



 IAS 2021

# Discovery and Development of LNPs targeting B Cells *in vivo*

What is coming next for *in vivo* gene therapy?

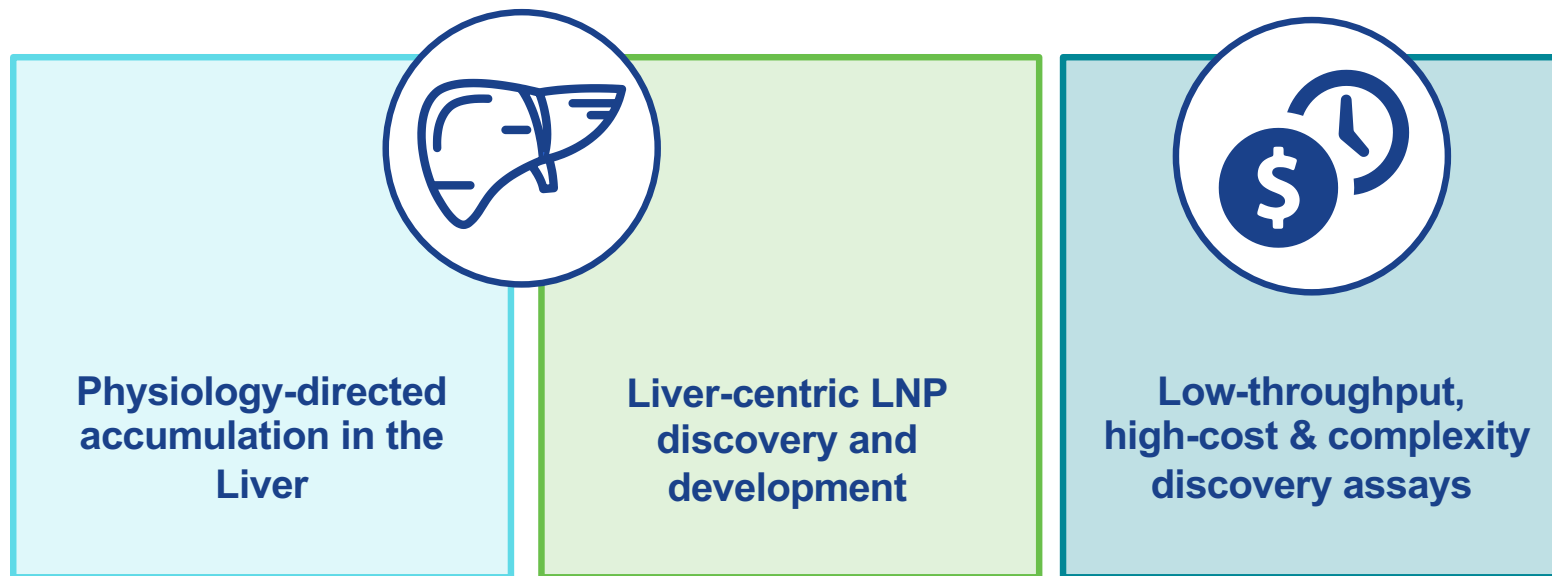
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## Lipid Nanoparticles offer an attractive delivery method of genetic medicines

- Clinically-validated
- Extensive manufacturing capabilities
- Capable of delivering a wide range of cargos (e.g. mRNA, sgRNA, nucleases & base editors)
- Facilitate transient expression
- Redosable

