

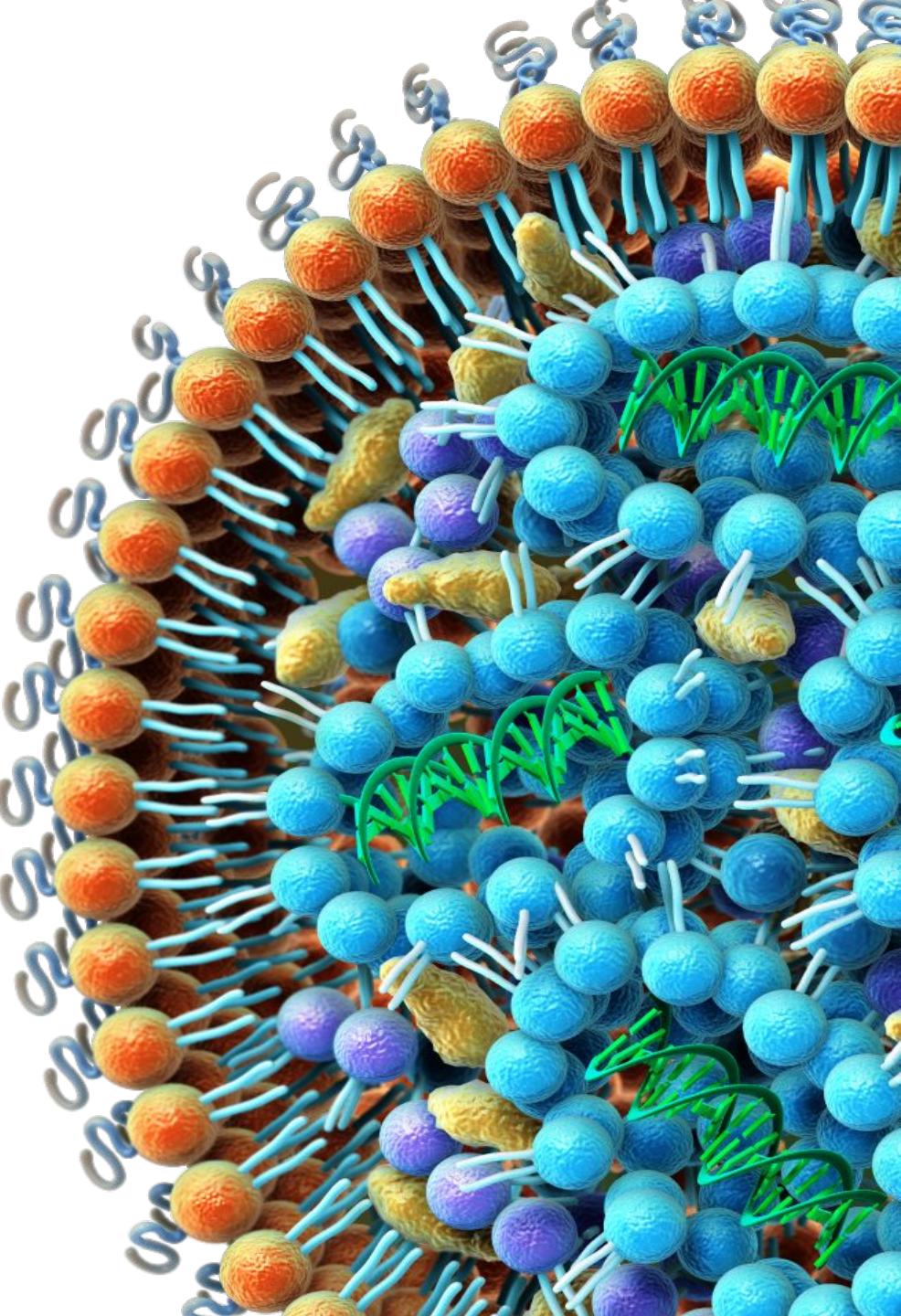


Booth 310

How Ionizable Lipids RNA-LNP Optimize Delivery Strategies

Dr. Ian Villamagna

25 July 2023





Mission

At Precision NanoSystems, our mission is to accelerate the creation of transformative medicine that significantly impacts human well being

At Cytiva, it's our mission to advance and accelerate therapeutics.



Within Genomic Medicine Development Delivery is the Biggest Unknown



What are the Challenges?

Nucleic Acid Delivery

Nucleic acids are unstable and do not readily enter cells

Drug Product Development, Manufacture & Scale-up

Genomic medicines are complex drug products and are traditionally difficult to develop and challenging to scale-up

Knowledge Gap

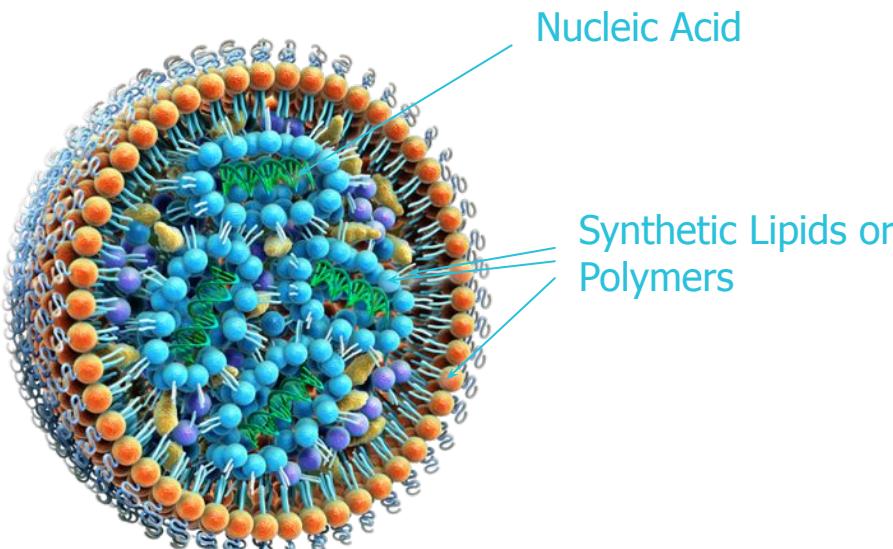
Genomic medicines are an emerging technology and few teams have the full compliment of experience in developing this drug product

Different Needs for Different Programs

Genomic medicines are being developed as personalized medicines and for mass administration, and by teams with a wide range of capabilities

Genomic Medicines are Complex and Require Specialized Reagents, Instruments, and Services

The development of genomic medicines is inherently complex, with multiple different areas that require optimization:



Nucleic Acid

Synthetic Lipids or
Polymers

Drug Product
(10 – 1000 nm)

LNP Composition

- Stability
- Lipid composition
- Excipients

RNA Quality

- Quantity
- Integrity
- Structure

Payload Design

- Sequence
- Production
- Biology

Encapsulation

- %EE
- Location of RNA

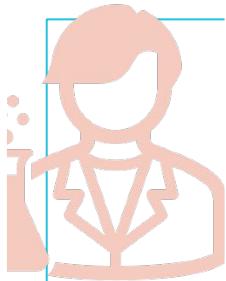
Scale Up

- Larger batches
- Process
- Development
- Downstream Process

Biological Testing

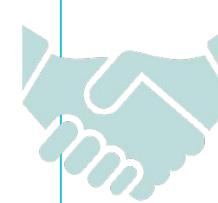
- Dosing
- Efficacy
- Safety
- Administration

Meeting our Customers' Needs Earlier to Accelerate Therapeutic Development



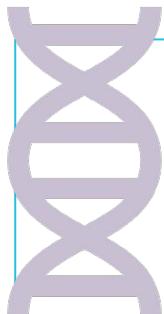
Every Scientist can be a Genomic Medicine Developer

- Lowering the Barrier to Entry
- Genomic Medicines Designed not Discovered
- Niche to Mainstream



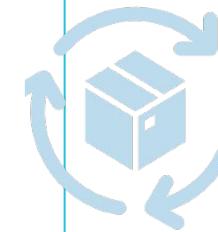
Partner for the Entire Drug Development Journey

- Ideation to Approved Drug
- Continuity through Drug Development
- **Show-Not-Tell** Therapeutically Relevant Proof of Concept Data



Be the Platform for Genomic Medicine

- Optimized Products, Services, Technologies, and Workflows
- Full Stack of Genomic Medicine Development Technologies
- End-to-End Solutions

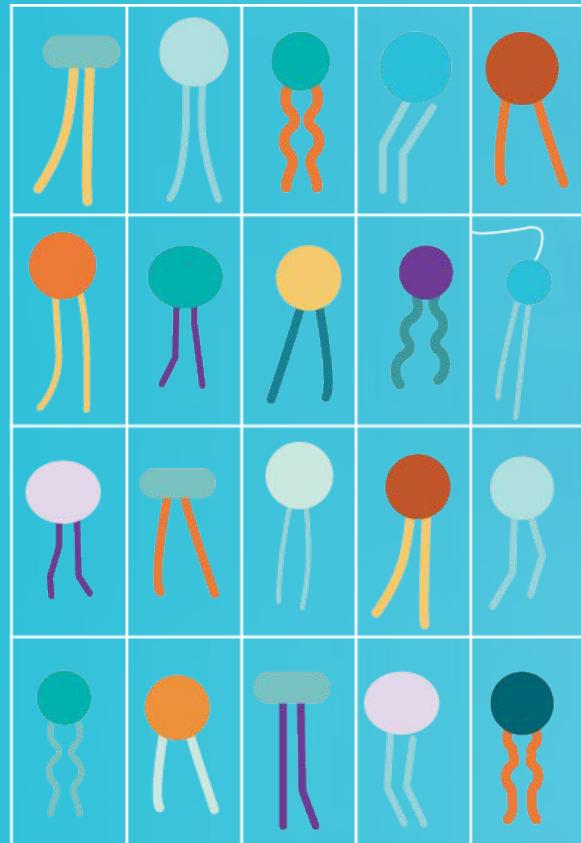


The Product is the Process

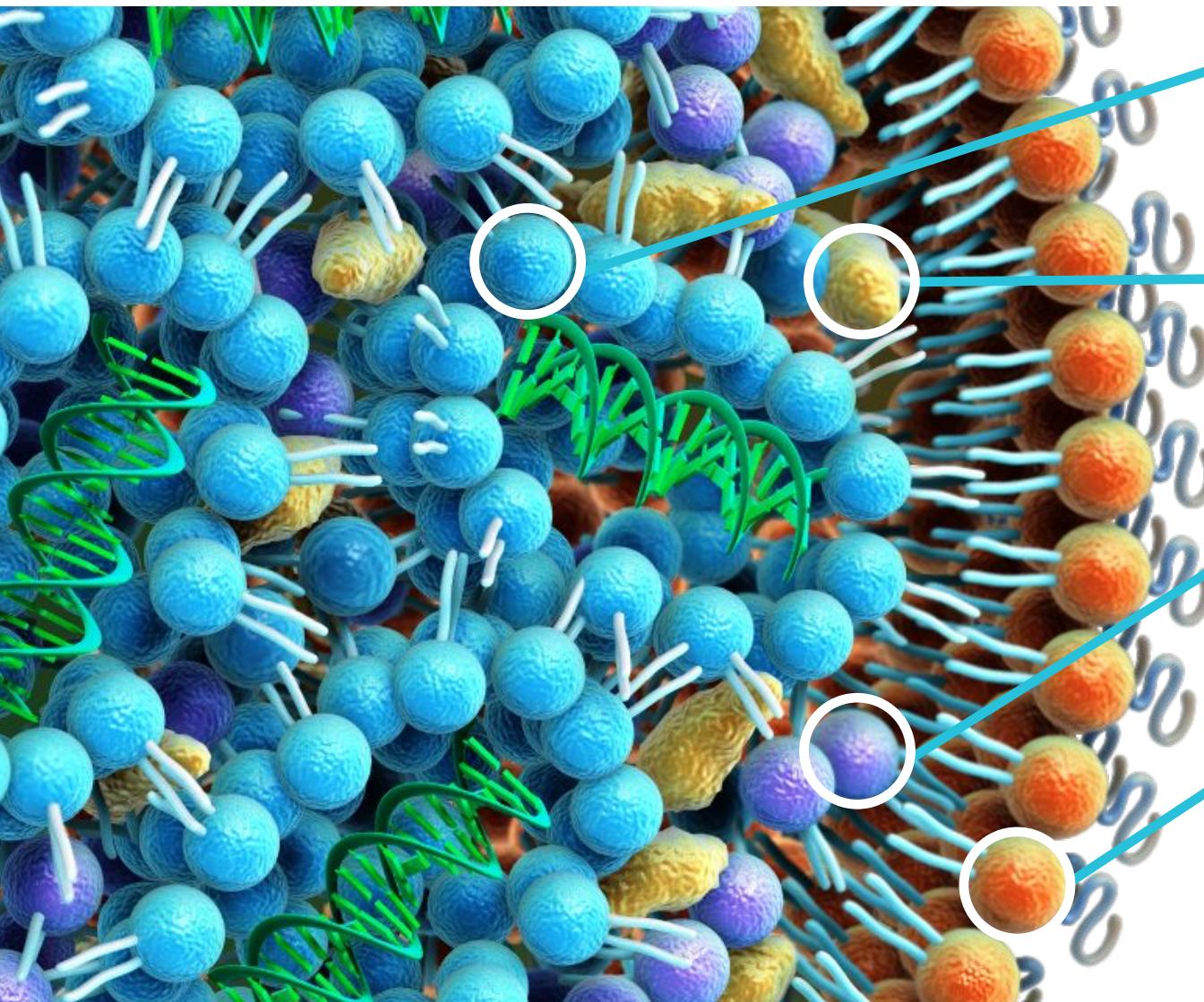
- Therapeutic and Process Development are Linked
- Manufacturing Efficiencies are Critical
- NxGen™ Delivers Precise, Reproducible Nanoparticles across Scales



Ionizable Lipid Portfolio



LNP components



Ionizable Cationic Lipid

- Neutral at pH 7, Cationic at pH ~4.5
- Binds & protects RNA
- Facilitates Endosomal Escape

Cholesterol

- Binds ApoE
- Mediates endocytosis via LDL receptor

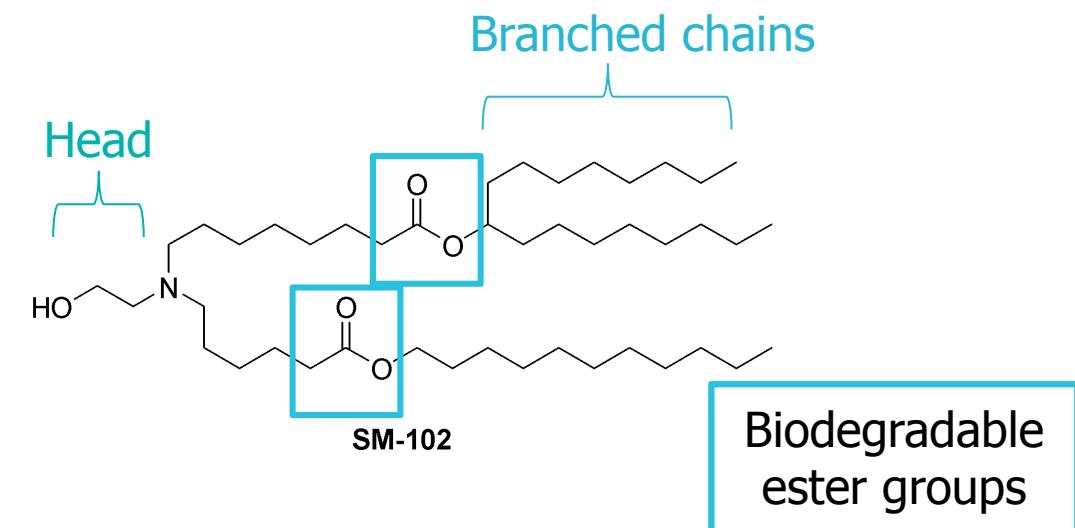
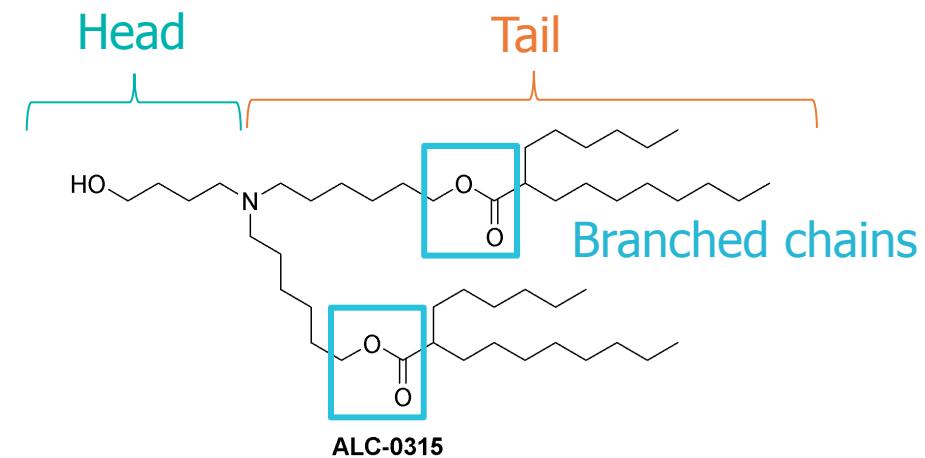
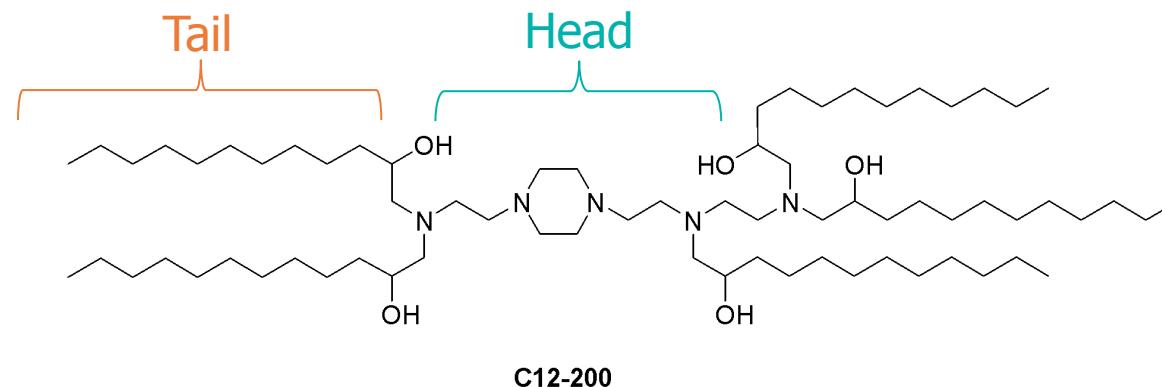
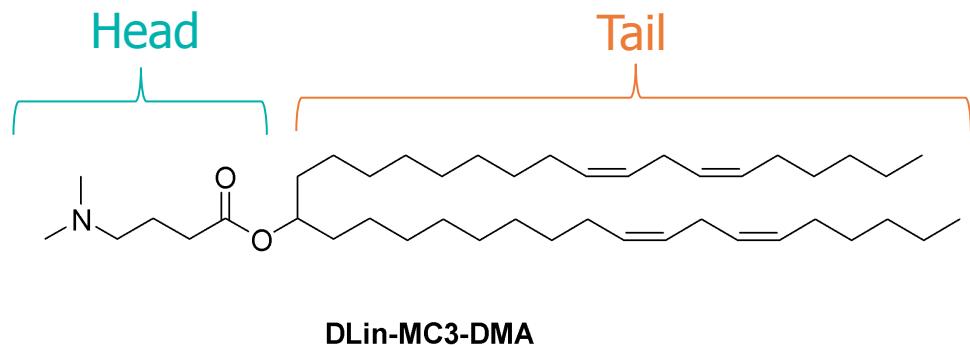
Helper Lipid (e.g. DSPC, DOPC)

