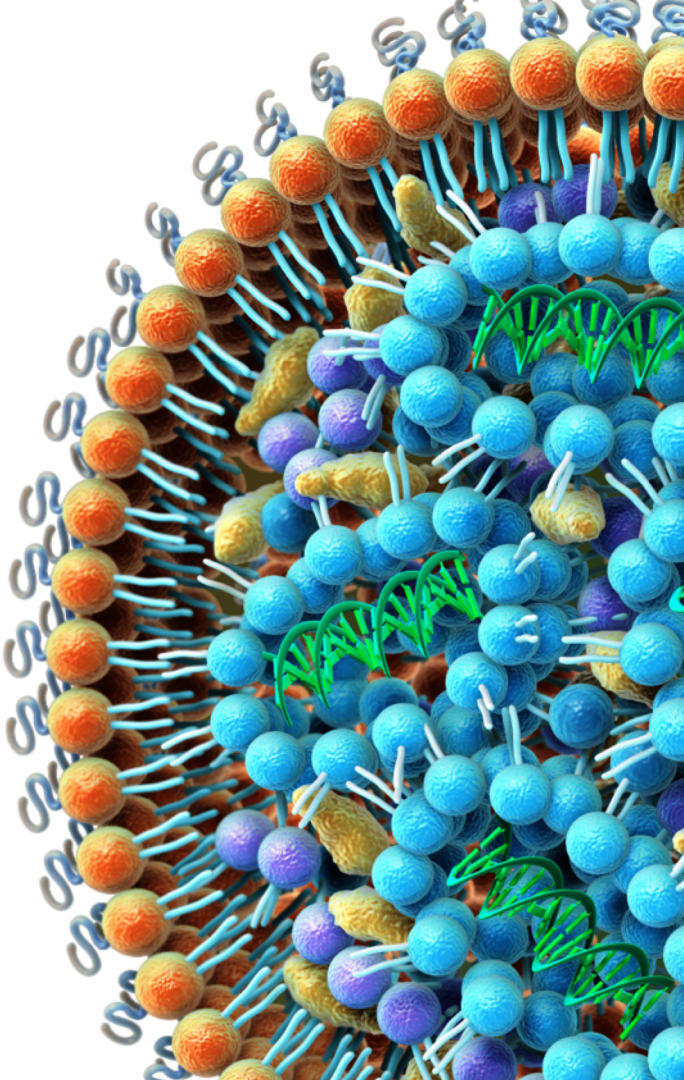
Accelerating the Development of Transformative Nanomedicines with NxGen™ Microfluidics Technology



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The Precision NanoSystems R&D team has demonstrated the development of a **model mRNA-LNP therapeutic** from discovery to scale-up production, with minimal formulation and process optimization.

1. Background & Overview
2. NxGen Microfluidics for Scalable Manufacture of LNPs
3. Formulation and Process Development of Model mRNA Drug

Our Vision

To accelerate the creation of transformative medicine that significantly impacts human well being.

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PNI's Clients are Developing Novel Drugs to Tackle Diseases with Significant Unmet Medical Need

