Understanding the inflammatory targeting of Lipid nanoparticles to deliver therapeutic mRNAs

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NEXT-GENERATION DELIVERY INNOVATIONS

Introduction: Inflammatory Bowel Diseases

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Inflammatory bowel diseases (IBDs) are a family of pathologies conditions that are characterized by chronic inflammation of the tissues in the digestive tract.

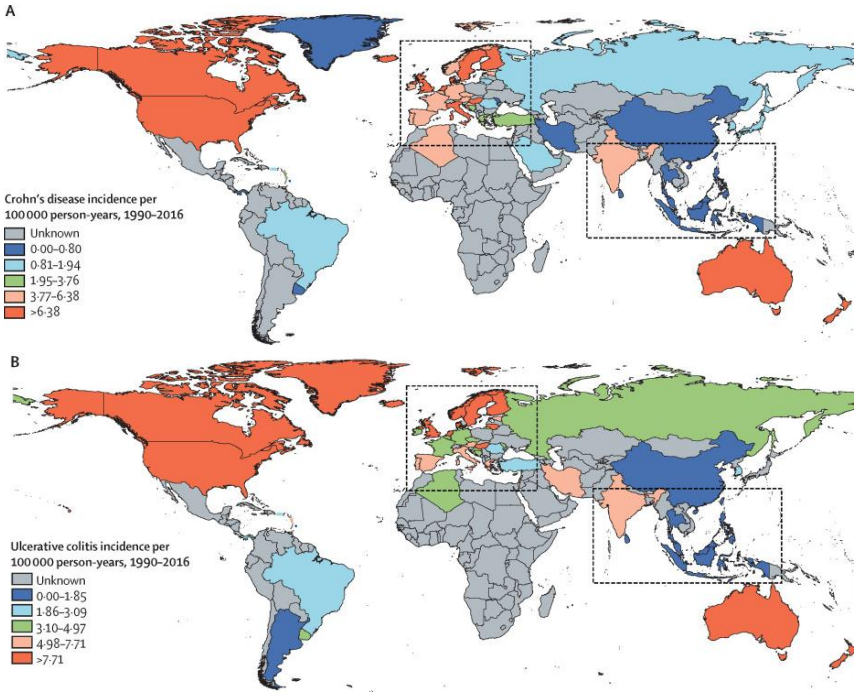
IBDs are commonly classified based on their pathological features in :

- **Crohn's disease (CD).** Thia condition often affects the deeper intestinal layers, especially but not exclusively in the small intestine.

- **Ulcerative colitis (UC).** This condition is characterized by inflammation and more superficial ulcers on the lining of the distal digestive system (colon and rectum).

CD and UC share symptoms like abdominal pain, diarrhea, rectal bleeding, cachexia and weight loss.

Furthermore, IBDs are considered mayor risk factors for Colorectal Cancer



Ng SC, Shi HY, et al. Lancet. 2017

Introduction: Inflammatory Bowel Diseases

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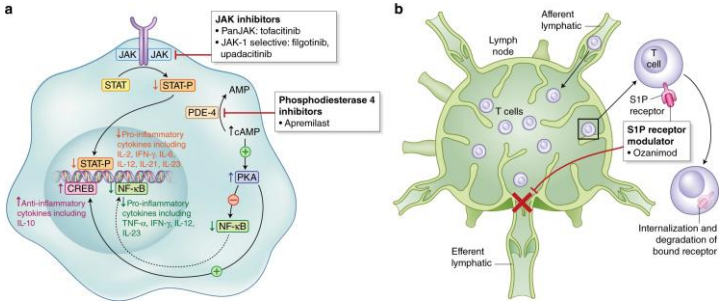
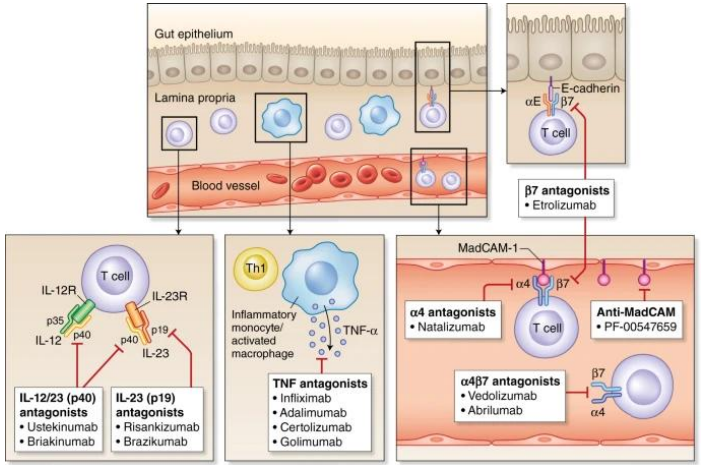
Biologicals