- Structural support, fills voids
- Been found to affect release

PEG-Lipid

- Stabilizes particle during formation
- Protect from opsonization
- Shed from particle over time following systemic injection

Common Ionizable Lipids



Strategies to Streamline Ionizable Lipid Selection

Main Library									
PNI 1	PNI 2	PNI 3	PNI 4	PNI 5	PNI 6	PNI 7	PNI 8	PNI 9	PNI 10
PNI 11	PNI 12	PNI 13	PNI 14	PNI 15	PNI 16	PNI 17	PNI 18	PNI 19	PNI 20
PNI 21	PNI 22	PNI 23	PNI 24	PNI 25	PNI 26	PNI 27	PNI 28	PNI 29	PNI 30
PNI 31	PNI 32	PNI 33	PNI 34	PNI 35	PNI 36	PNI 37	PNI 38	PNI 39	PNI 40
PNI 41	PNI 42	PNI 43	PNI 44	PNI 45	PNI 46	PNI 47	PNI 48	PNI 49	PNI 50
PNI 51	PNI 52	PNI 53	PNI 54	PNI 55	PNI 56	PNI 57	PNI 58	PNI 59	PNI 60
PNI 61	PNI 62	PNI 63	PNI 64	PNI 65	PNI 66	PNI 67	PNI 68	PNI 69	PNI 70
PNI 71	PNI 72	PNI 73	PNI 74	PNI 75	PNI 76	PNI 77	PNI 78	PNI 79	PNI 80

Biodegradable, semi-biodegradable and non-biodegradable lipids

PNI 1	PNI 2	PNI 3	PNI 4	PNI 5	PNI 6	PNI 7	PNI 8	PNI 9	PNI 10
PNI 11	PNI 12	PNI 13	PNI 14	PNI 15	PNI 16	PNI 17	PNI 18	PNI 19	PNI 20
PNI 21	PNI 22	PNI 23	PNI 24	PNI 25	PNI 26	PNI 27	PNI 28	PNI 29	PNI 30
PNI 31	PNI 32	PNI 33	PNI 34	PNI 35	PNI 36	PNI 37	PNI 38	PNI 39	PNI 40
PNI 41	PNI 42	PNI 43	PNI 44	PNI 45	PNI 46	PNI 47	PNI 48	PNI 49	PNI 50
PNI 51	PNI 52	PNI 53	PNI 54	PNI 55	PNI 56	PNI 57	PNI 58	PNI 59	PNI 60
PNI 61	PNI 62	PNI 63	PNI 64	PNI 65	PNI 66	PNI 67	PNI 68	PNI 69	PNI 70
PNI 71	PNI 72	PNI 73	PNI 74	PNI 75	PNI 76	PNI 77	PNI 78	PNI 79	PNI 80

**Diverse Library of Novel
Ionizable Lipids**

Lead Candidate Selection

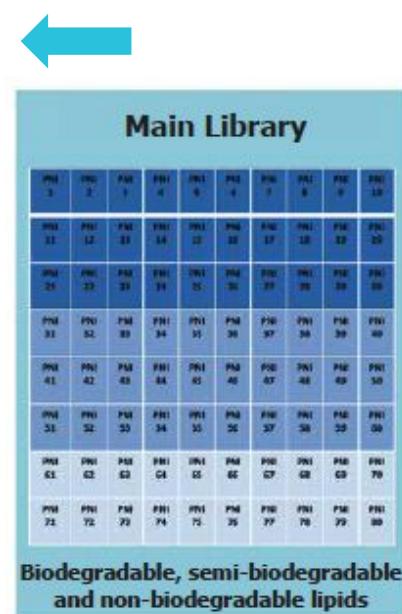
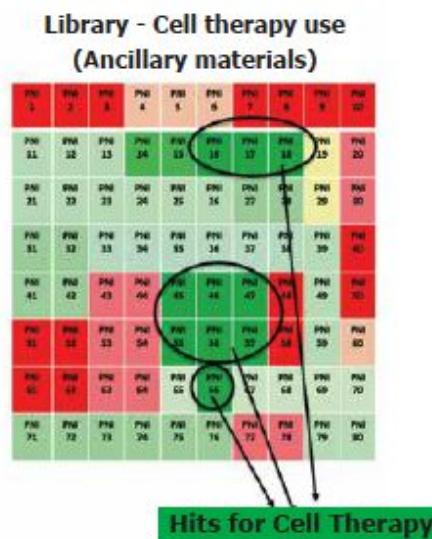
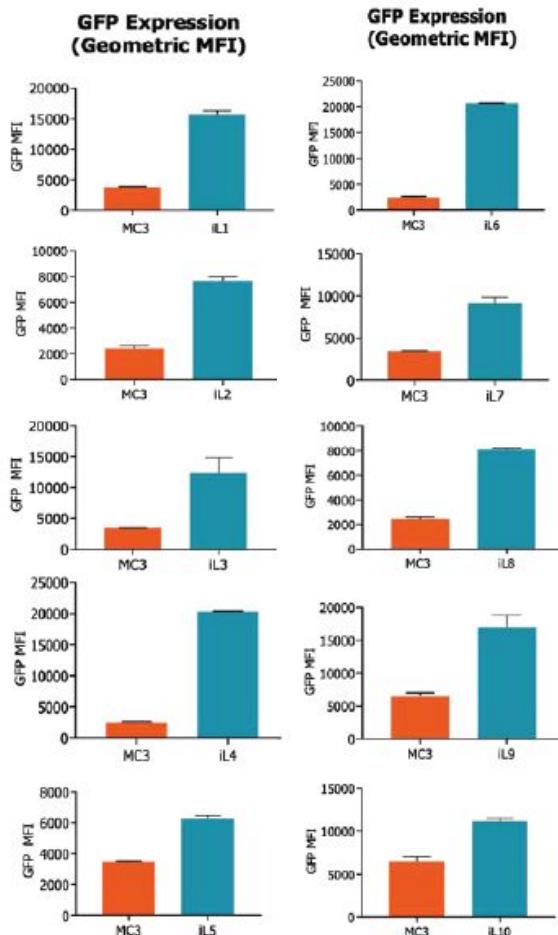
**Novel Compositions Designed for
Specific Applications**

Diverse
Portfolio

Well-characterized ionizable lipid portfolio streamlines screening across applications

Lipid Nanoparticle Portfolio Screening

Our ionizable lipid portfolio contains multiple ionizable cationic lipids more potent than MC3

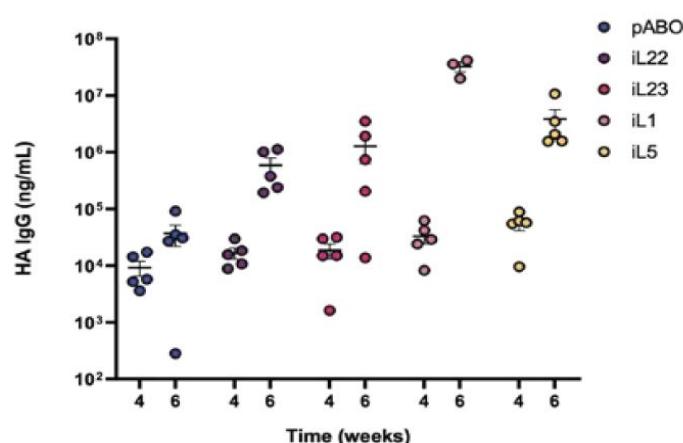
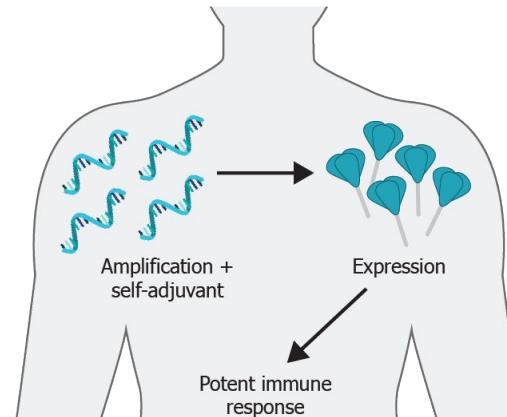


Applications Demonstrated

- Vaccines
- Protein Replacement
- Cell Therapy

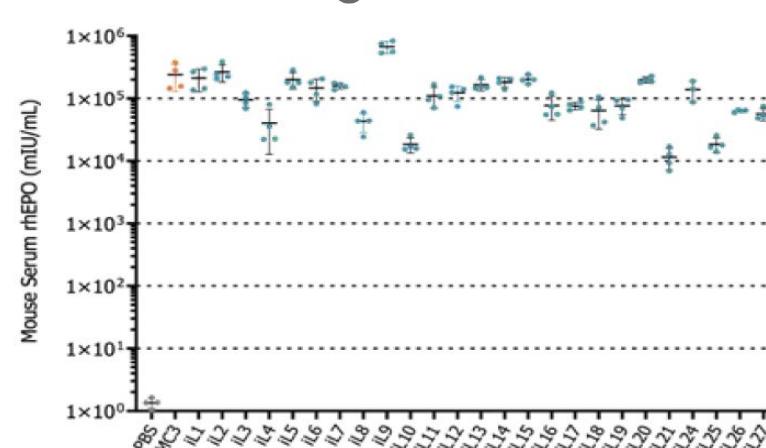
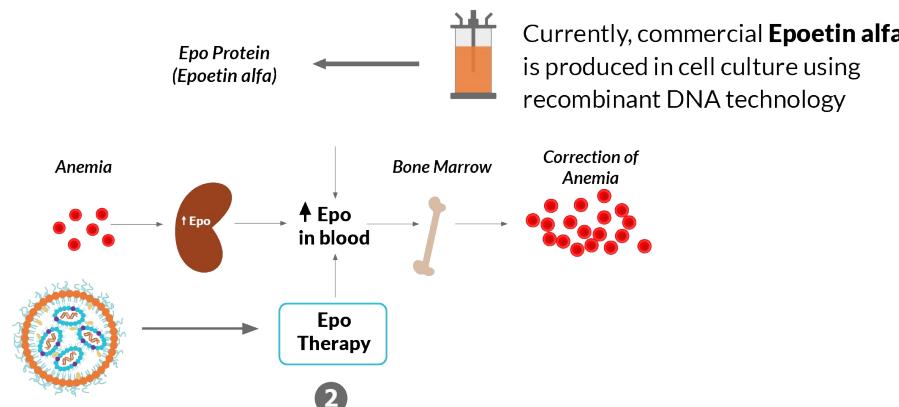
GenVoyTM LNPs Enable Delivery for Key Applications in Genomic Medicine

Vaccines



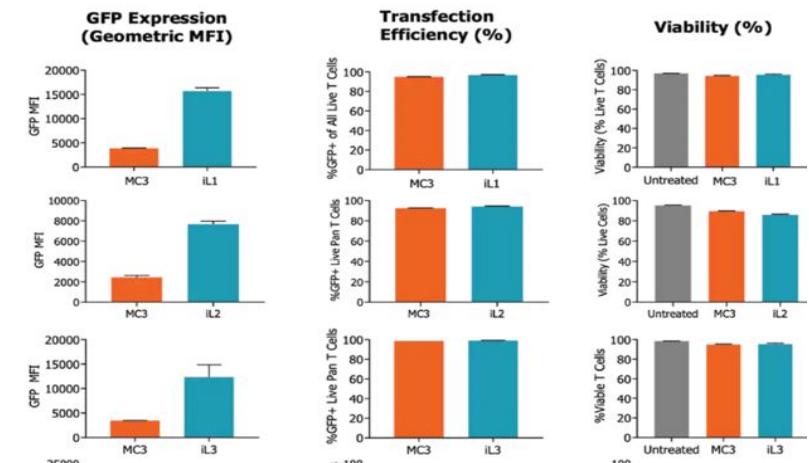
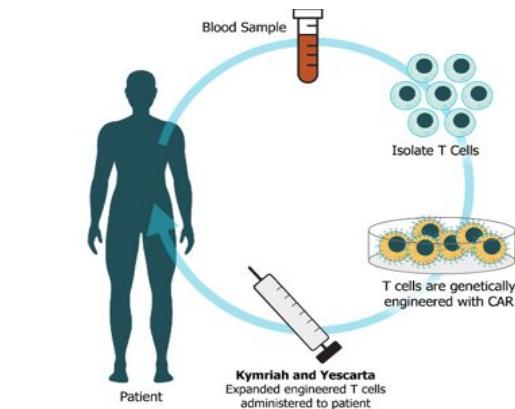
HA IgG Generation in Mice

Gene Therapy



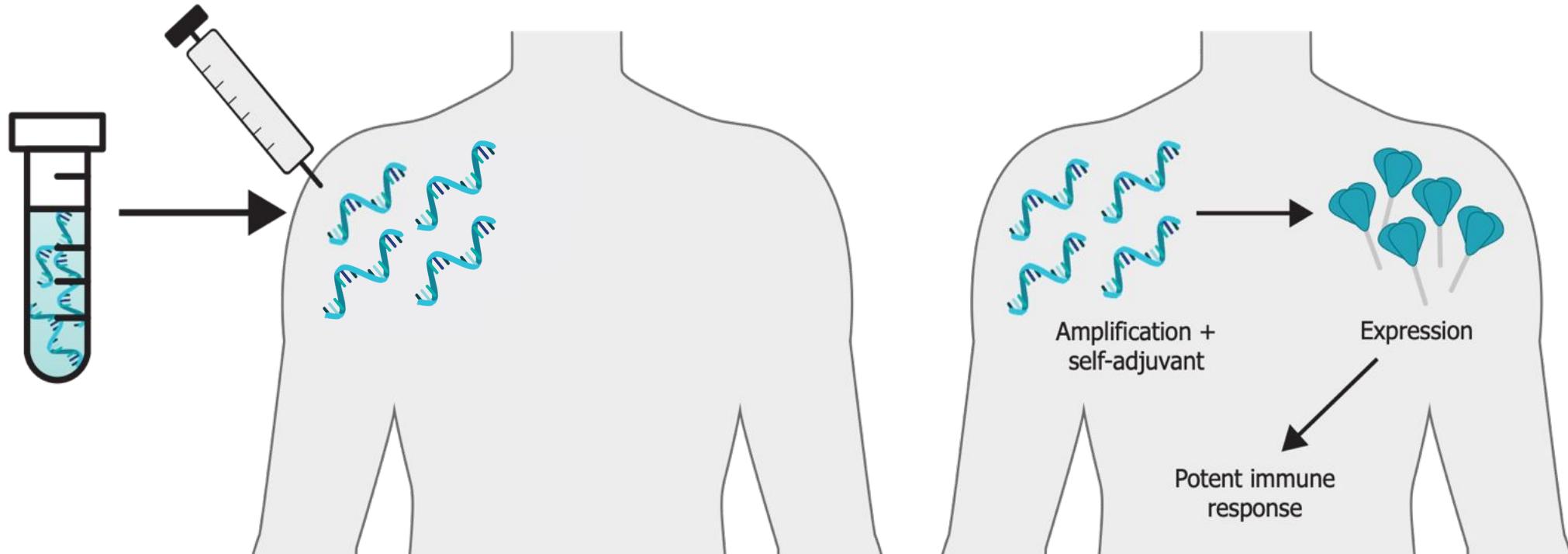
Epo Production in Mice + Gene Editing

Cell Therapy (ex vivo)

