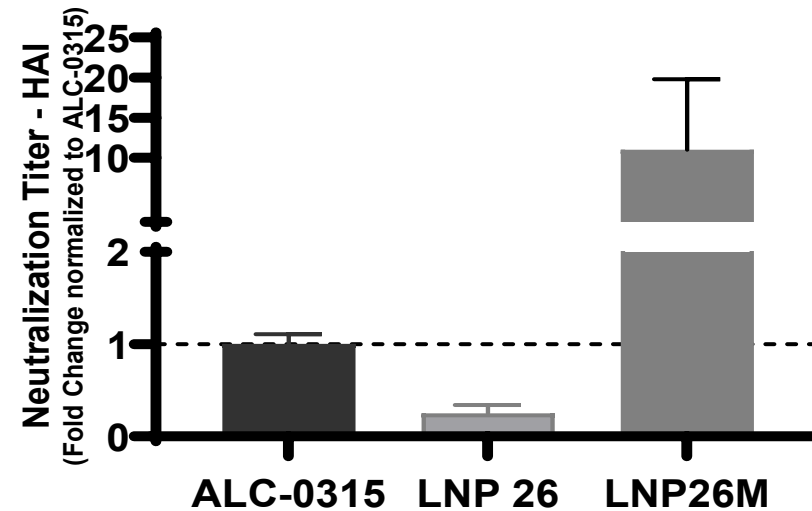


- ❖ Unmod. mRNA induced higher frequency and functional antigen specific CD8 T cells than mod. mRNA.
- ❖ Despite high CD8 T cell frequency, lipoplex failed to induce active T cell response based on cytokine secretion and lytic activity marker.



# 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

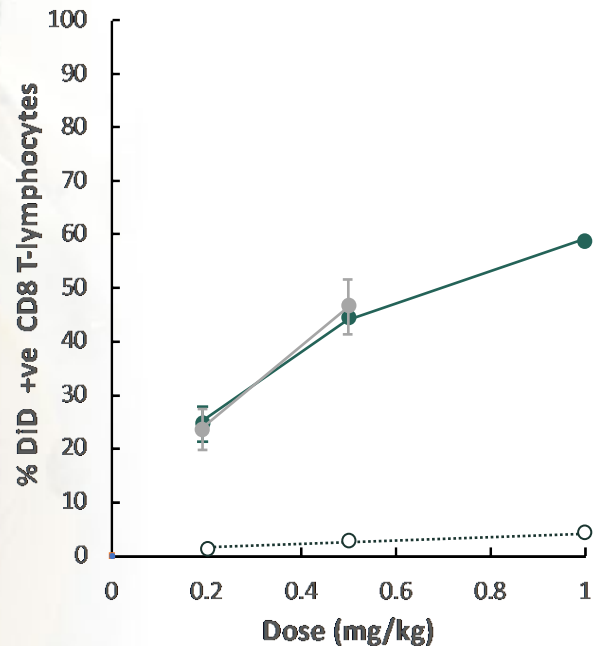
# LNP Development for mRNA Cancer Immunotherapy

## APCs Targeting for Improved Potency

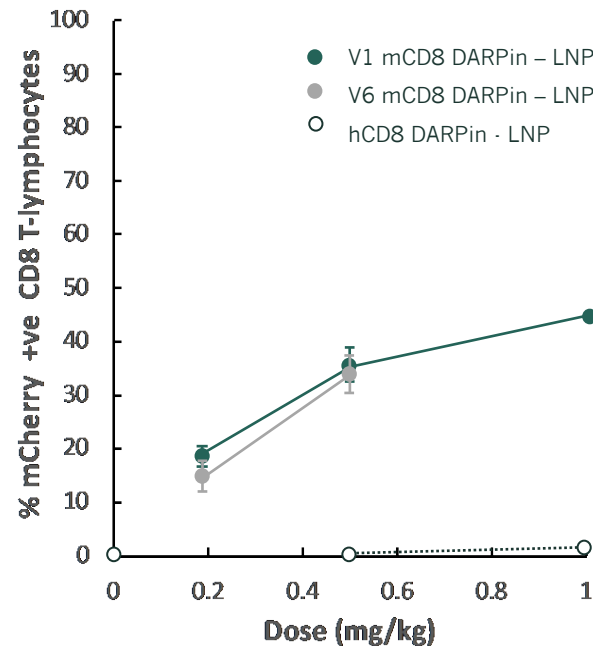


**Active targeting Proof of concept:** Target cell binding and reporter gene expression

**LNP binding**



**Reporter gene expression**



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

# 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 @ 1/3<sup>rd</sup> 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.