Small molecules

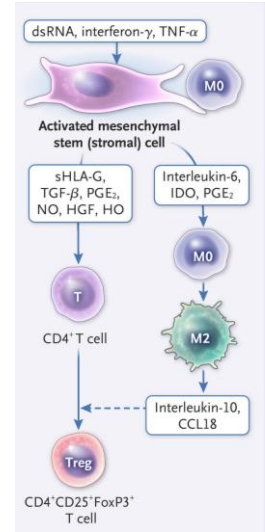
- Corticosteroids
- Aminosalicilates



Monoclonal antibodies



Cell Therapy



Vieujean, S., et al.. Nat Rev Gastroenterol Hepatol 22, (2025).
Baumgart DC, Le Berre C. N Engl J Med, 2021
Paramsothy, S., et al. Mucosal Immunol, 2018.

Limitations of current therapied for IBDs and other chronic inflammatory pathologies and our solution

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Limitations of current treatments:

- Efficacy in a fraction of patients
- Loss of efficacy over time.
- Adverse side effects.

The use of RNA technologies offers innovative possibilities for the treatment of IBDs:

- Unlock **'undruggable' molecular targets** with lower off target effects often associated to small molecules (siRNAs, **mRNAs**, CRISPR-Cas9).
- Induce the **in situ prolonged production of immunomodulatory proteins** to re-establish a physiological microenvironment (**mRNA**, CRISPR-Cas9).
- Achieve **improved targeting** of the inflamed tissue via passive or active targeting: **LNPs**).

The great hurdle: Improving LNPs targeting.

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ADVANCED SCIENCE

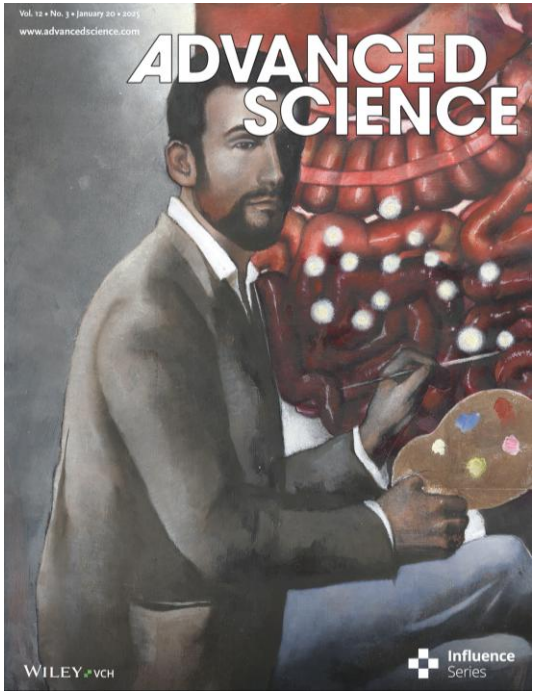
Influence Series

Research Article | Open Access

Lipid Nanoparticles With Fine-Tuned Composition Show Enhanced Colon Targeting as a Platform for mRNA Therapeutics

Riccardo Rampado, Gonna Somu Naidu, Olga Karpov, Meir Goldsmith, Preeti Sharma, Assaf Ezra, Lior Stotsky, Dor Breier, Dan Peer