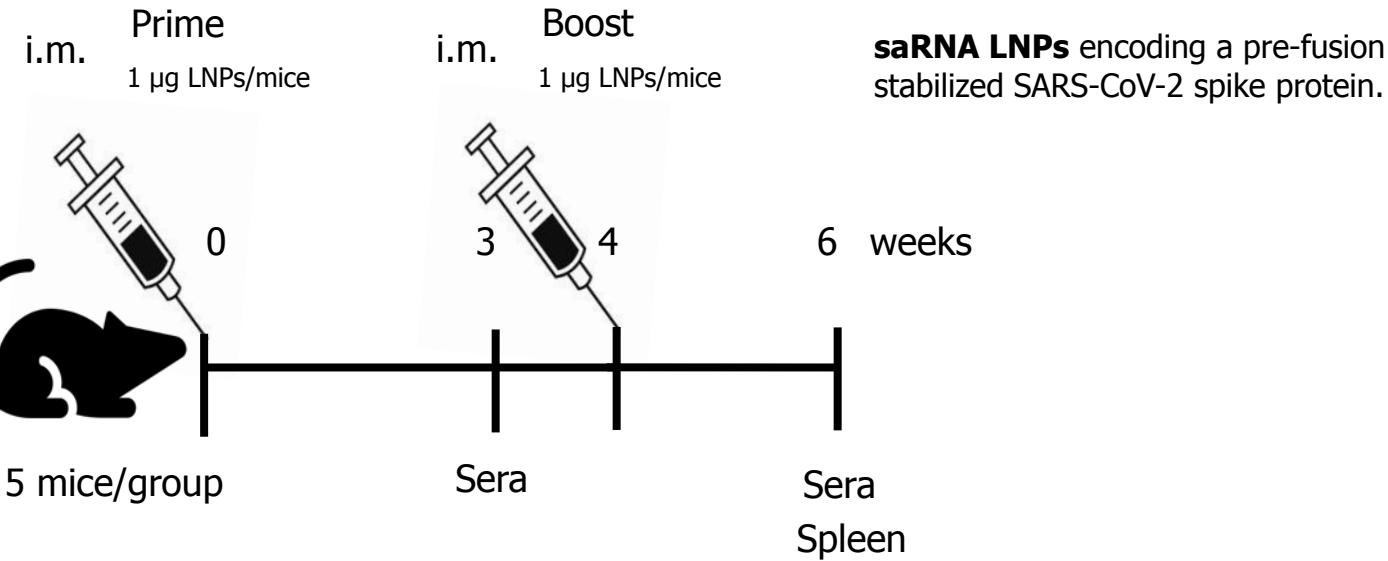


GFP Expression in Primary Human T Cells

Vaccines



In Vivo Testing of saRNA LNPs



Sera

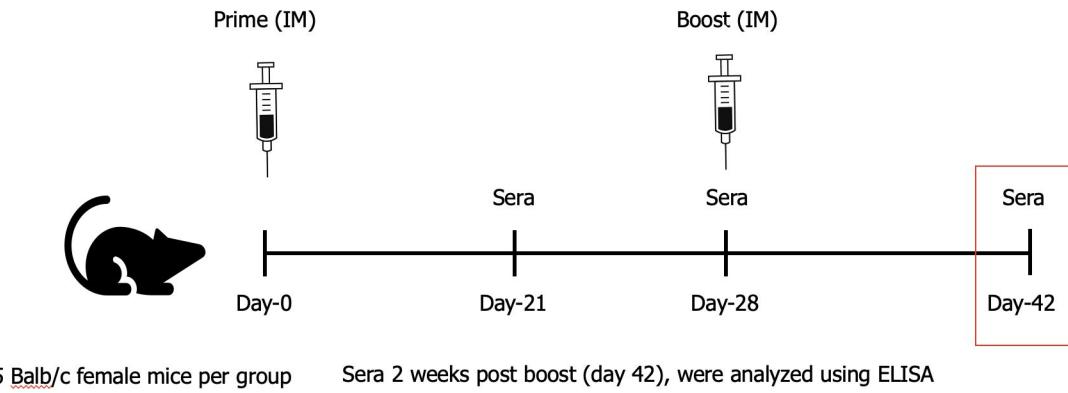
- SARS CoV2 specific IgG ELISA
- Cytokine measurements/Neutralization assays

Spleen

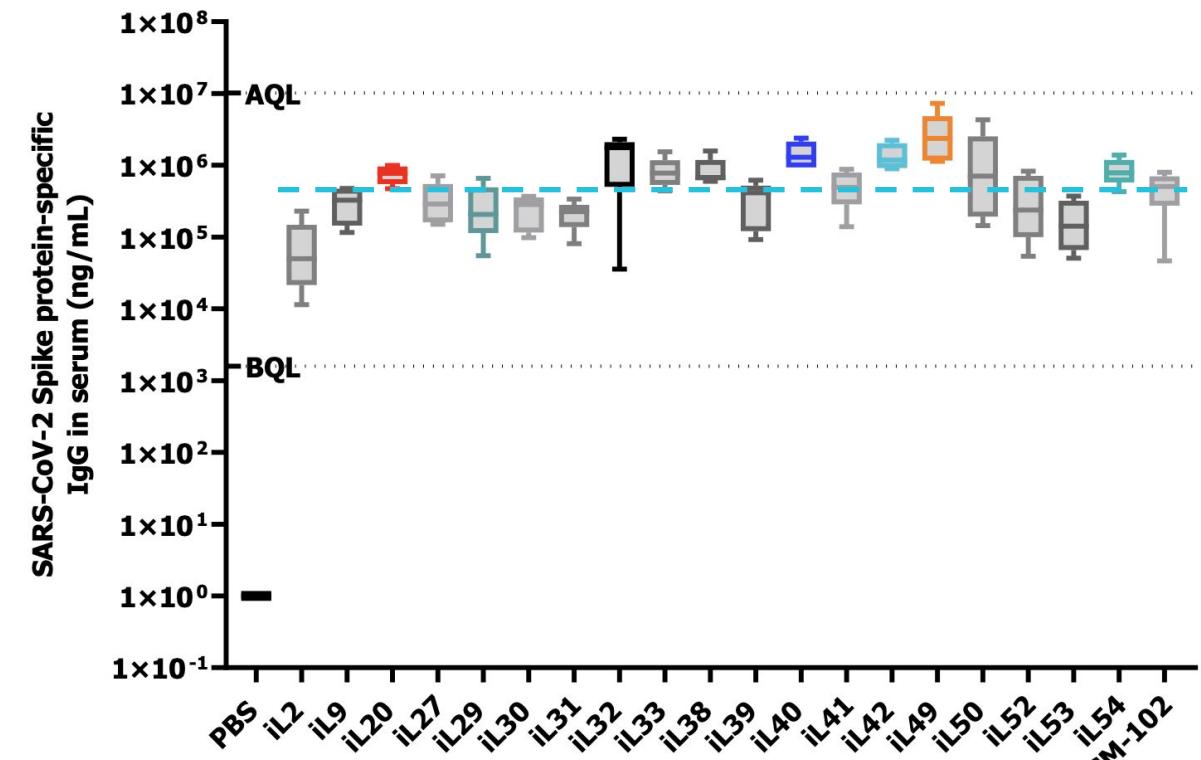
- *Ex vivo* restimulation with SARS-CoV-2 peptides
- Intracellular cytokine staining/Cytokine measurements

SARS-CoV-2 Spike Encoded saRNA

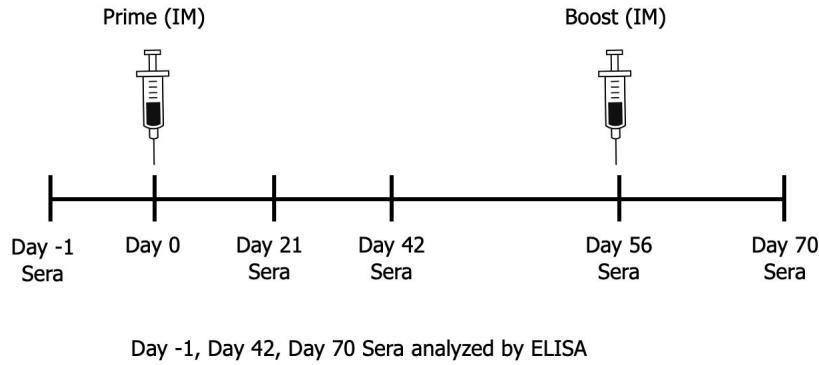
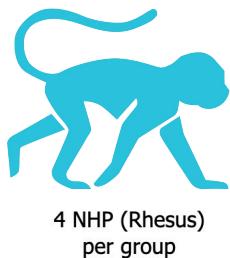
ELISA Data for 2 weeks sera post boost (Day 42)



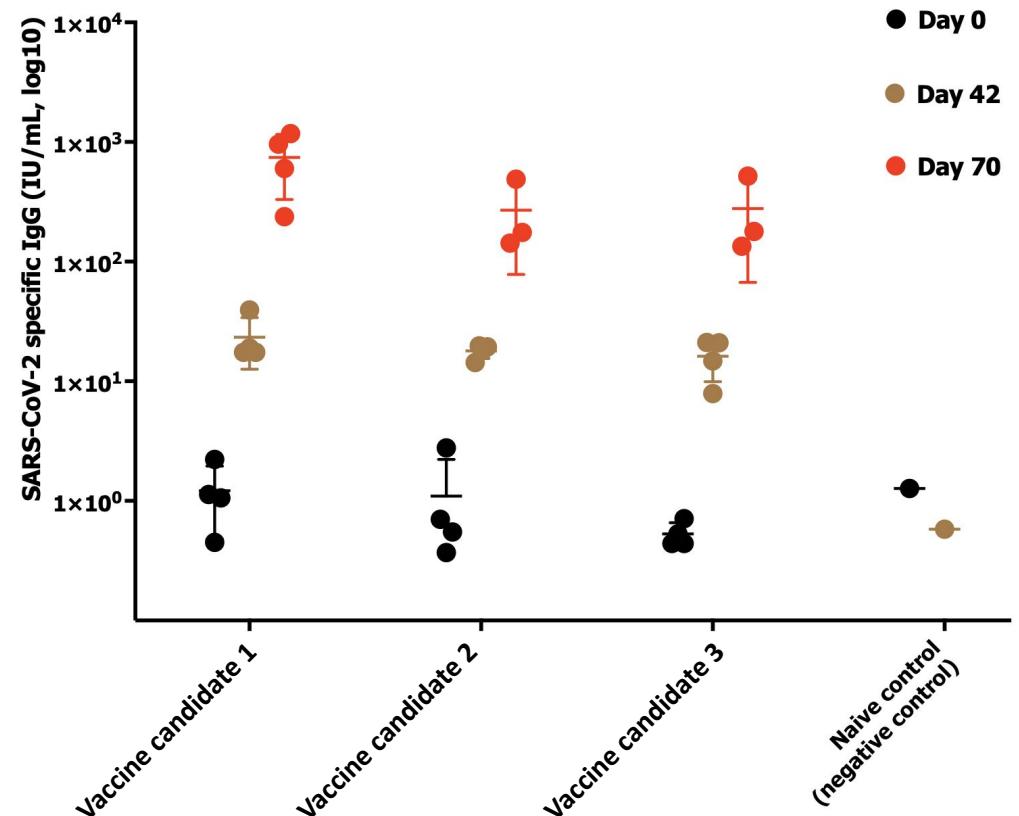
Data indicates that a no. of PNI lipids are extremely effective for vaccine applications



Vaccine Candidates Showed High IgG Levels in NHPs



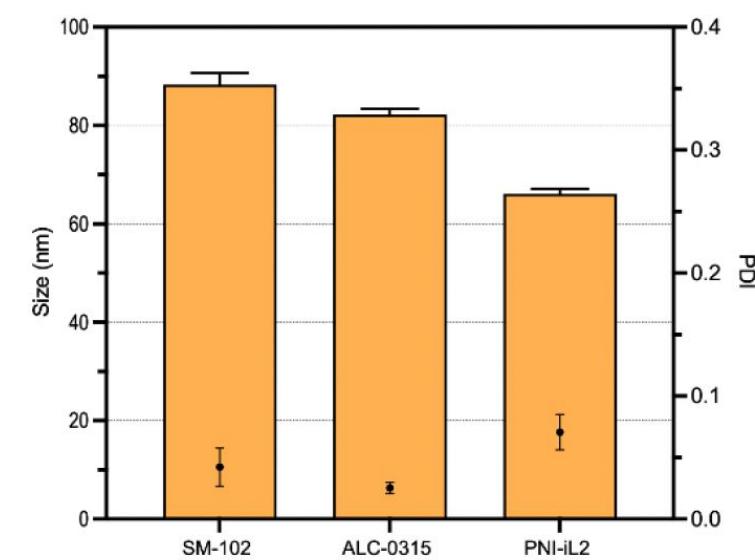
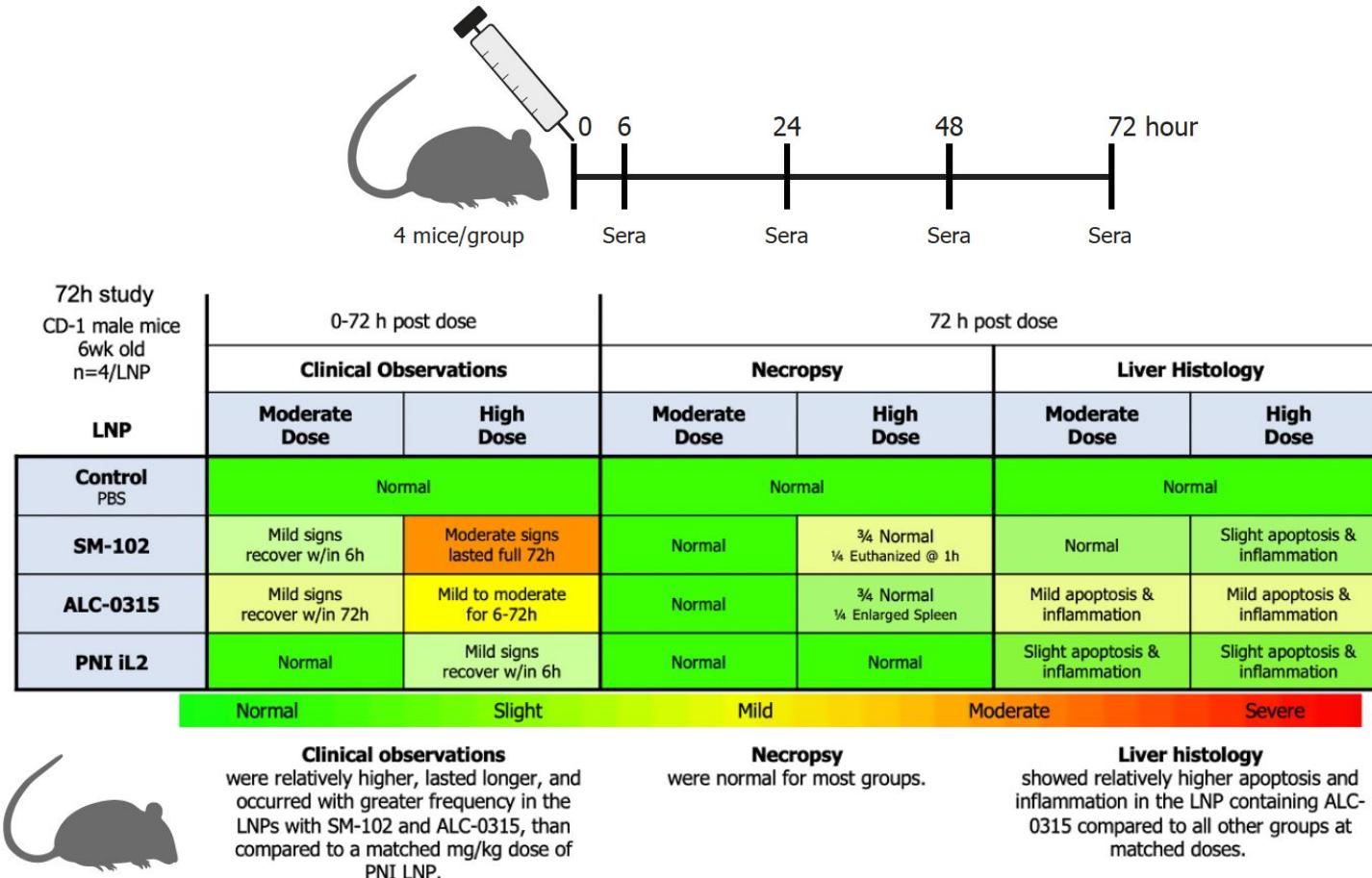
- Significant difference in IgG levels at Day 42 compared to pre-bleeds.
- High response was observed on Day 42 for all the candidates following Prime
- The response on Day 70 is much higher than other time points, a response typical of the boost.