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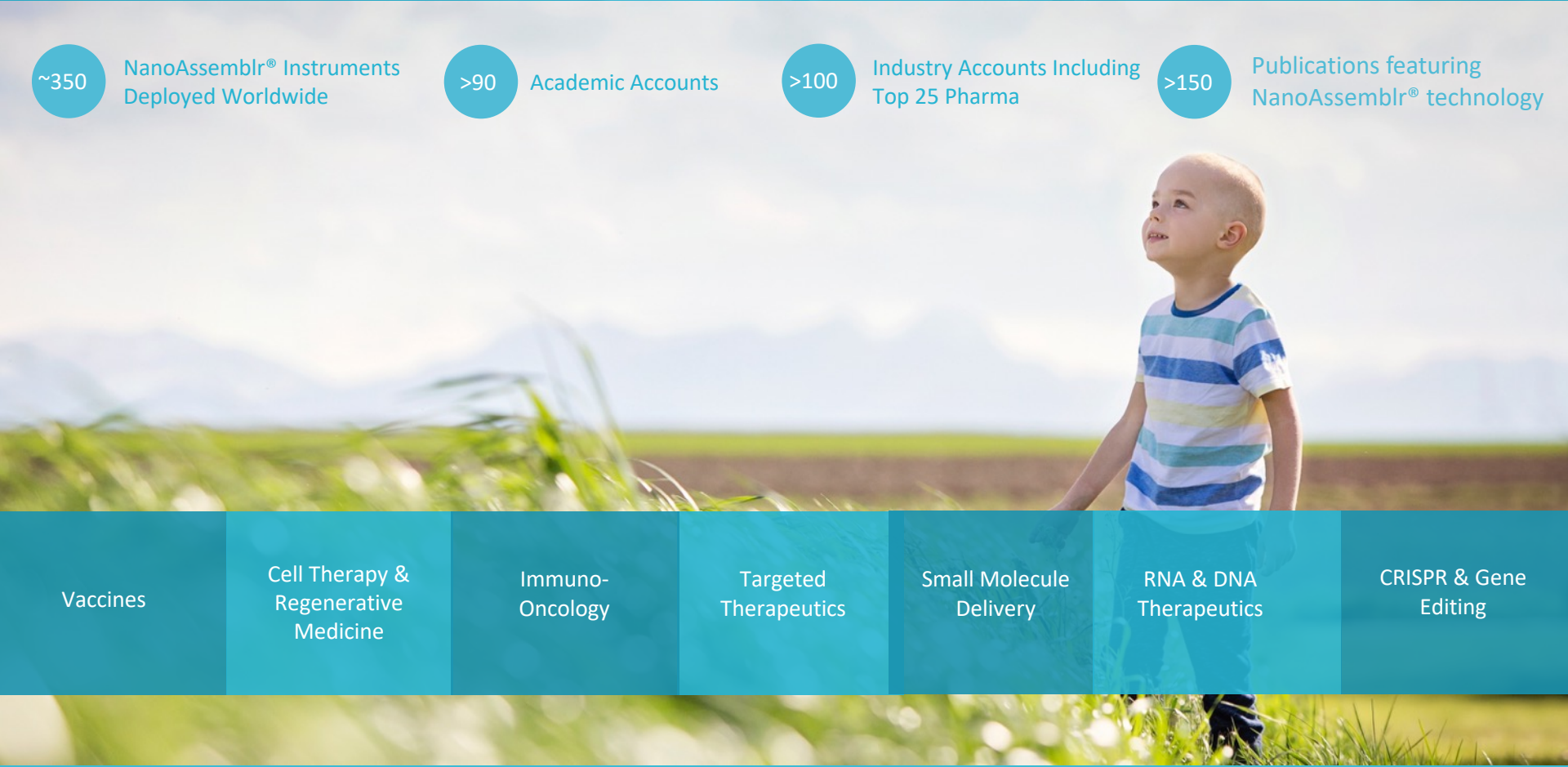
- ~350 NanoAssemblr® Instruments Deployed Worldwide
- >90 Academic Accounts
- >100 Industry Accounts Including Top 25 Pharma
- >150 Publications featuring NanoAssemblr® technology



- Vaccines
- Cell Therapy & Regenerative Medicine
- Immuno-Oncology
- Targeted Therapeutics
- Small Molecule Delivery
- RNA & DNA Therapeutics
- CRISPR & Gene Editing

Core Technologies Overview

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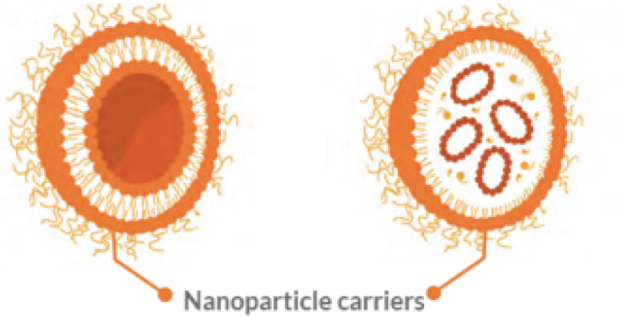
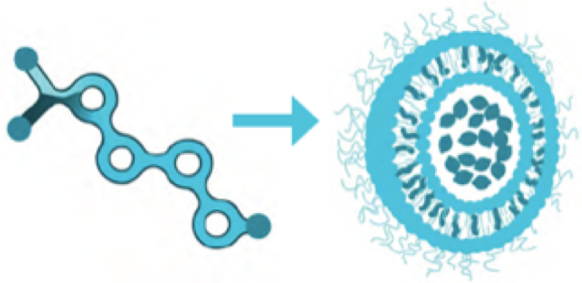
1. Nanoparticle Drug Delivery Technology



Genvoy-ILM™ RUO Reagents

2. NxGen Microfluidics Nanoparticle Manufacturing Technology



NanoAssemblr® Platform:
Spark™, Ignite™, Blaze™, and cGMP

GenVoy-ILM Lipid Nanoparticles for Nucleic Acid Encapsulation & Delivery

Background & Overview

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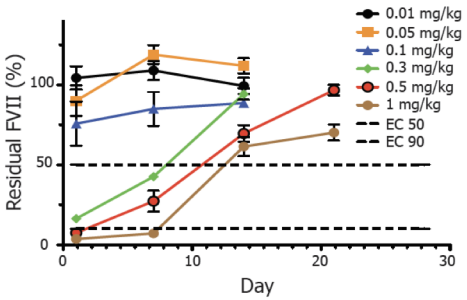
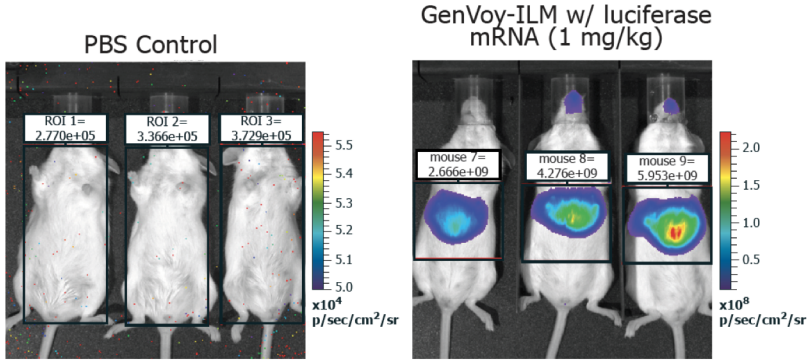
Deliver siRNA for sustained gene knockdown