Rationale: improve LNPs systemic targeting to inflamed tissues



Fine-tuning LNPs composition

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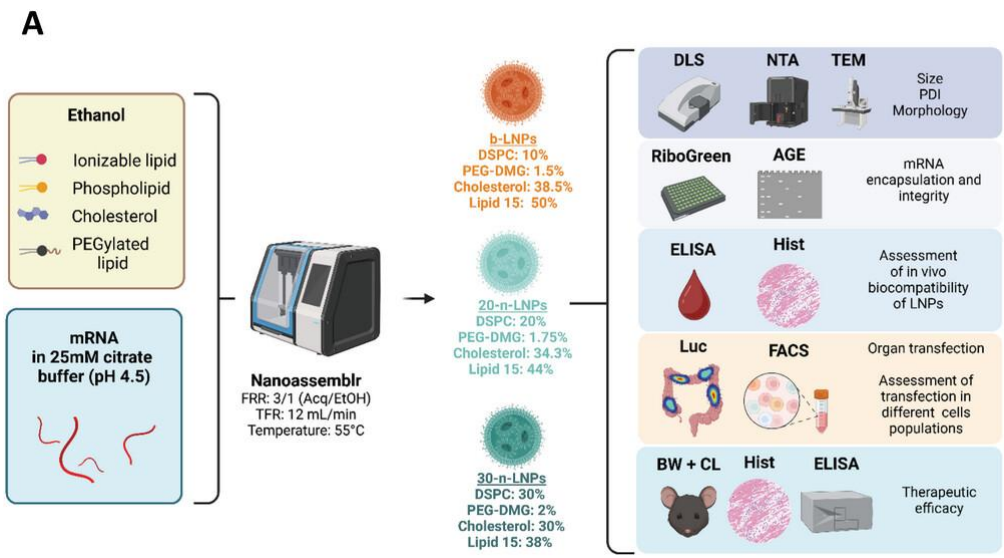
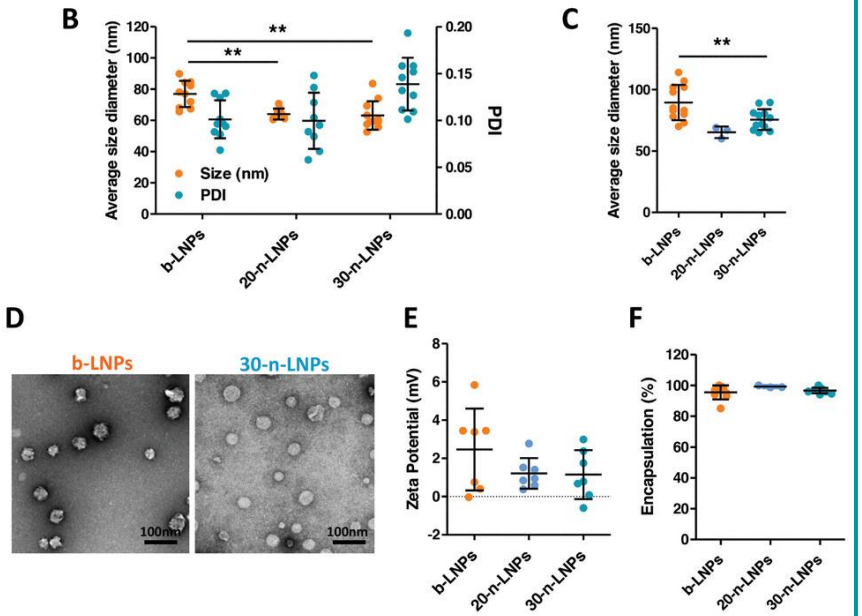