WHO SARS-CoV-2 human IgG standard was used to establish a quantitative curve for relative quantification ant-spike IgG in the serum specimens

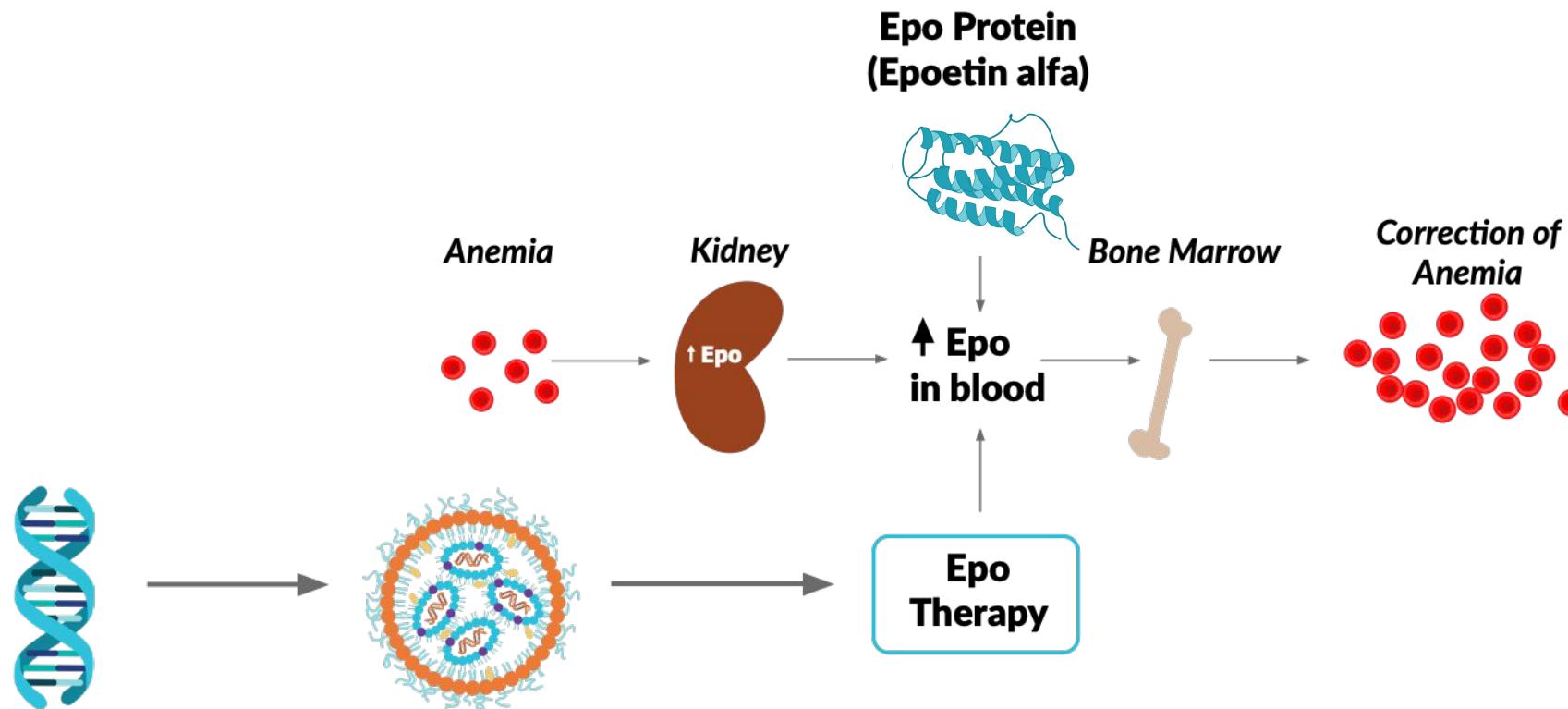
Calibration Control with known IgG concentrations and serum naïve Rhesus Monkeys (NHP02SRMUN, BIOIVT) were used as positive and negative controls

Tolerability of Lipids following IV administration

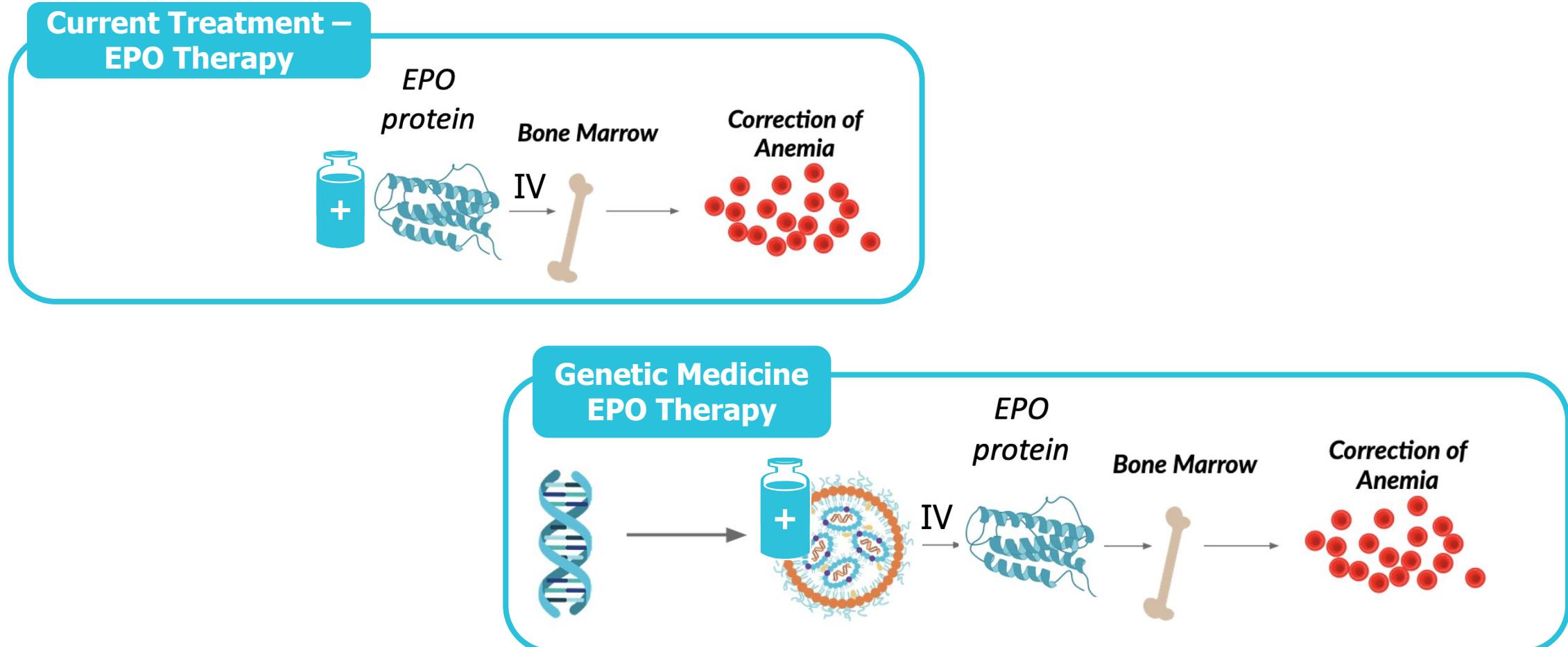


PNI Ionizable Lipid showcased good tolerability in a blinded study.

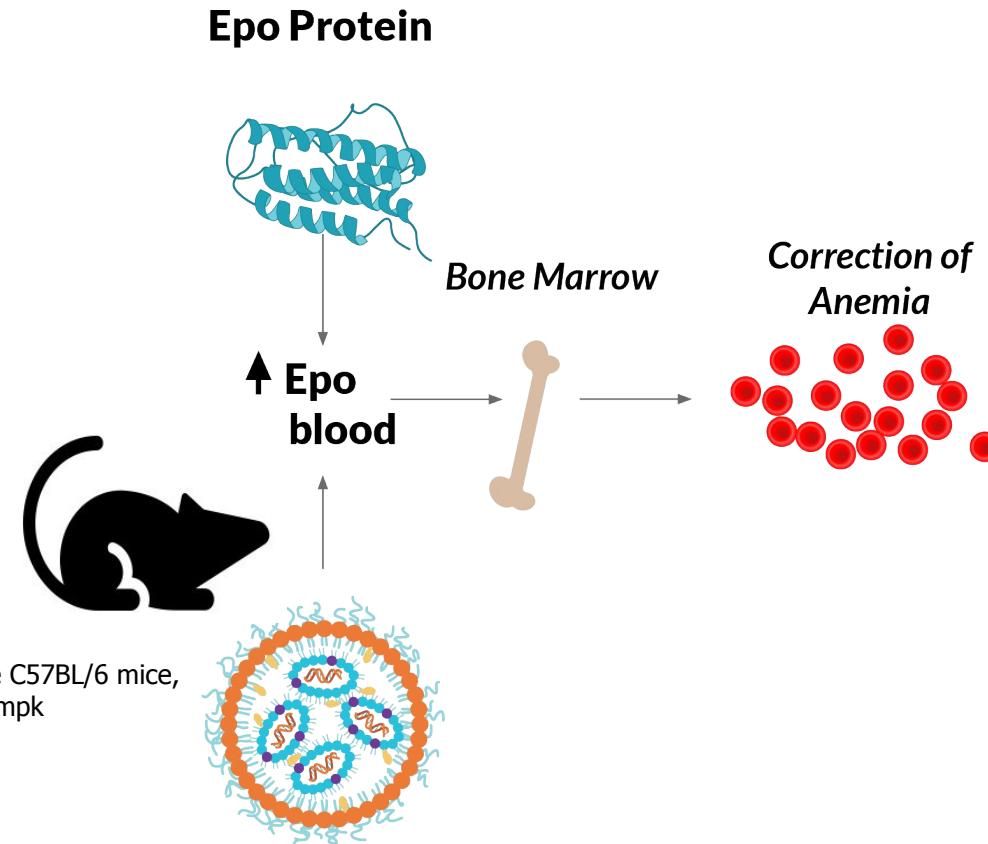
Gene Therapy



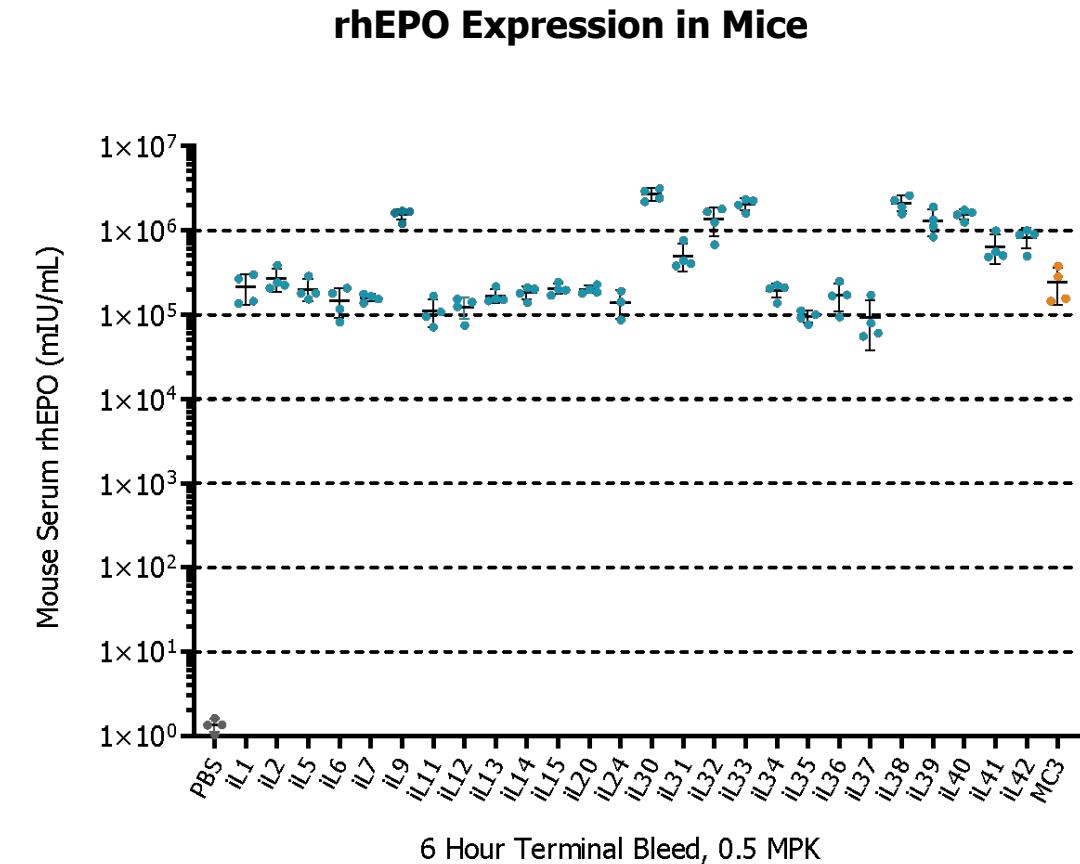
Gene Therapy



Erythropoietin (EPO) Expression – An Example for Protein Replacement Therapy

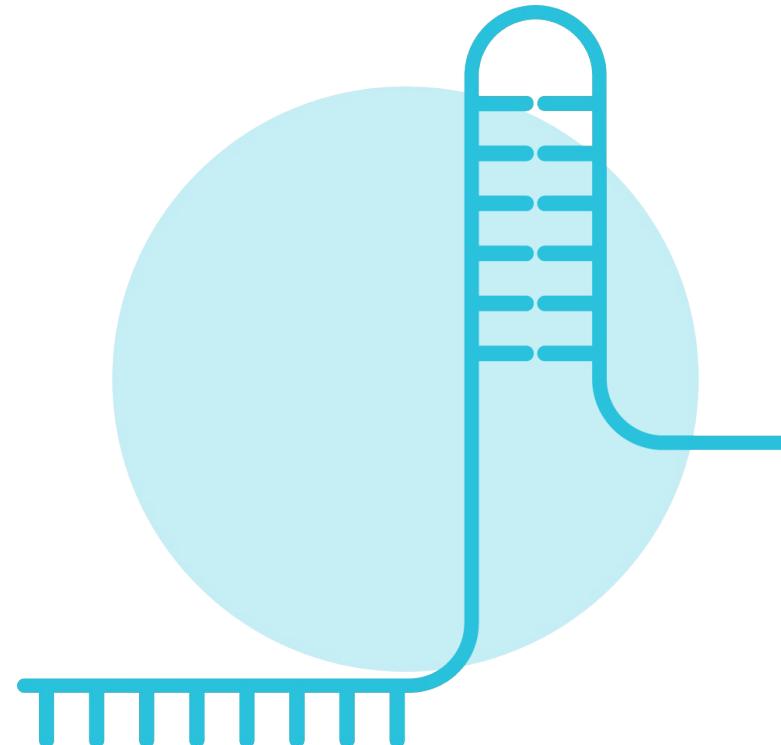


Data indicates that Precision NanoSystems' ionizable lipids demonstrate its ability to deliver mRNAs encoded for therapeutically relevant proteins



Gene Editing

CRISPR & Base Editing



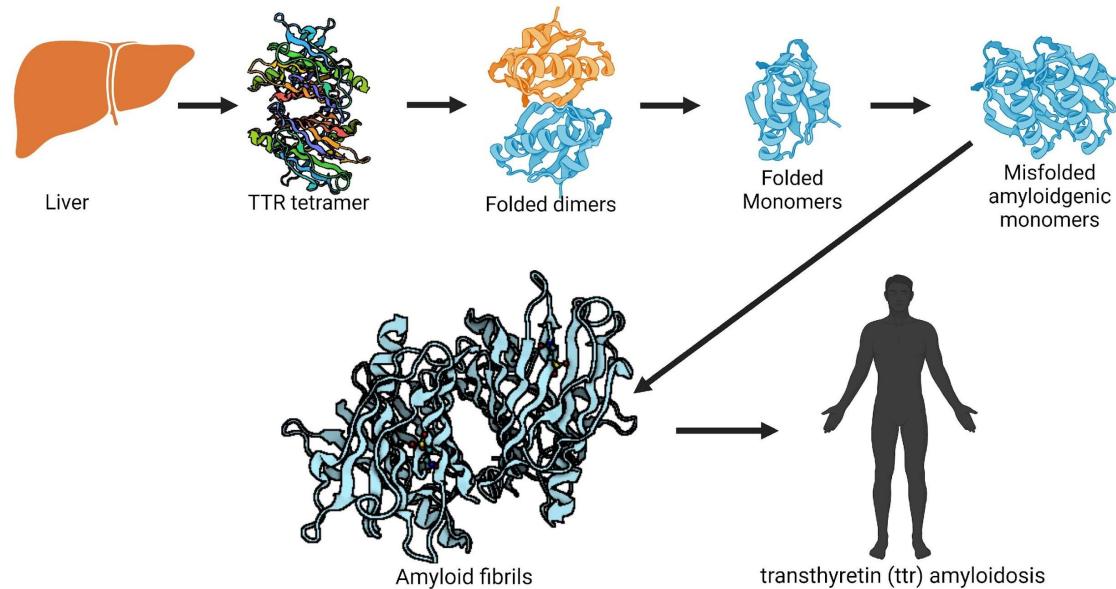
CRISPR to Reduce Transthyretin Amyloidosis - Intellia's NTLA-2001