A single injection of GenVoy-ILM Factor VII siRNA-LNP was administered to mice via the tail vein at the RNA doses indicated and plasma levels of Factor VII protein were measured up to 21 days post-administration.

Deliver mRNA for gene expression



A single injection of GenVoy-ILM Luciferase mRNA-LNP was administered to mice via the tail vein at an RNA dose of 1 mg/mL. Luciferase expression was measured 6-hours post-mRNA-LNP administration.

GenVoy-ILM has been validated for gene silencing and mRNA-mediated gene expression applications

NxGen Microfluidics for Scalable Manufacture of LNPs

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Nanoparticles are More Complex than Previous Generations of Drugs

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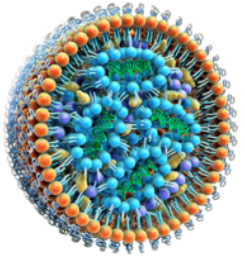
Aspirin
21 atoms
1 molecule

Somatropine
~ 3,000 atoms
1 molecule

Herceptin
~ 25,000 atoms
1 molecule

RNA LNP
~ 17,x 10^7 atoms
~100,000 molecules

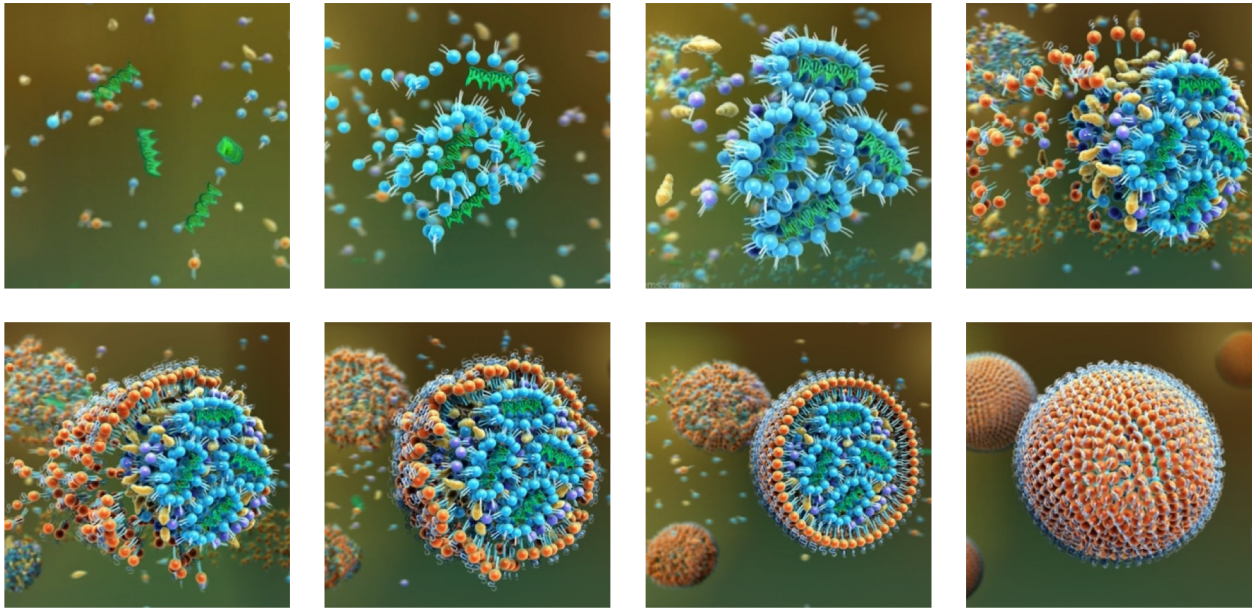


1 nm

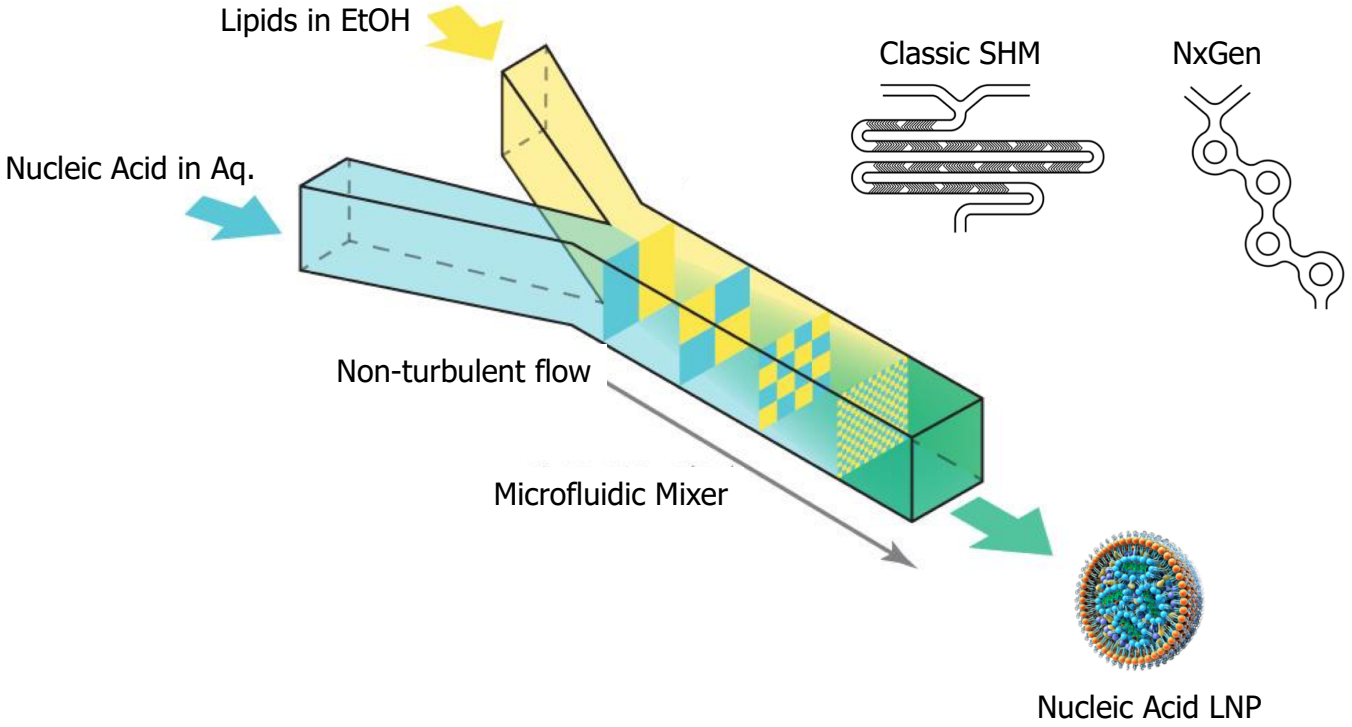
10 nm

100 nm

Optimal Nanoparticle Products are Achieved by Controlling the Self-Assembly Process



Microfluidics leverage non-turbulent flow and rapid mixing for control over nanoparticle self-assembly



The Evolution of NxGen Microfluidics

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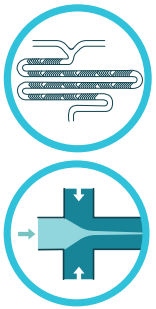