Special thanks to Niv Cohen

LNPs characterization



In vivo assessment of LNPs targeting

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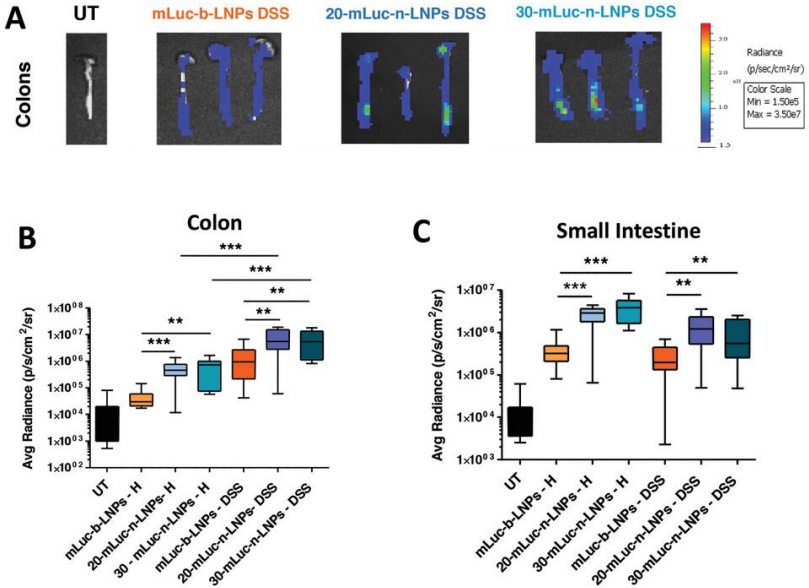
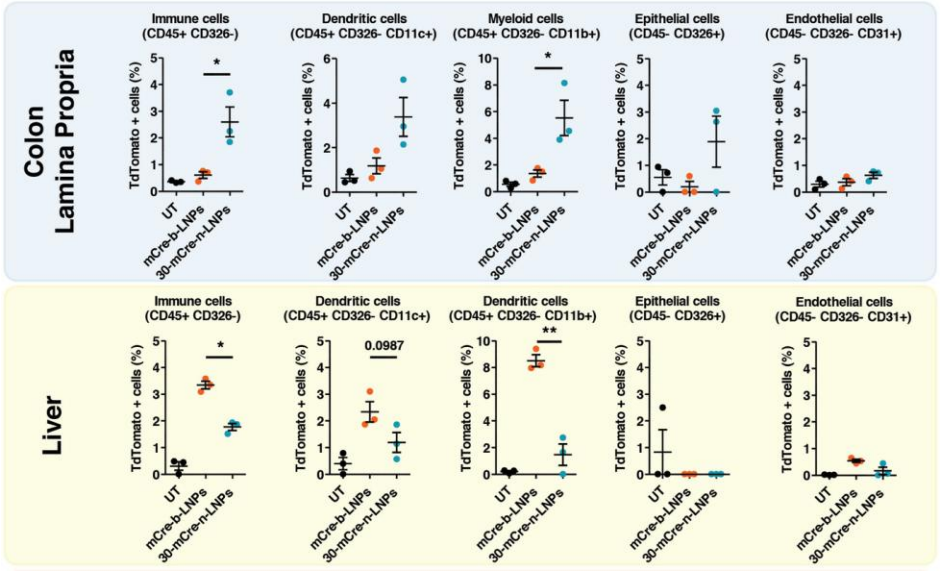
Biodistribution – Luc mRNA



Biodistribution in tdTtomato mice



Linking targeting mechanism and therapeutic efficacy

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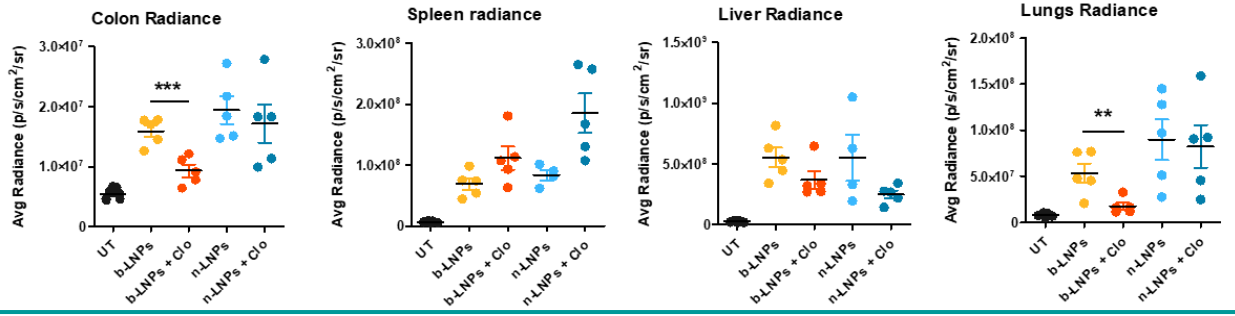
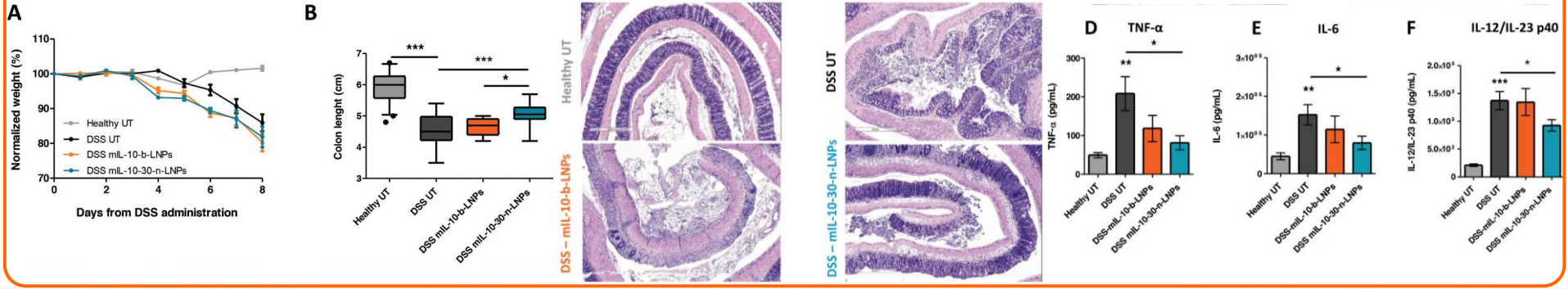
Assessment of LNPs biodistribution after injection of clodronate liposomes to deplete circulating immune cells