Intellia's NTLA-2001 Phase -1 clinical trial data shows high promise for Transthyretin amyloidosis as single dose treatment

NCT04601051

Transthyretin Amyloidosis (ATTR)



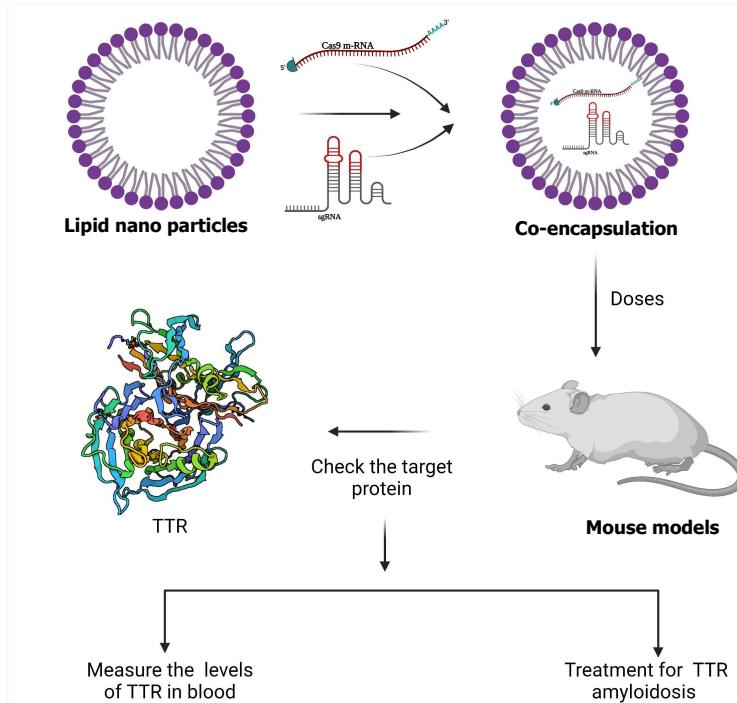
- A life-threatening genetic disease, caused by progressive accumulation of misfolded transthyretin (TTR) protein in tissues of nerves and heart
- Polyneuropathy & Myopathy can result
- Leads to cardiovascular disorders

○ Current treatment options

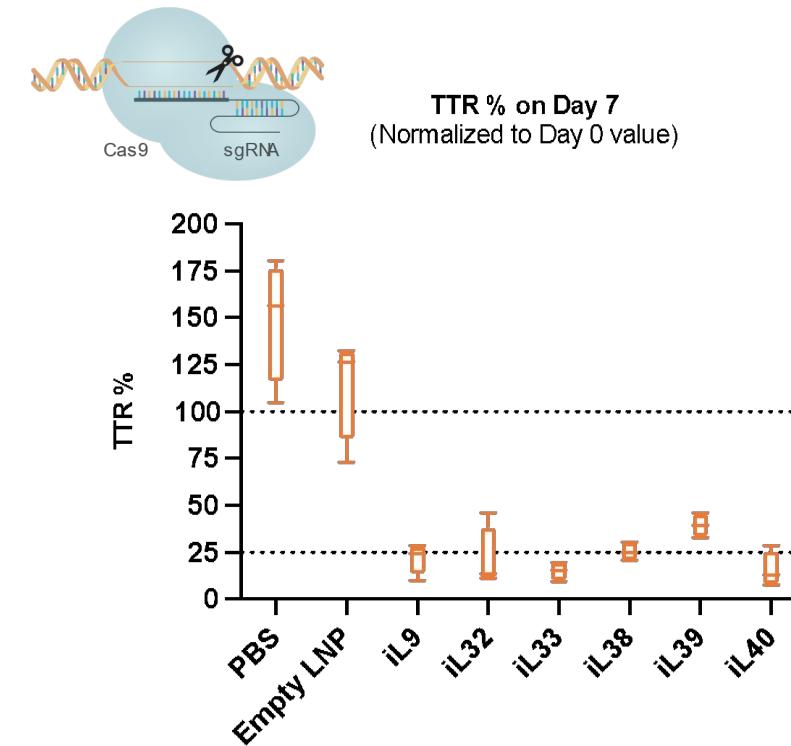
- Patisiran® (Onpattro™)
- Inotersen (Tegsedi™)

Image credit - BioRender

TTR CRISPR Gene Editing – Preliminary Data with Precision NanoSystems Ionizable Lipids as a Delivery System



A Single Administration of CRISPR/Cas9 Lipid Nanoparticles Achieves Robust and Persistent In Vivo Genome Editing.)

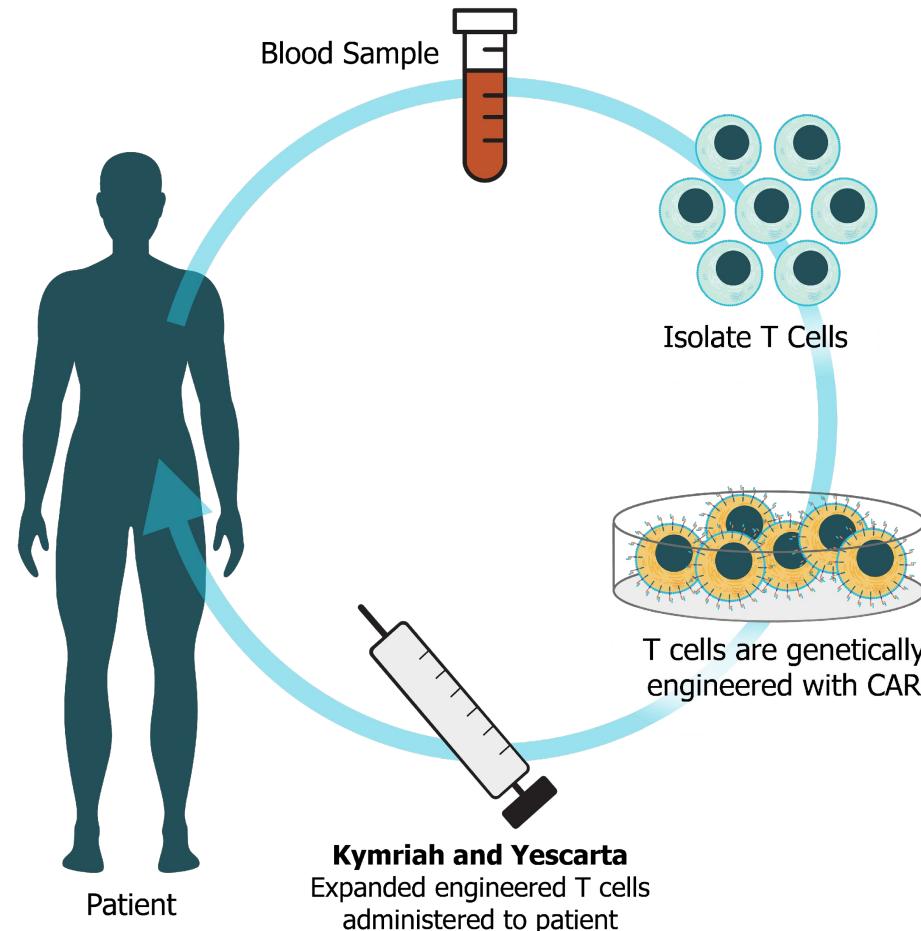


TTRguide-Cas9 mRNA LNP: Co-encapsulation of guide and Cas9 mRNA at 1:1 wt ratio

Preliminary results show more than 75% reduction in TTR protein levels with majority of tested lipids with one injection (3 mg/Kg)

Finn et.al., Cell Reports, 2017 (DOI: 10.1016/j.celrep.2018.02.014)

Cell Therapy



- The first FDA-approved CAR-T cell therapy



Image credit: Novartis

5 years from FDA approval. Novartis

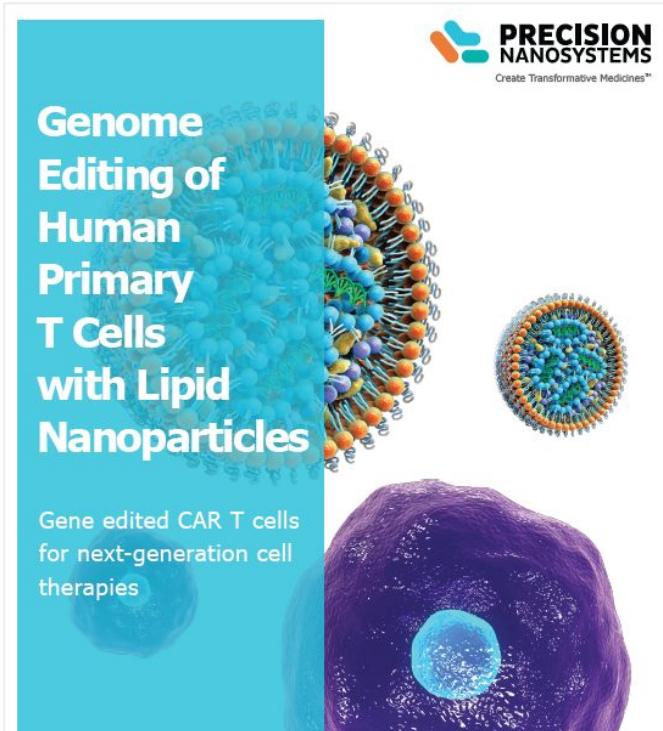


Image source:
<https://emilywhiteheadfoundation.org/news/celebrating-10-years-cancer-free/>

LNP mediated delivery of nucleic acid therapeutics have the potential to become similar **life saving genomic medicines**

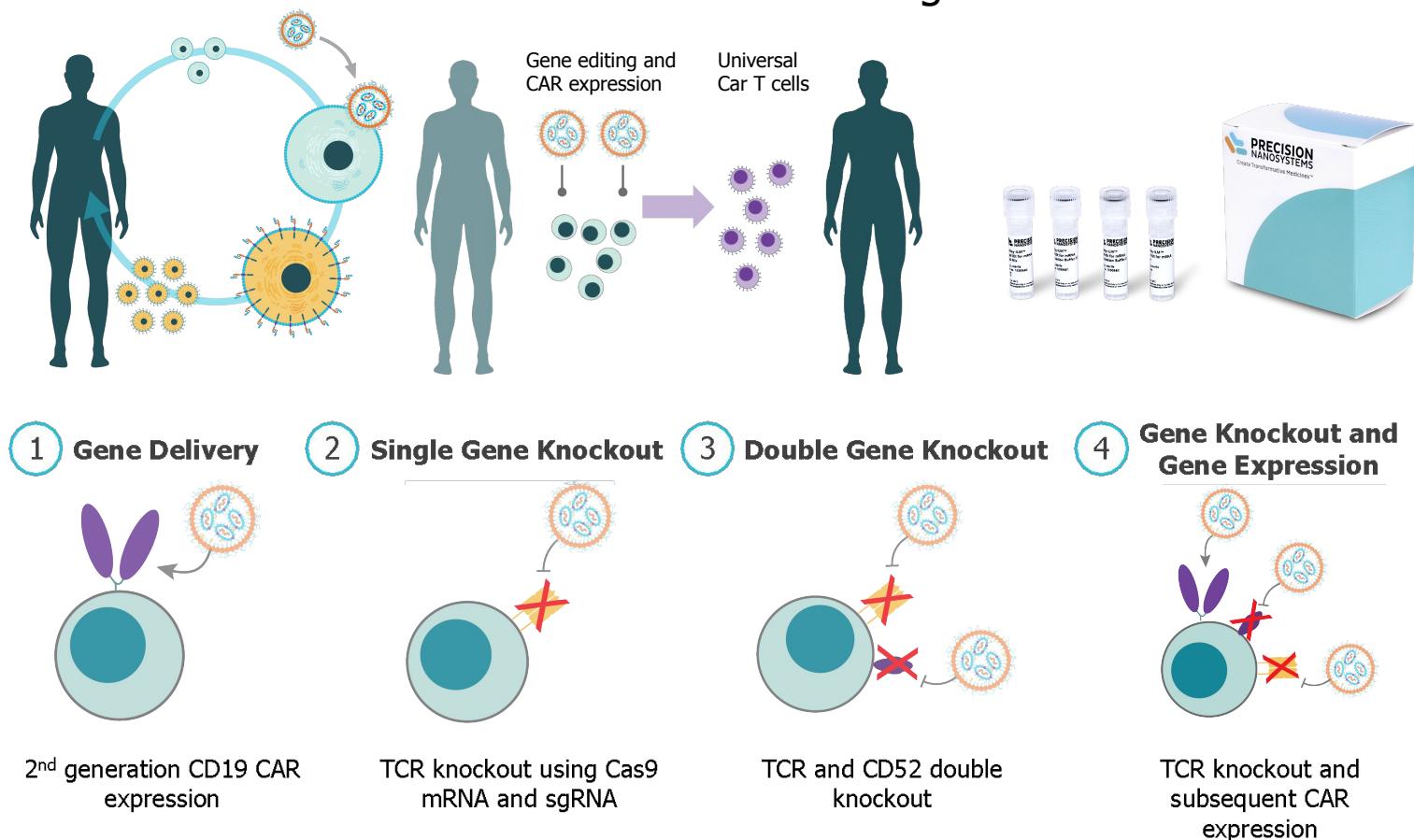
Off-the-shelf T Cell LNP Reagent for Accelerating T Cell Therapies

Immense possibilities with **Precision NanoSystems' Ionizable Lipids in T cell product kit.**