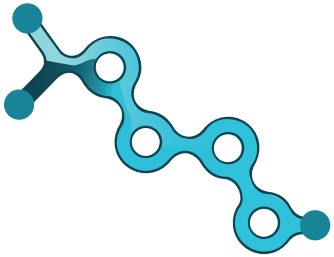
High Energy Techniques	In-Line Macromixing	Microfluidic Approaches	NxGen Microfluidics
			
		- Some scaling challenges remain	+ Easy to Scale
		- Mixers are difficult to make	+ Mixers are Easy to make
- Limited applications	- Limited applications	+ Expanded Applications	+ Potential multi-mixer integration opens possibilities
- Difficult to reproduce	- Difficult to reproduce	+ Reproducible	+ Reproducible
- Harsh process conditions	+ Gentler process conditions	+ Non-turbulent process conditions	+ Non-turbulent process conditions
- Difficult to scale	+ Improved Scalability		

Precise - Non-turbulent particle formation to ensure the most reproducible results for a wide range of nanoparticle types

Scalable - More than 25X single mixer throughput simplifies scaling up while maintaining particle quality and batch-to-batch reproducibility

Innovative - Platform designed to rapidly take ideas to patients

NxGen Microfluidics Designed for All Stages of Development

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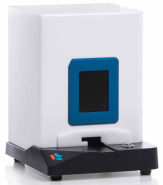
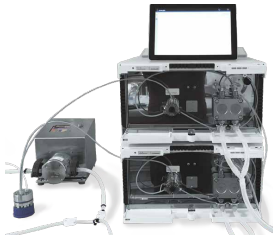
Discovery and Development | Preclinical Development | Clinical Development

Spark™ — Lead Candidates — Ignite™ — Optimized Formulations — NxGen Blaze™ & Blaze+™ — Clinical Candidate — GMP — Clinical Data