Therapeutic Efficacy using IL-10 mRNA



Expanding the horizon: Acute Respiratory Distress Syndrome (ARDS)

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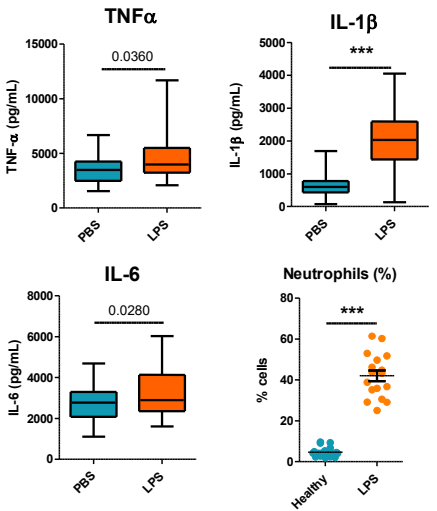
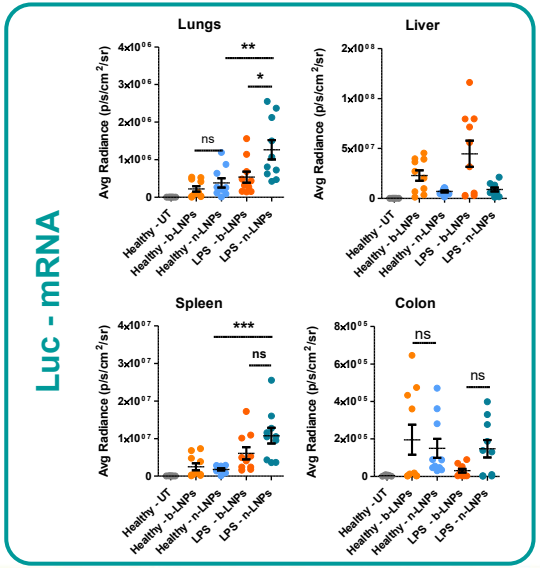
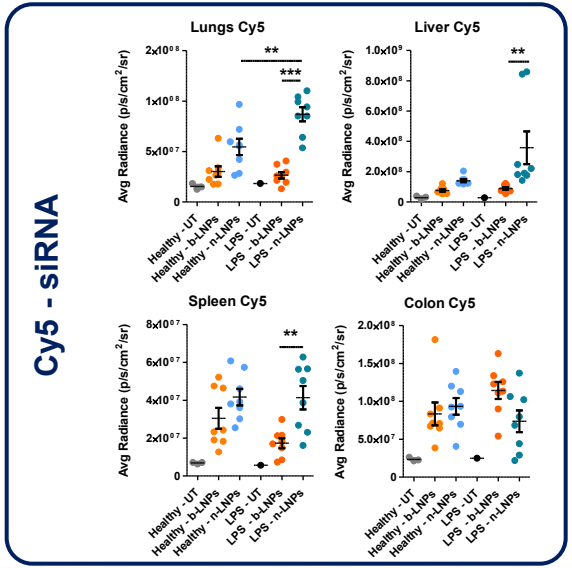
To understand the relevance of immune cells (circulating and not) in determining n-LNPs targeting, we decided to test their behavior using an orthogonal model of acute inflammation. **we selected a model of lung inflammation caused by intra-tracheal instillation of 10µg of LPS per mouse 24h before LNPs injection.**
Lungs inflammation was verified by measuring the levels of cytokines in the lungs by ELISA.
IL-1β resulted significantly increased, while the other cytokines only displayed a non-significant increase.
We performed IVIS on both Luc and Cy5 across different organs**, and indeed LPS treatment increased n-LNPs uptake expression in the lungs and spleen.**