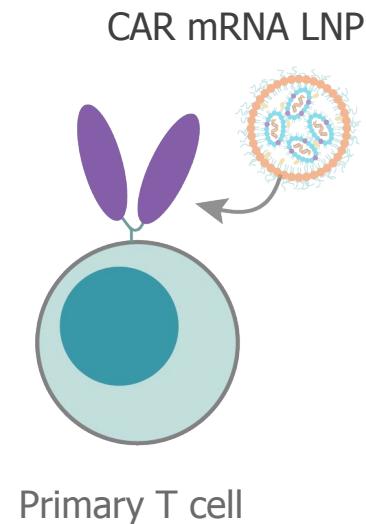
Application Note

First-to-market: An off-the-shelf T cell LNP reagent

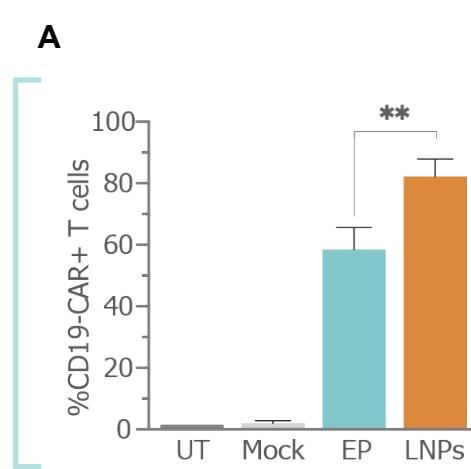


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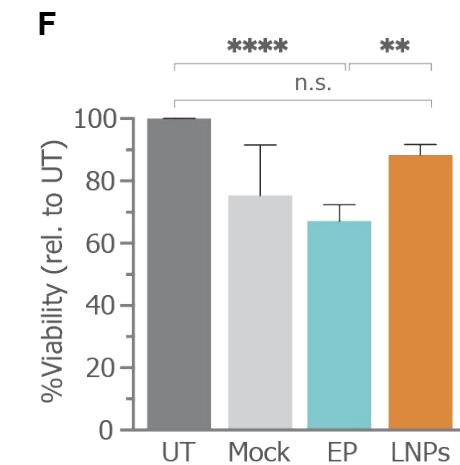
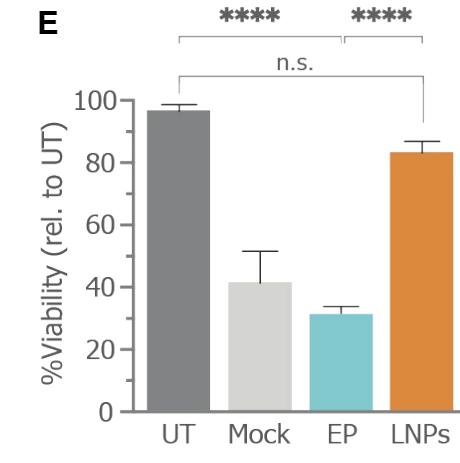
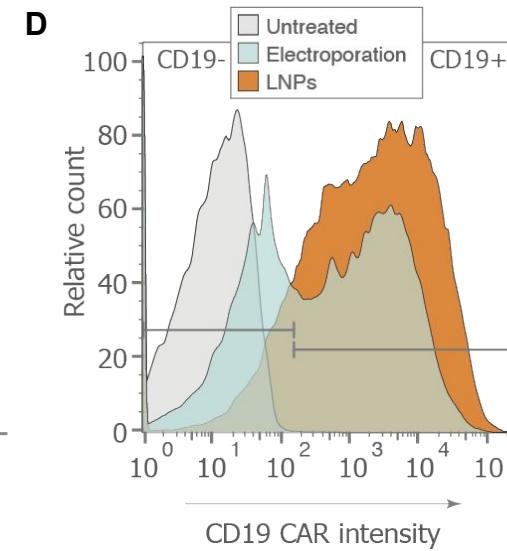
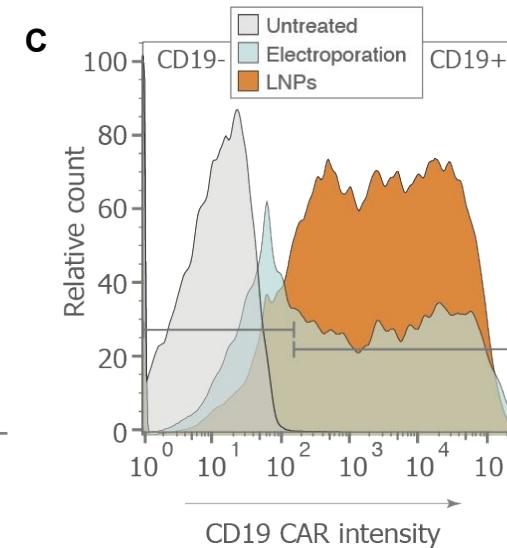
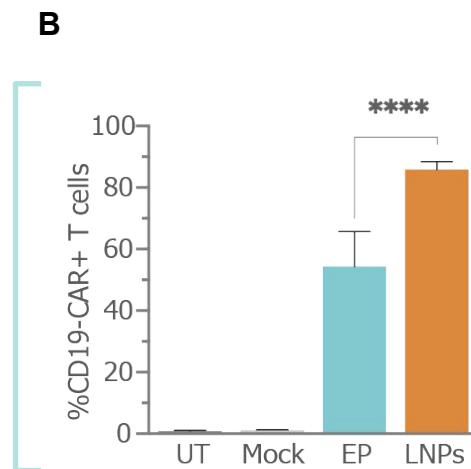
mRNA Delivery with High Efficiency and Cell Viability



24 h
detection

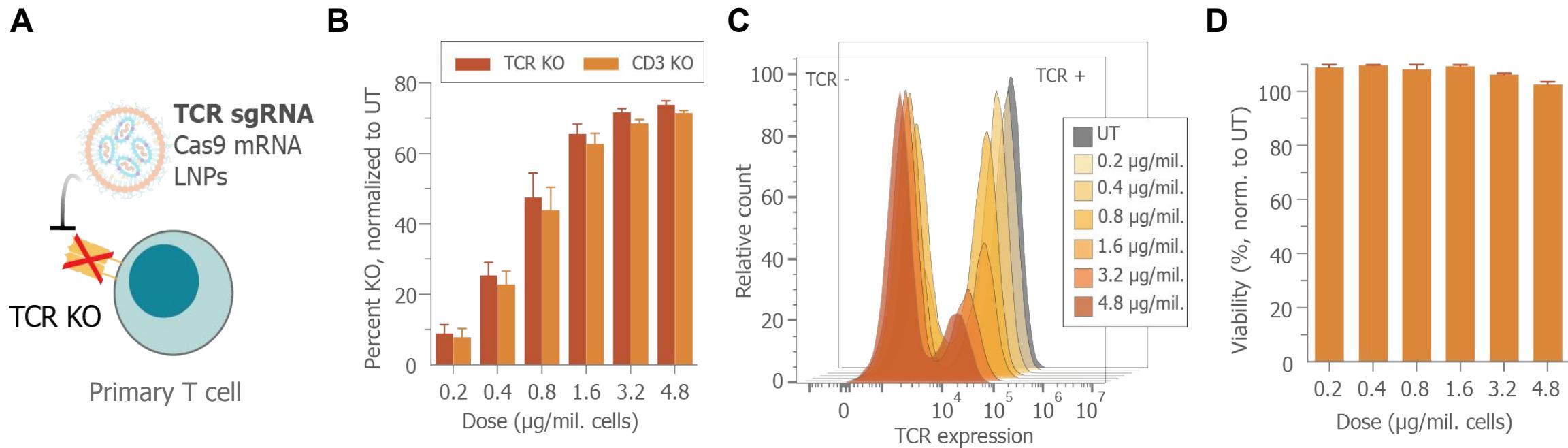


48 h
detection



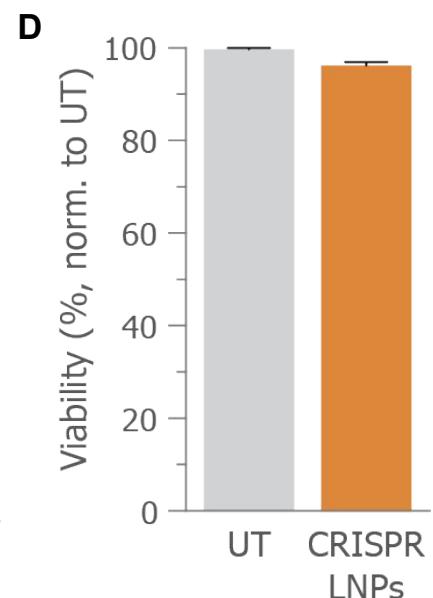
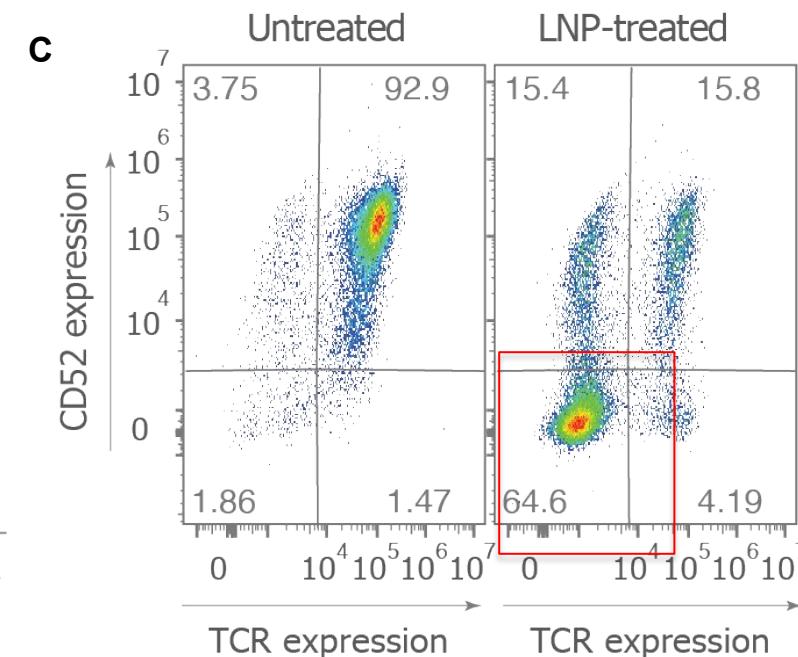
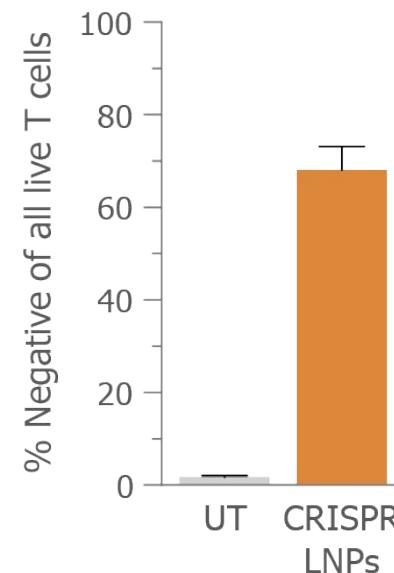
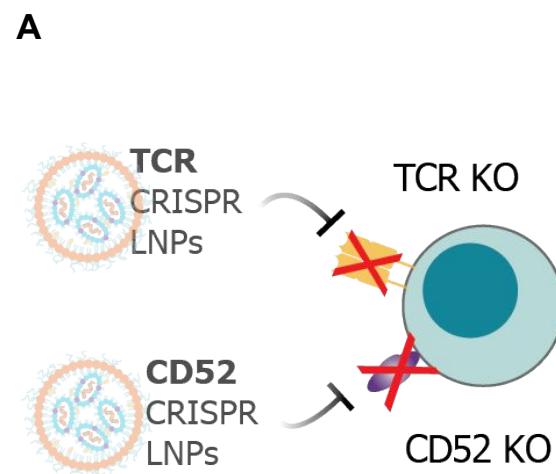
2

Single Target Knockout with High Efficiency and Cell Viability

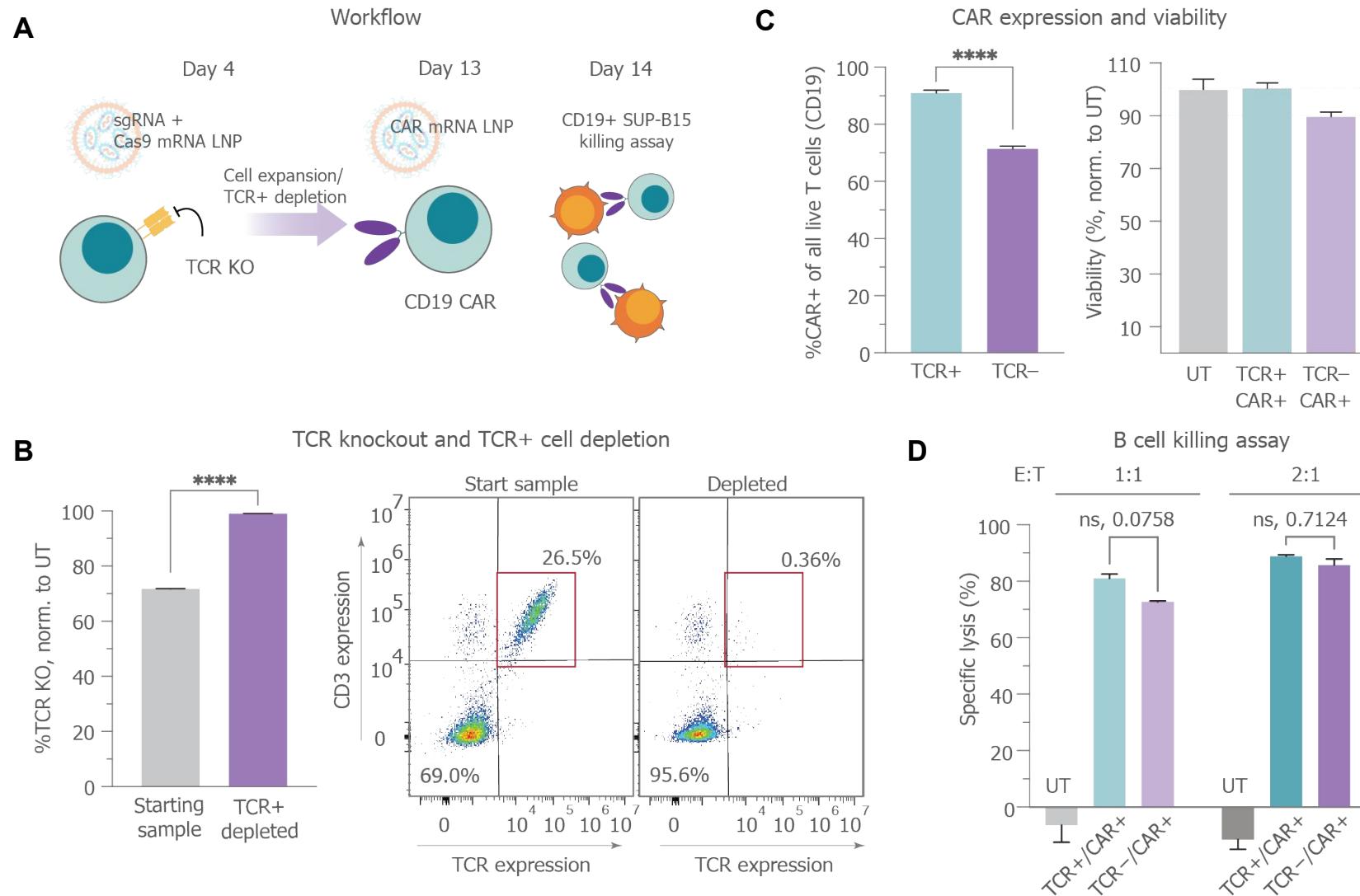


3

Double Target Knockout to Model Allogeneic Cell Therapy

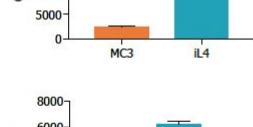
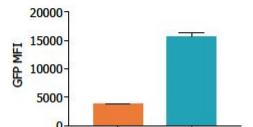


4 Multi-step Cell Engineering of Knockout Followed by Delivery

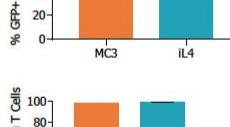
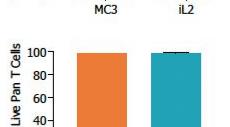
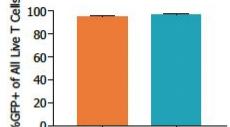


GFP expression in primary human T cells using PNI proprietary Lipid & LNP composition

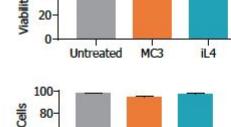
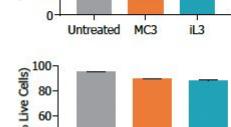
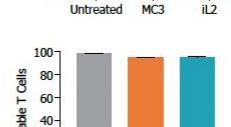
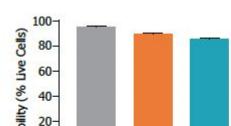
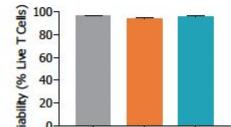
GFP Expression (Geometric MFI)



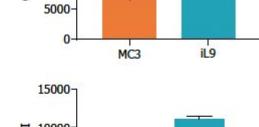
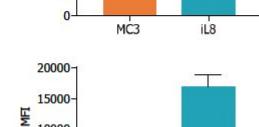
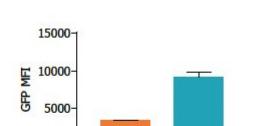
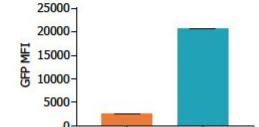
Transfection Efficiency (%)



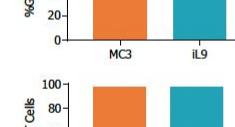
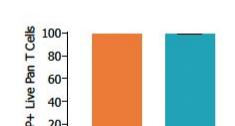
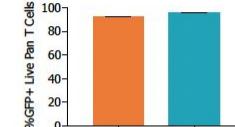
Viability (%)



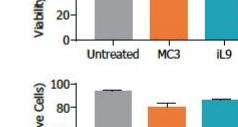
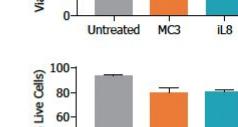
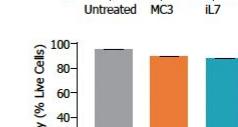
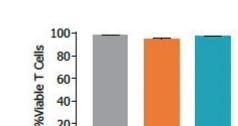
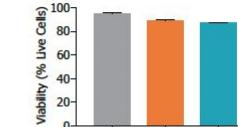
GFP Expression (Geometric MFI)