Screen

Rapidly prepare low-volume nanoparticle formulations with a push of a button

25-250 µL

Develop

Rationally optimize a wide range of nanomedicine formulations

1-20 mL

Advance

Efficiently scale bench formulations for expanded preclinical studies

10 mL - 10 L

Break Ground

Confidently transfer nanomedicine manufacturing to cGMP environment

> 20 L / h

Formulation and Process Development of Model mRNA Drug

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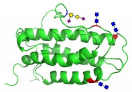
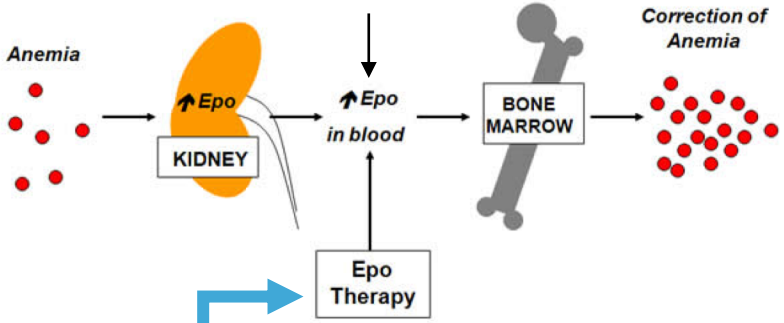
We developed, formulated and scaled up a model messenger RNA (mRNA) therapeutic

Anemia caused by kidney disease or cancer chemotherapy is treated with recombinant erythropoietin (Epo)

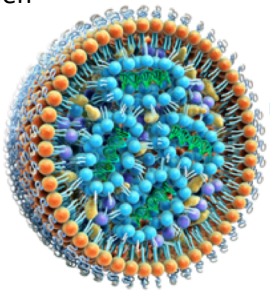
Epo Protein (Epoetin alfa)



Currently, commercial **Epoetin alfa** is produced in cell culture using recombinant DNA technology