Cellular biodistribution in the inflamed lungs

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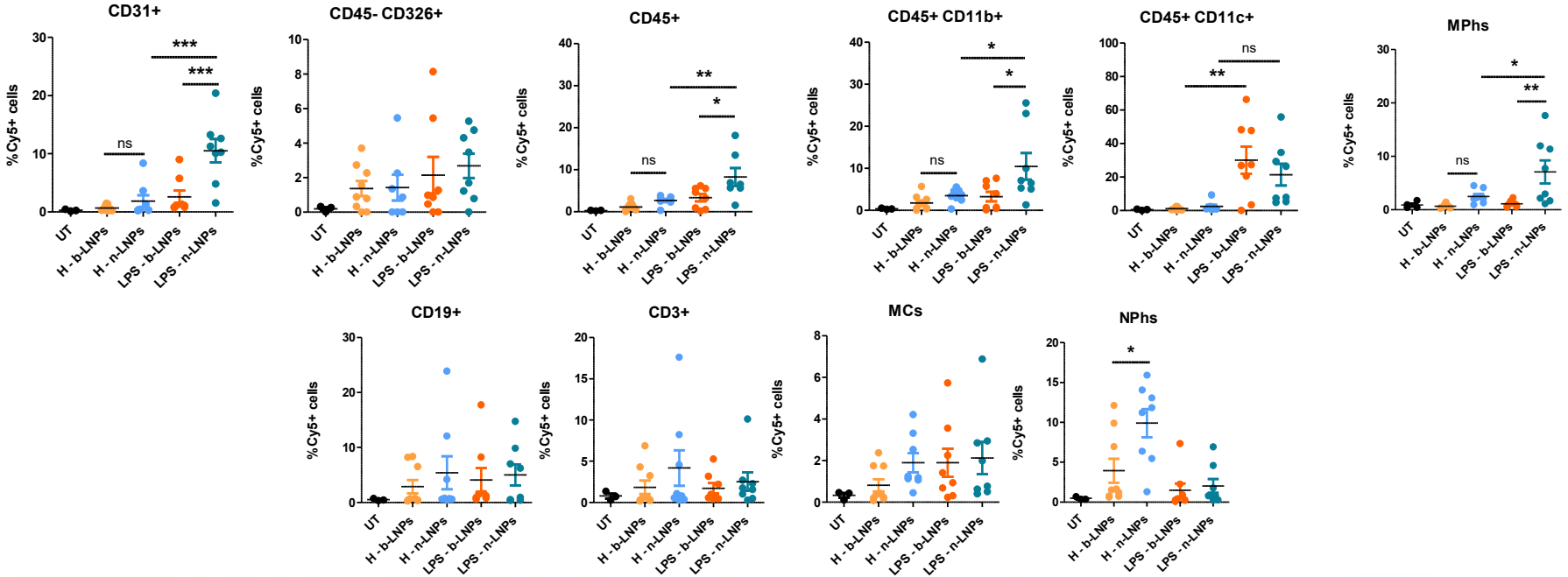
Cy5-siRNA-Loaded LNPs were administered IV in mice carrying LPS-induced lungs inflammation. Lungs were processed for flow cytometric analysis after 6 hours from injection.



Future steps

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- Better understand the delivery mechanism of LNPs into inflamed tissues during IBDs and ARDS.
- Further improve LNPs targeting efficacy by testing different lipid components (e.g. phospholipids, ionizable lipids).
- Test as the therapeutic efficacy of relevant cytokines loaded LNPs to quench ARDS.