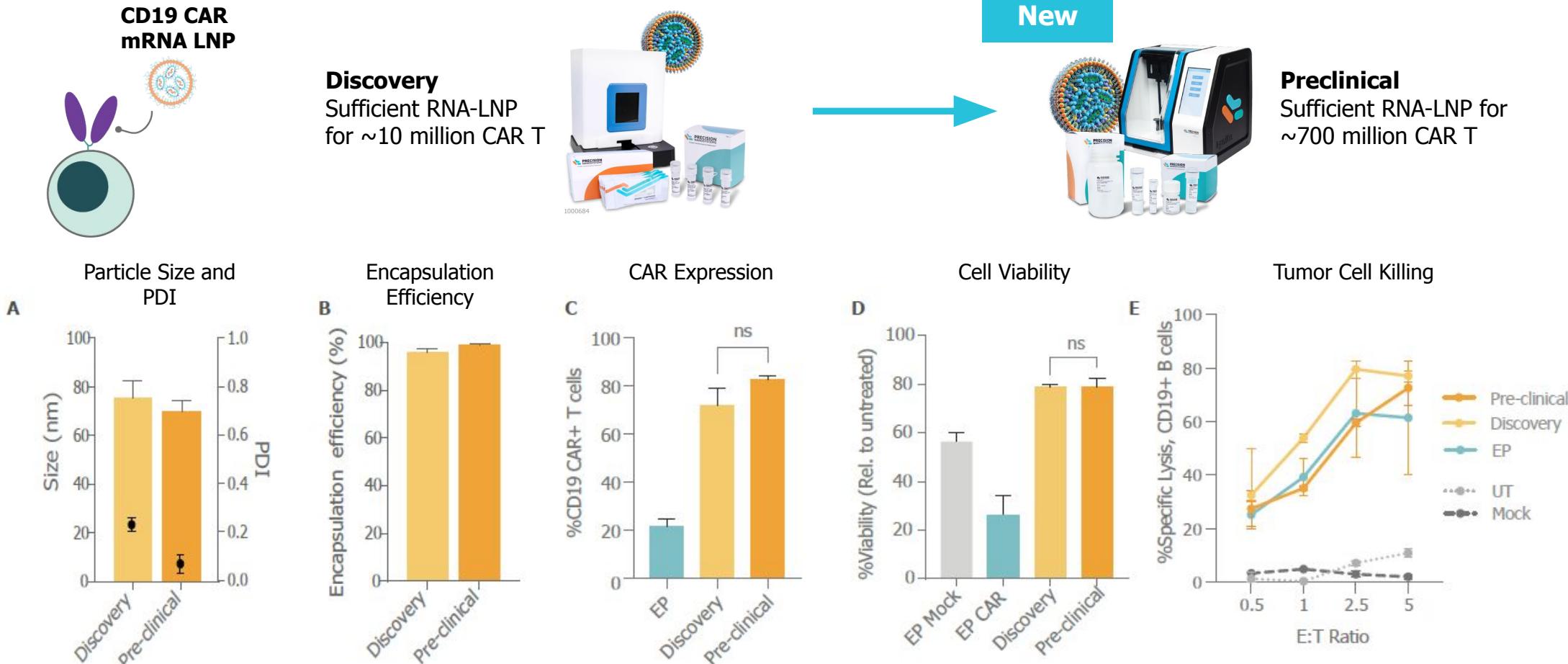
Transfection Efficiency (%)



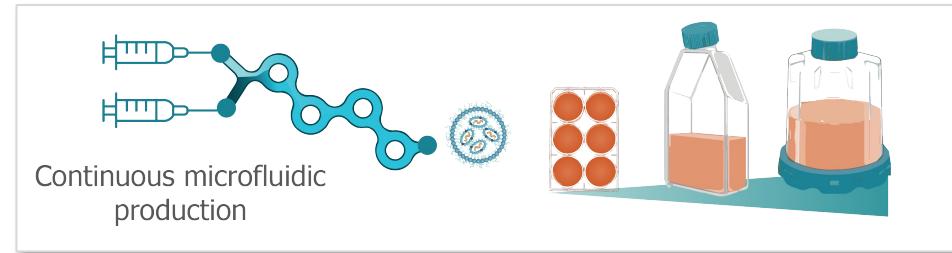
Viability (%)



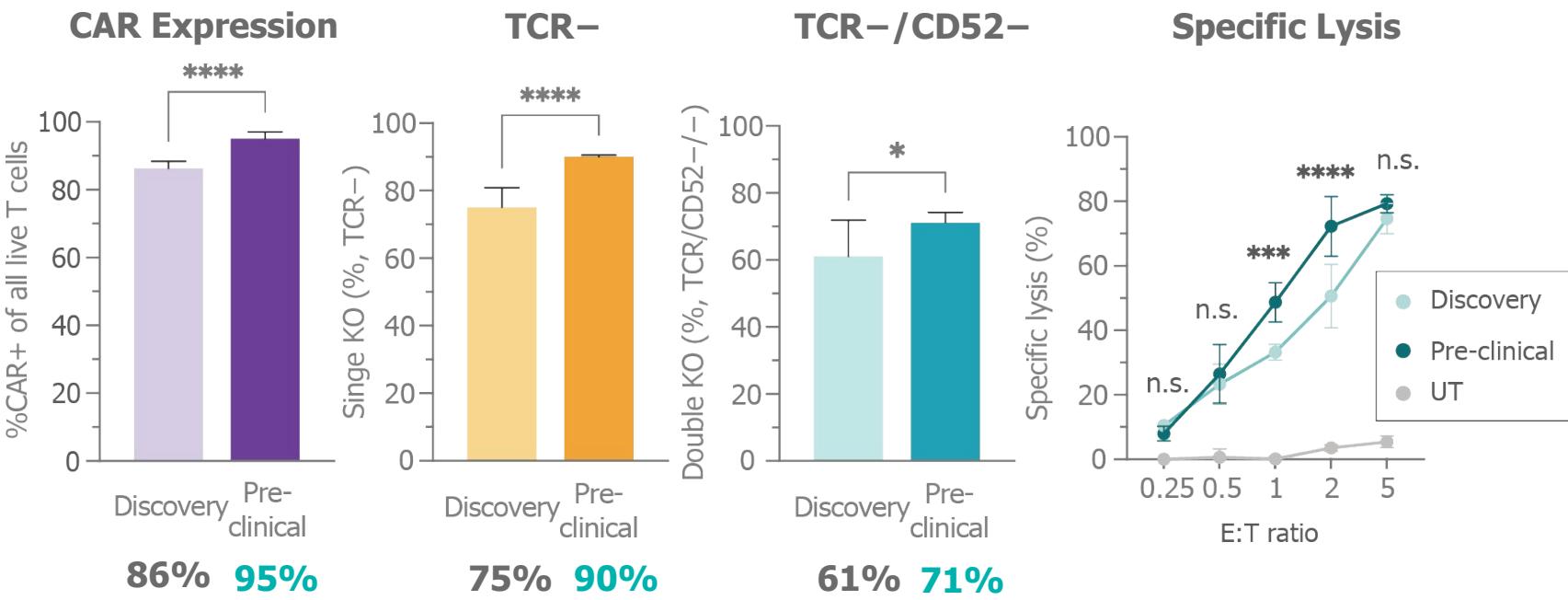
Enable Gene Editing and Delivery in Human Primary T Cells using Lipid Nanoparticles: Seamlessly Scalable from Discovery to Preclinical



Enable Gene Editing and Delivery in Human Primary T Cells using Lipid Nanoparticles: Seamlessly Scalable from Discovery to Preclinical



	Discovery Scale	Pre-clinical Scale
RNA wt.	10 µg	4 mg
LNP vol.	0.5 mL	18 mL
CAR T numbers	20 million	1 billion



Expertise Drives Optimal LNP Formulations for New Applications

LNP composition significantly affects CD34+ HSPC editing efficiency

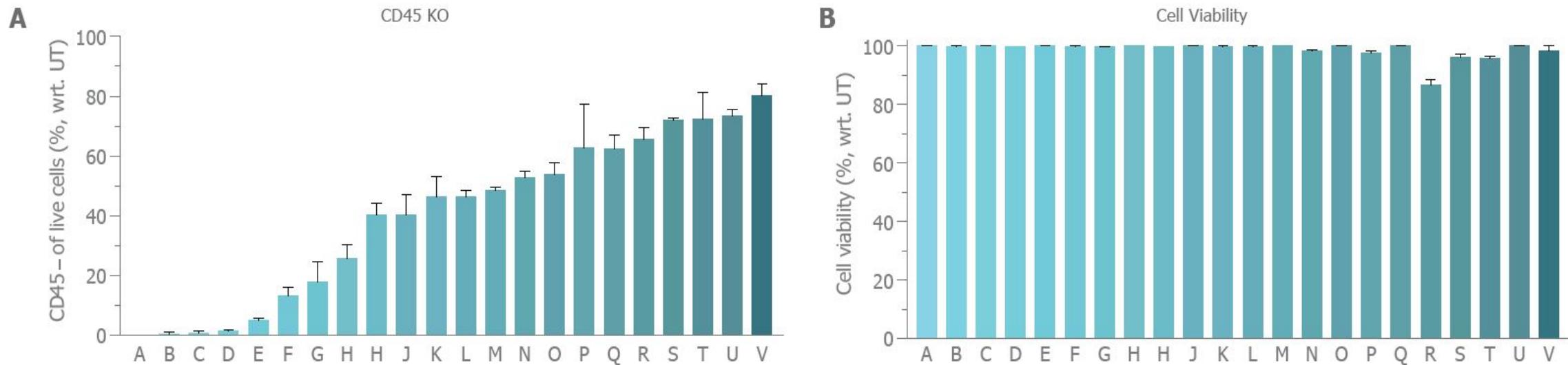


Figure 2. Various LNP compositions were designed from a proprietary lipid library and screened to identify lead candidates. **A)** CD45 knockout efficiency and **B)** cell viability as analyzed by flow cytometry.

Optimized
Pharmacokinetic
Profiles

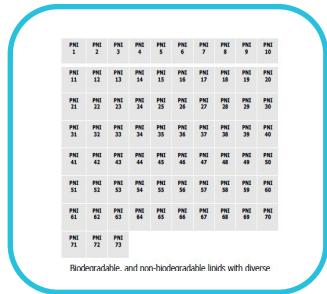
Leverage Precision NanoSystems expertise optimize delivery efficiency, potency, and biodistribution for novel genomic medicines



Access to our Ionizable Lipids

The “Lipid Menu”

Ionizable lipid portfolio



Category 3 “Exploratory”
Fit-for-purpose lipid formulation

Category 2 “Ready to test”
LNP panels with in-house POC data

Category 1 “Ready to use”
LNP formulation in RUO kits, can be licensed for clinical use

Client tested examples with preliminary positive results
Ocular delivery (intravitreal)
Myeloid delivery (intravenous)

Vaccine use (intramuscular)
Liver delivery (intravenous)

T-cell kit for *ex-vivo* use

RUO Reagent Kits Optimized for NanoAssemblr® Systems

Discovery

Preclinical

Clinical

Commercial

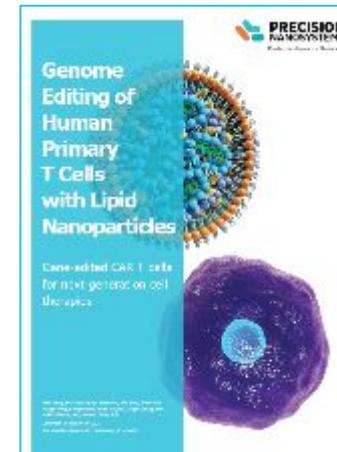
Research Use Only Lipid Nanoparticle Reagent Kits

GenVoy-ILM™ for Ignite

- Tool for trying LNP technology for the first time
- Benchmark for developing formulations

T Cell Kit for Spark and Ignite

- Validated for CRISPR and multiplex gene editing



Off-the-shelf
LNP kits

Lowering the barrier to entry for developing genomic medicines by offering easy to use LNP kits with a clear path to the clinic

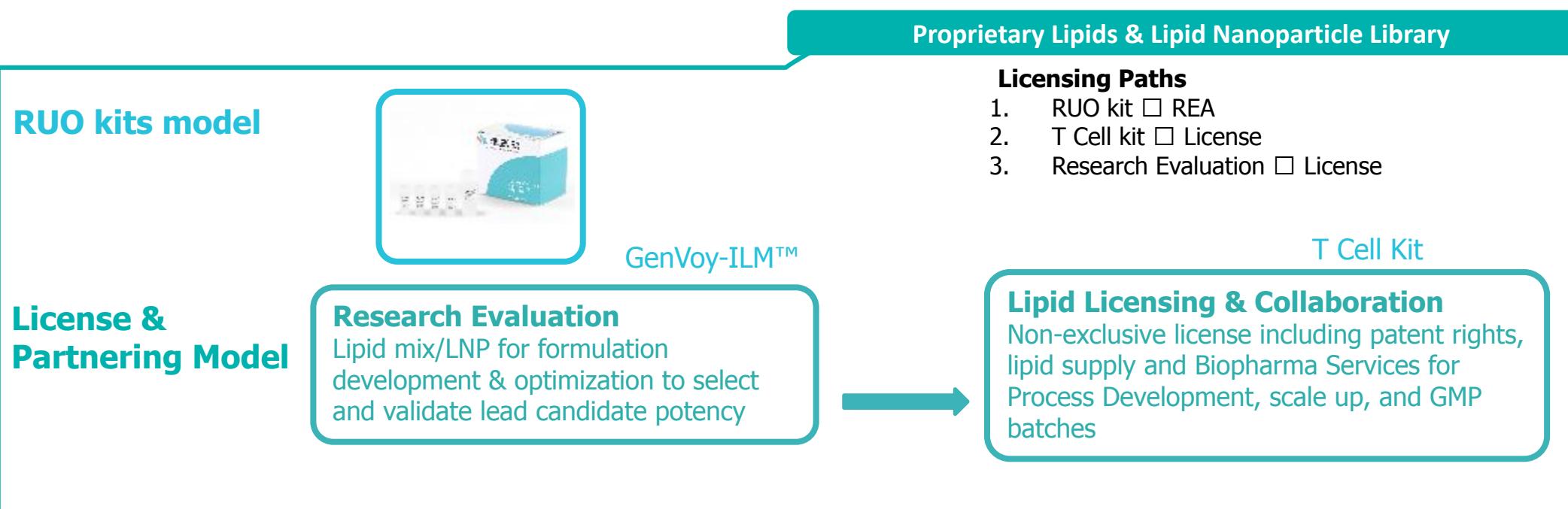
Proprietary Clinical Lipids & Lipid Nanoparticle Portfolio

Discovery

Preclinical

Clinical

Commercial



Flexible
Licensing

Affordable non-exclusive licensing and flexible deal packages to enable custom solutions

Selected Lipid Licensee & Collaborators

Precision NanoSystems and Replicate Bioscience in licensing deal to scale up genomic medicines

NEWS PROVIDED BY
[Replicate Bioscience](#) →
 Jul 26, 2022, 08:00 ET

SHARE THIS ARTICLE



REPLICATE

(PRNewsfoto/Replicate Bioscience)

- Companies aim to support development of up to 15 new genomic medicine products
- Replicate's commercial licensing of lipid nanoparticle technology from Precision NanoSystems at foundation of deal

<https://www.newswire.ca/news-releases/precision-nanosystems-and-replicate-bioscience-in-licensing-deal-to-scale-up-genomic-medicines-888682943.html>

Precision NanoSystems and Aurora Vaccines Join Forces to Accelerate the Development of Vaccine Candidate for Hepatitis C Virus

Thursday, July 14, 2022

[Company Profile](#) | [Follow Company](#)



Vancouver, BC, July 14, 2022--(T-Net)--**Precision NanoSystems** (PNI), a leader in non-viral delivery of genomic medicines, announced that it has entered into a strategic collaboration agreement with Aurora Vaccines to accelerate the development and manufacture of its Hepatitis C vaccine candidate.