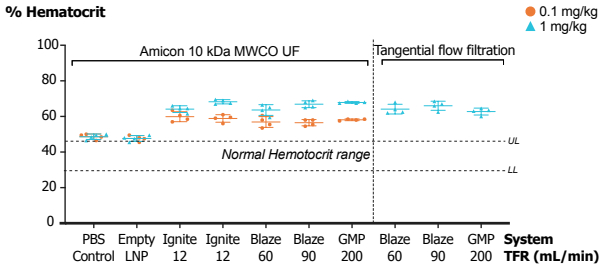


1. We encoded human Epo in mRNA, packaged it in an LNP using GenVoy-ILM and NxGen Technology

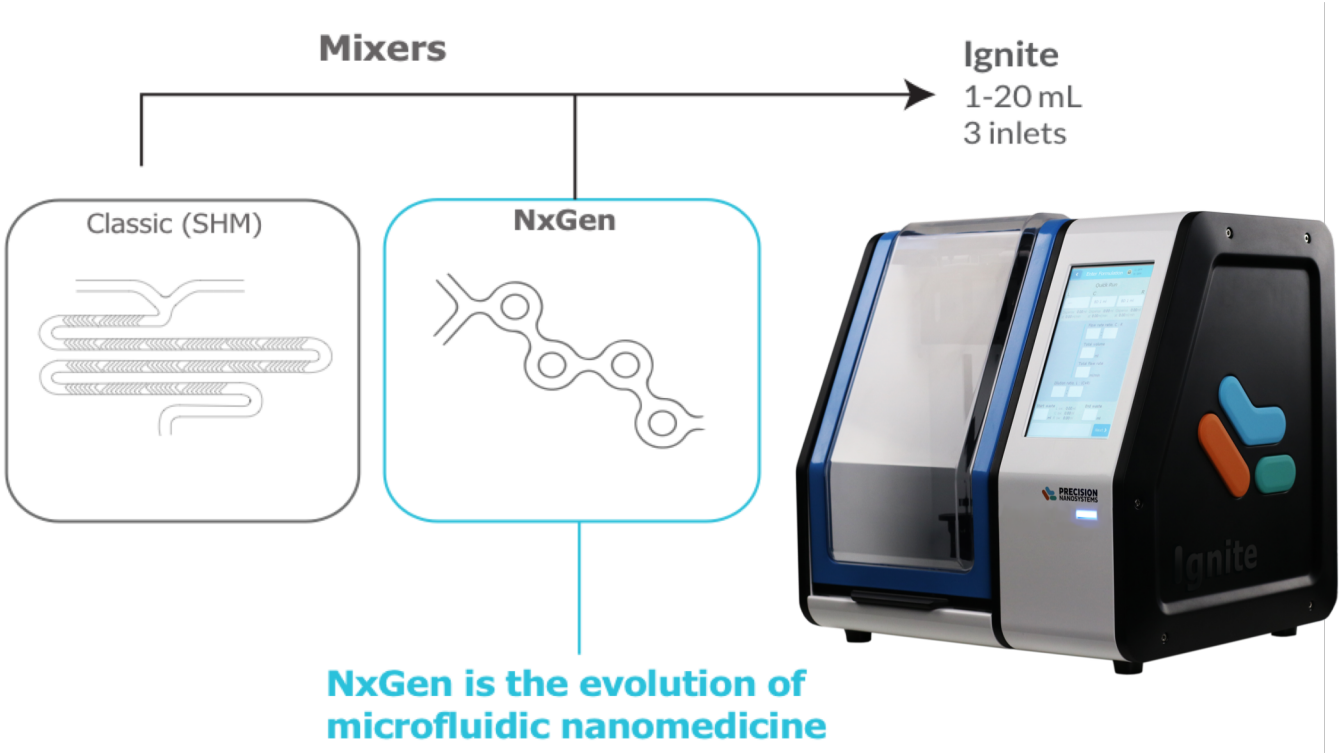


2. The LNP delivers the mRNA to liver cells which express EPO protein, which stimulates red blood cell production

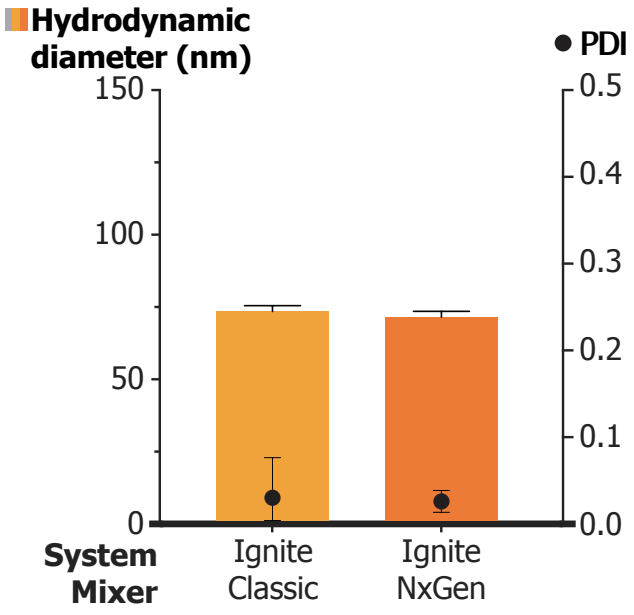
3. We observed an increase in red blood cell production in mice with consistent results across scales and NanoAssemblr instruments

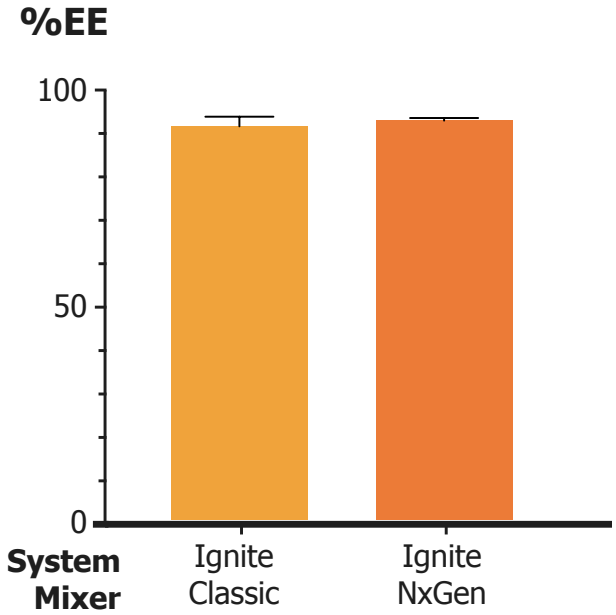


NxGen Mixer and Classic Mixer Compared for LNP Production



Epo-encoded mRNA-LNPs prepared with either mixer had equivalent size, polydispersity and mRNA encapsulation





Formulation	GenVoy-ILM
Org. Phase	GenVoy-ILM 25 mM in ethanol
Aq. Phase	0.174 mg/mL CleanCap® 5moU rhEPO mRNA in PNI Formulation Buffer
FRR	3:1
TFR	12 mL/min
Volume	1.5 mL
Replicates	4
Downstream Processing	Dilution, Amicon

Epo mRNA-LNP using GenVoy-ILM had similar size (~75 nm), polydispersity (<0.1) and encapsulation efficiency (>90%) across NxGen and SHM

Epo-encoded mRNA-LNPs made with either Mixer Induced Equivalent *in vivo* Biological Activity