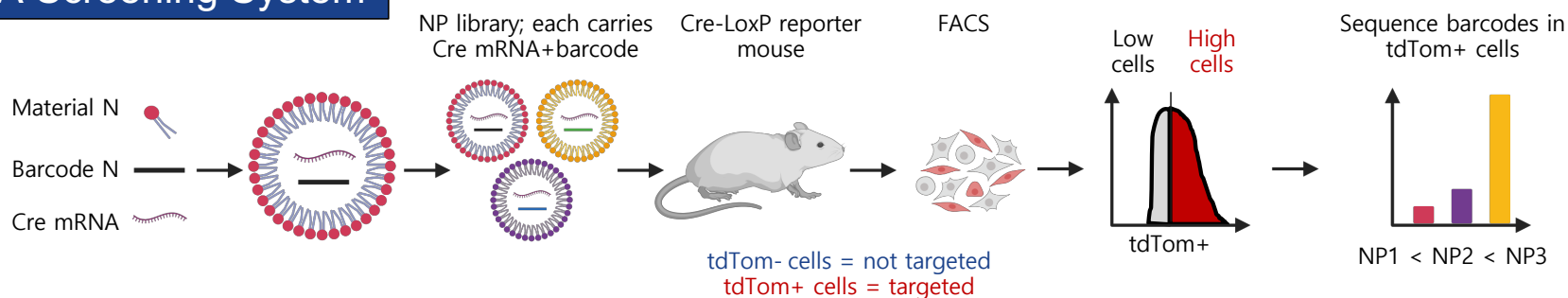
## Three factors have slowed development of non-liver LNPs



**Historical LNP discovery is inefficient.** An ideal LNP discovery process would be (i) very high throughput, (ii) *in vivo* (mice → NHPs), and (iii) analyze delivery to any desired combination of on- / off-target cell types.

# DNA Barcoding to test 100s LNPs simultaneously in vivo

## mRNA Screening System



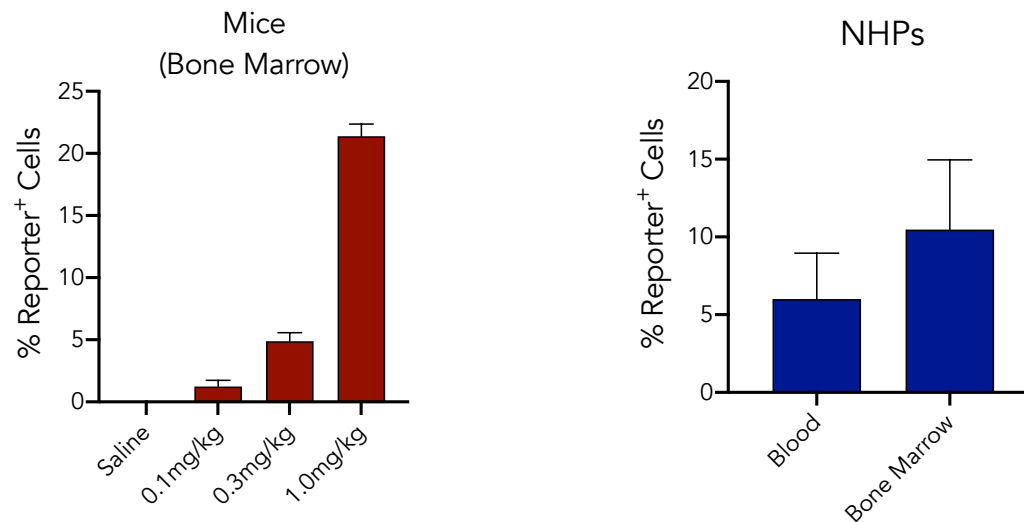
## Nanoparticles That Deliver RNA to Bone Marrow Identified by in Vivo Directed Evolution

Cory D. Sago, Melissa P. Lokugamage, Fatima Z. Islam, Brandon R. Krupczak, Manaka Sato, and James E. Dahlman\*

## High-throughput in vivo screen of functional mRNA delivery identifies nanoparticles for endothelial cell gene editing

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## Identification of LNPs for delivery of mRNA to B Cells in mice & NHPs



- We screened > 1,000 chemically distinct LNPs for the delivery of mRNA to B cells in mice
- After the validation of several hit LNPs in mice, we advanced one LNP into NHPs showing the transfection of ~10% B cells isolated from the bone marrow
- Future work will continue to characterize the subset(s) of B cells transfected

## Summary

- LNPs are an attractive delivery modality of gene editing applications
- Utilizing DNA barcoding approaches that allow the screening of 100s LNPs simultaneously *in vivo* we were able to identify several LNPs with tropism to B cells
- We advanced hit LNPs into NHPs and observed mRNA delivery to 10% B cells in the bone marrow