<https://www.bctechnology.com/news/2022/7/14/Precision-NanoSystems-and-Aurora-Vaccines-Join-Forces-to-Accelerate-the-Development-of-Vaccine-Candidate-for-Hepatitis-C-Virus.cfm>



End to End Solutions for Genomic Medicine
Development

Genomic Medicines are Complex and Require Specialized Reagents, Instruments, and Services



The development of genomic medicines is inherently complex



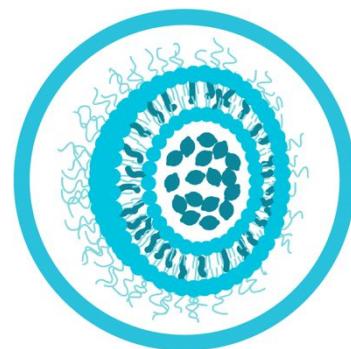
Biopharma Services

Drug development expertise at all stages



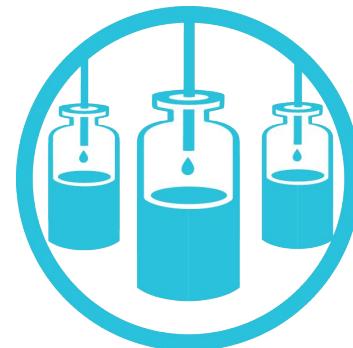
Payload—Genetic API

saRNA Platform



GenVoy Delivery Platform

Proprietary PNI lipids to enable development from the bench to the clinic and beyond

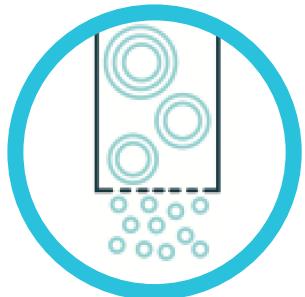


NanoAssemblr Manufacturing

Scalable production for all stages of development

- Process
- Development
- Downstream Process
- Effects
- Safety
- Administration

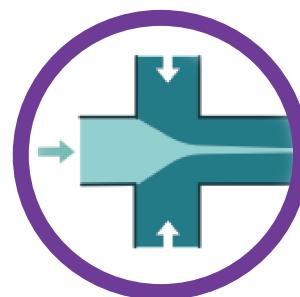
Nanoparticles can be made a number of ways



Sonication/Extrusion



T-tube and Impingement Jet Macromixing

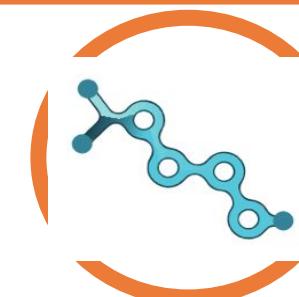


Other Microfluidic Approaches

- Limited applications
- Difficult to reproduce
- Harsh process conditions
- Difficult to scale
- Limited applications
- Difficult to reproduce
- Not suited for rapid development
- + Gentler process conditions
- + Demonstrated scale-up for limited applications

- Challenges scaling up
- Not designed for specific nanoparticle manufacturing
- + Expanded applications
- + Reproducible
- + Non-turbulent process conditions
- + Suited to small volume formulations

PNI/Pall NxGen technology comes with freedom of usage (IP protected)



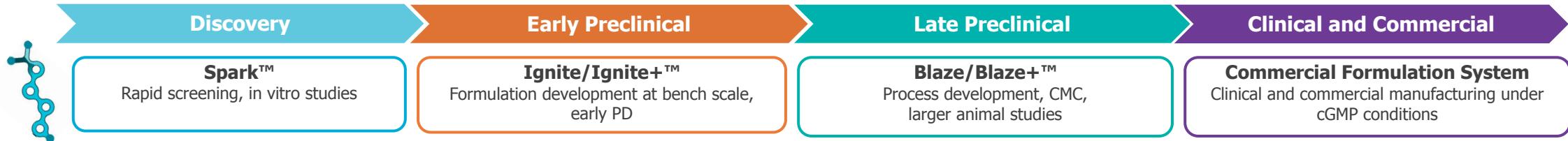
NxGen Microfluidics

- + Easy to scale
- + Broad range of applications
- + Potential multi-mixer integration opens possibilities
- + Reproducible
- + Non-turbulent process
- + PNI's Second Generation Technology

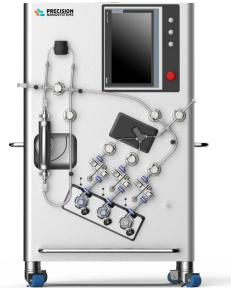
PRECISION
NANOSYSTEMS
Create Transformative Medicines™

+ Compatible with **Series Mixing Technology** and other complex architectures

Scalable Solutions from Research Through to Commercial



Existing preclinical systems to accelerate drug development through de-risking MFG runs at bench scale

				
NxGen™ Mixer	NxGen™	NxGen™ NxGen™ 500	NxGen™ 400 NxGen™ 500	NxGen™ commercial cartridge 12 L/h* NxGen™ commercial cartridge 48 L/h
Volume per Run[^]	25 µL – 250 µL	1 mL – 60 mL	20 mL – 10 L	1L – 100 L (8.3hr) 1L – 400 L (8.3hr)
RNA per Run[#]		Up to 4.5mg Up to 13.5mg	Up to 2.3g	Up to 22.3g Up to 90g

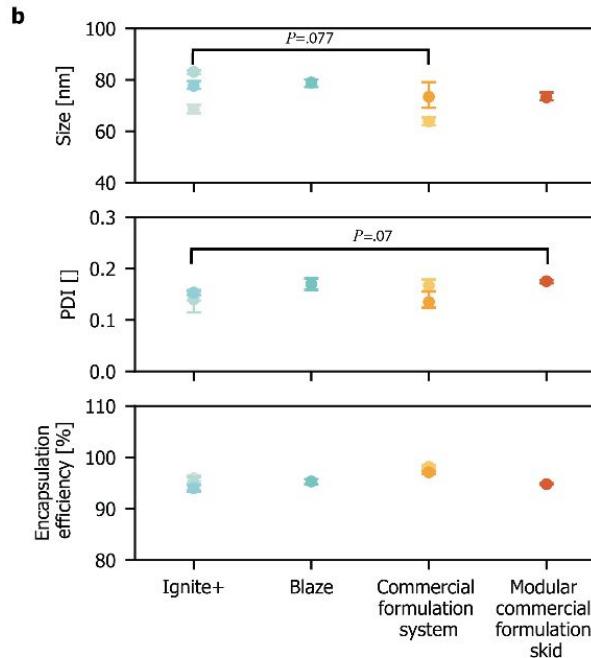
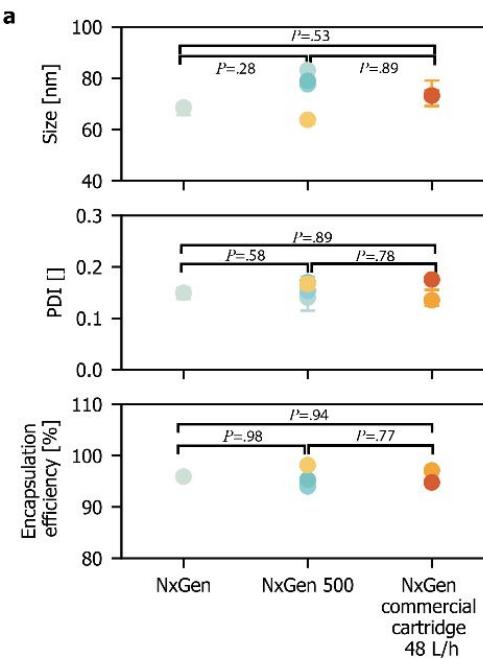
NxGen™ technology enables consistent mixing parameters across all scales

*NxGen™ commercial cartridge 12 L/h is equivalent to NxGen 500

[^]Undiluted mRNA-LNP formulation

#3:1 FRR, 0.3mg/ml RNA

Consistent CQAs Following Downstream Processing

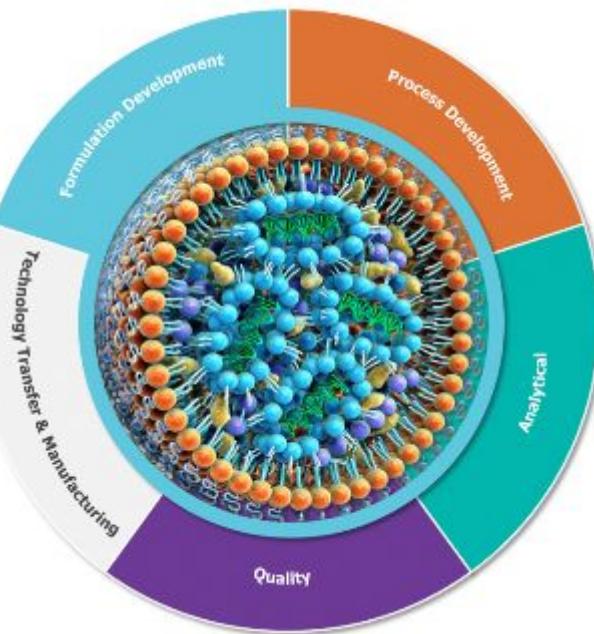


Condition	NanoAssembl(r) system	NxGen mixer cartridge	Total flow rate [L/h]	Batch volume [mL]	RNA Encapsulated [mg]
1	Ignite+	NxGen	0.72	30	1.1
2	Ignite+	NxGen 500	6.9	30	1.1
3	Ignite+	NxGen 500	12	30	1.1
4	Blaze	NxGen 500	6.9	30	1.1
5	commercial formulation system	NxGen commercial cartridge 12 L/h [NxGen 500]	12	100	3.3
6	commercial formulation system	NxGen commercial cartridge 48 L/h	48	100	3.3
7	modular commercial formulation skid	NxGen commercial cartridge 48 L/h	48	150	5.0

- LNP size, PDI, and EE% post-formulation, dilution, TFF and sterile filtration are consistent across a range of flow rates on Ignite+, Blaze, GMP System and commercial systems

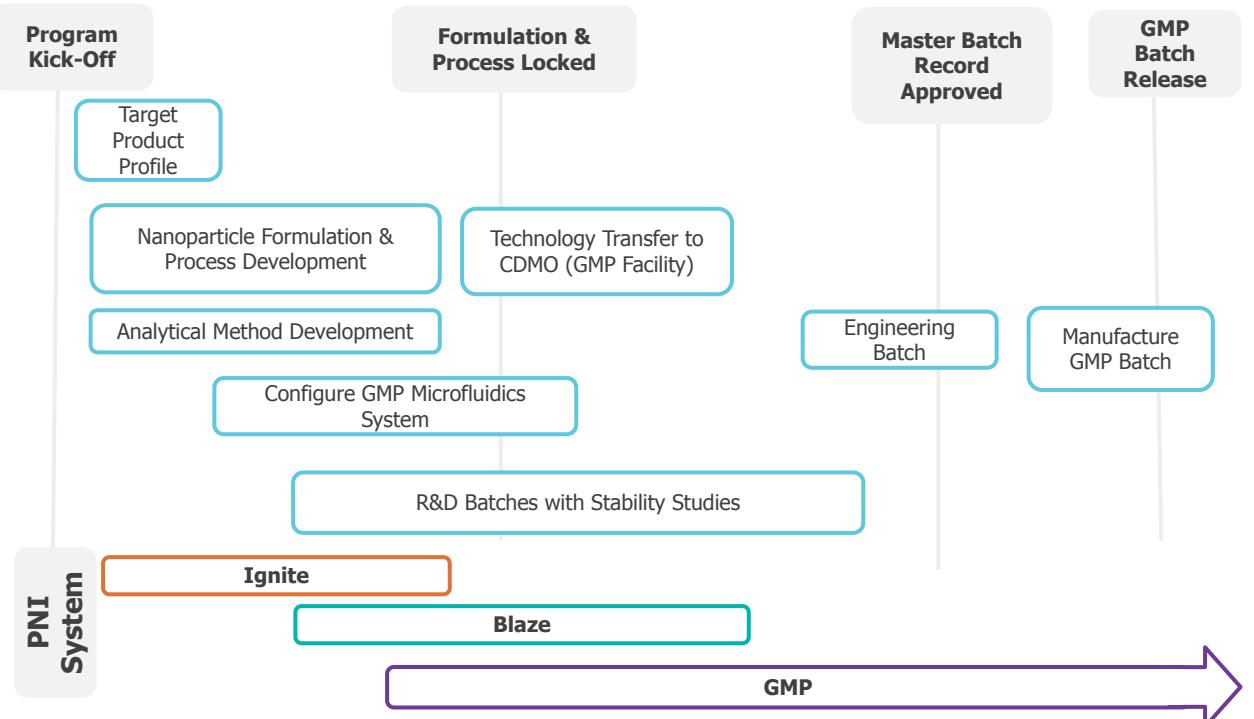
Expertise & Capabilities for Developing Nucleic Acid Therapeutics

Core Capabilities for mRNA-LNP Vaccine Development



Drug
Development
Expertise

Expertise Across the Entire Path to the Clinic



Trusted Expertise

Experience across a broad range of drug payloads and carriers. Cumulative experience on over 150 projects, 26 clinical stage programs, production of >44 GMP batches producing 2 approved drugs.

Unparalleled Formulation and Drug Development Expertise



Value-Added Services and Expertise

Formulation Development

- Formulation development to optimize product's physico-chemical properties and biological activity
- Identify critical quality attributes and draft drug product specifications
- Projects encompass a broad spectrum of payloads and delivery technologies

Process Development

- Process transfer from Ignite™ and scale-up with Blaze™ and GMP
- Example projects include scale-up process development, nanoparticle purification, terminal sterilization processes, and design of experiment (DoE) studies to optimize manufacturing parameters

Analytical

- Comprehensive analytical capabilities to support drug development, including genomic medicines
- Example methods include: UPLC (QQQ, CAD, PDA, ELSD) for lipids/drug substance, bioanalyzer for DNA, RNA, protein quantification & in vitro RNA potency assays

Technology Transfer & Manufacturing

- Build custom GMP platform per client specifications and prepare demonstration batch at scale on GMP manufacturing system
- Prepare GLP-Tox batch & perform release and stability testing
- Provide relevant documentation & on site training

Quality

- Support IQ/OQ of GMP manufacturing systems
- Assist with CMC regulatory submissions
- Programs supported by relevant Quality Management Systems (QMS) including Pharmaceutical Quality System for drug products and ISO-9001 (under development) for manufacturing systems

Precision NanoSystems Biomanufacturing Centre – Coming Soon



1055 Vernon Drive, Vancouver, BC, Canada



New Headquarters

Approx 75,000
sq.ft. 4th floor
Offices

3rd floor Labs and
Offices 2nd floor B-1



BMC – 2nd Floor

32,000 sq.ft. Launching H1, 2024
Cleanrooms, Labs,
Office, Warehouse

2024 Biomanufacturing Centre

- An end-to-end, turnkey facility offering genetic payload, lipid delivery, and NanoAssemblr manufacturing platforms
- Includes modular GMP cleanrooms for mRNA drug substance manufacturing and two suites for drug product manufacturing with solution preparation, drug compounding, and fill/finish facilities
- Controlled non-classified GMP space with QC lab, QC microbiology lab, QC stability and raw material storage chambers, process engineering lab, and controlled ambient storage with shipping and receiving area
- First GMP manufacturing line qualification expected in 2023
- **Manufacturing capacities*:**
 - Clinical Formulation**
 - Clinical batches up to 20-50 L pre-dilution
 - Formulated drug product with up to 10 g of RNA payload
 - Filling capabilities up to 2400, 2-mL vials
 - Commercial Formulation**
 - Commercial batches up to 50-100 L pre-dilution
 - Formulated drug product with up to 50 g of RNA payload



*Tentative estimations based on an saRNA LNP vaccine product



Summary

Precision NanoSystems Solutions Are Versatile



Vaccines

- E.g., mRNA & DNA
- Focus on infectious diseases and cancer
- Population-based to individualized

Gene Therapy

- E.g., siRNA, mRNA, DNA, CRISPR
- Focus on rare and genetic diseases
- Population-based to individualized

Cell Therapy

- E.g., siRNA, mRNA, DNA, CRISPR
- Focus on oncology regenerative medicines
- Autologous & allogeneic

Protein and Small Molecule Nanomedicines

- Focus on all major indications
- Improved targeting, specificity, release kinetics and solubility



Nucleic Acids

- Exogenous genes that silence, express or edit a genetic mutation causing a disease

Messenger RNA (mRNA)

CRISPR Guide RNA (gRNA)

Self-amplifying mRNA (SAM)

**Long noncoding RNA (lncRNA)
and other emerging modalities**

Small RNA (siRNA, microRNA)

DNA



Lipid Nanoparticles (LNPs)



Deliver Nucleic Acids & Proteins

Liposomes



Deliver Nucleic Acids, Proteins & Small Molecules

Exosomes



Deliver Nucleic Acids, Proteins & Small Molecules

Polymer Particles



Deliver Nucleic Acids, Proteins & Small Molecules

Emulsions



Deliver Small Molecules

Peptide NPs



Deliver Proteins and Nucleic Acids

NPs Encapsulating Viruses



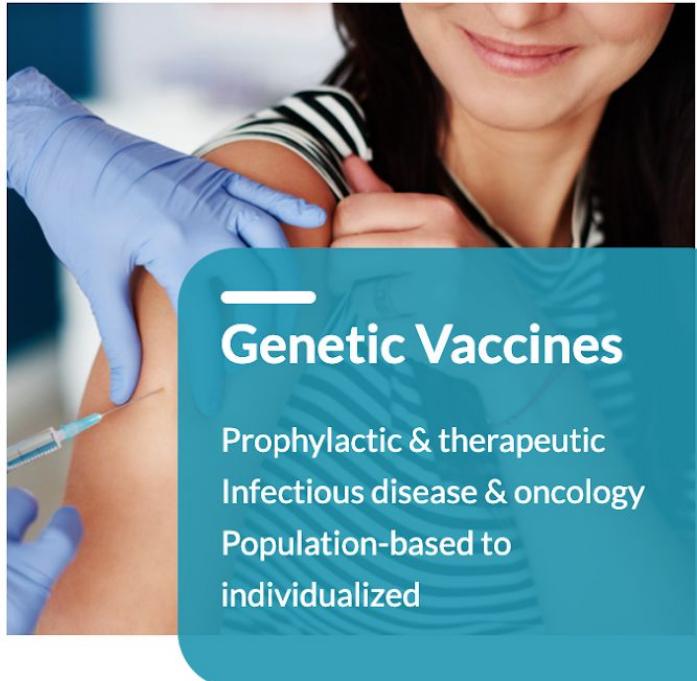
Deliver DNA

We are part of the Danaher Life Sciences family



Accelerating Tomorrow's Genomic Medicines

From idea to approved medicine.



These therapeutic modalities have broad application in the prevention and treatment of diseases including infectious disease, rare disease and cancer

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Thank you for listening!

Questions?

Visit us at Booth 310!



Create Transformative Medicines™