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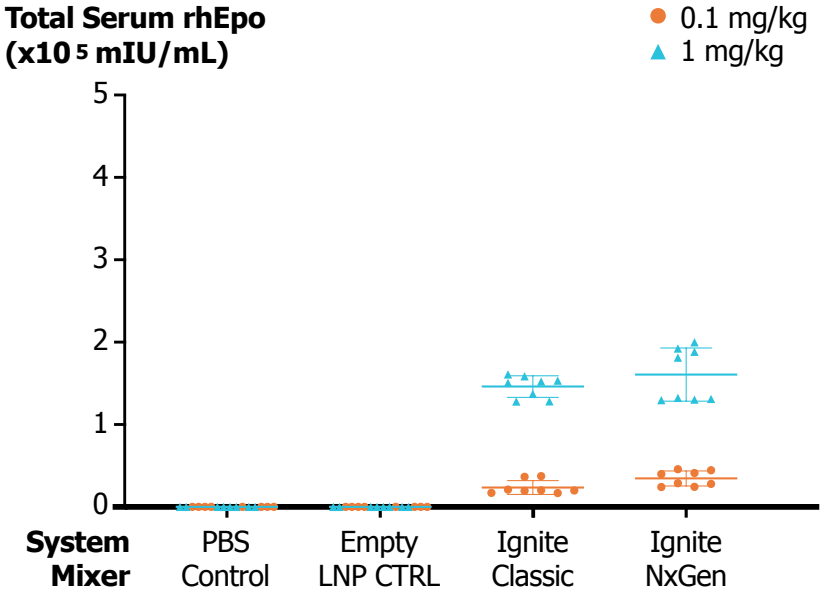
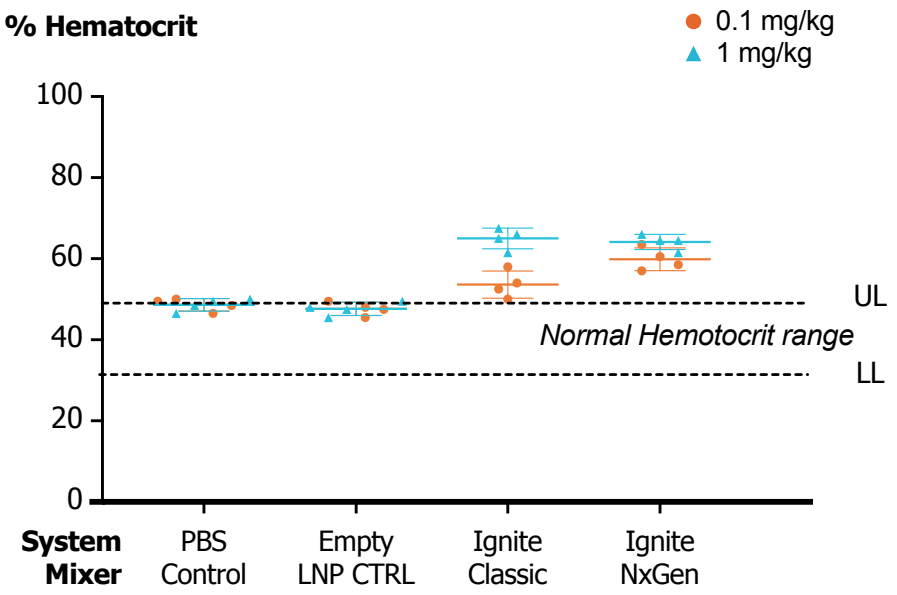
Increased Serum Epo Levels



Increased Red Blood Cell Production



Following i.v. administration in mice, Epo-encoded mRNA-LNP using GenVoy-ILM had similar Epo levels in serum and hematocrit increase across NxGen and Classic

De-risking Manufacturing Process of mRNA-LNP Using NxGen Technology

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Philosophy of our process: modeling GMP process at earlier scales

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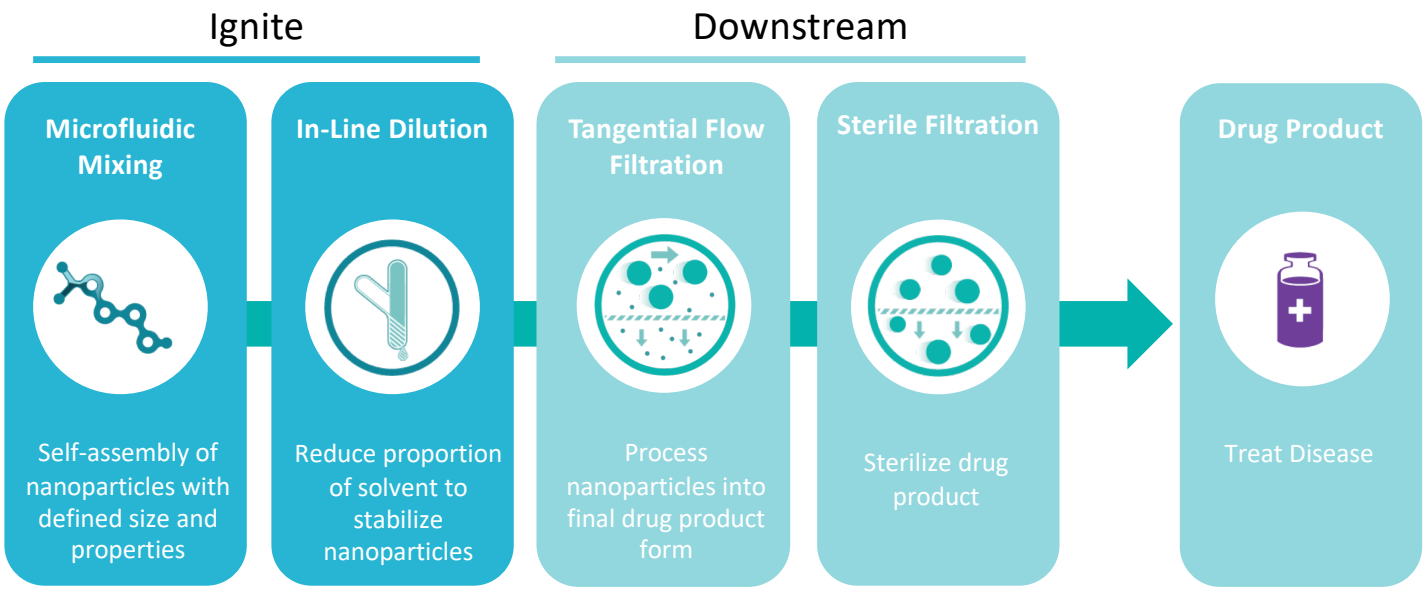
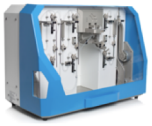


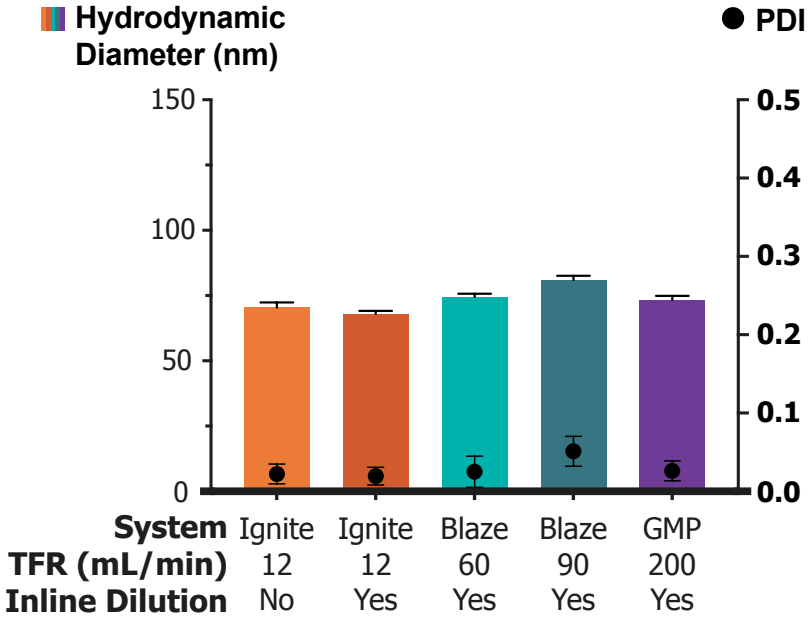
Reduce risk during transition from Research to Development and accelerate timelines to IND

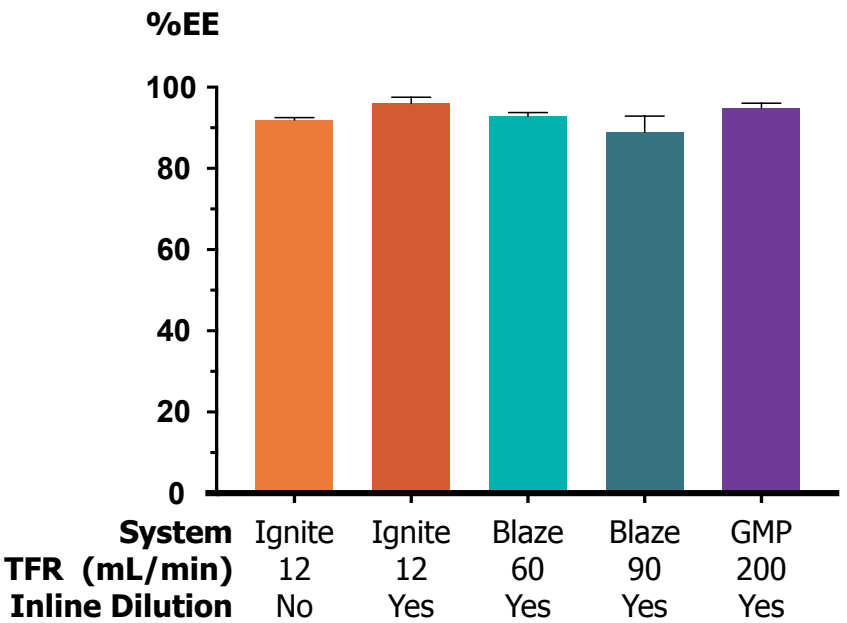
Experimental Design


	Ignite	Blaze	GMP
Mixers	NxGen, NxGen w/in-line dilution	NxGen 400, NxGen 500	NxGen 500
Org. Phase	12.5 mM GenVoy-ILM in Ethanol		
Aq.Phase	0.174 mg/mL CleanCap 5moU Epo mRNA in RNA formulation buffer (pH 7.0)		
Total micromixing volume	4 mL	25, 55 mL	325 mL
FRR [Org : Aq]	3:1		
TFR	12 mL/min	60 mL/min 90 mL/min	200 mL/min
In-line dilution ratio (Buffer:Micromix volume)	3:1	3:1, 2:1	3:1
Downstream processing	UF	UF or TFF	UF or TFF

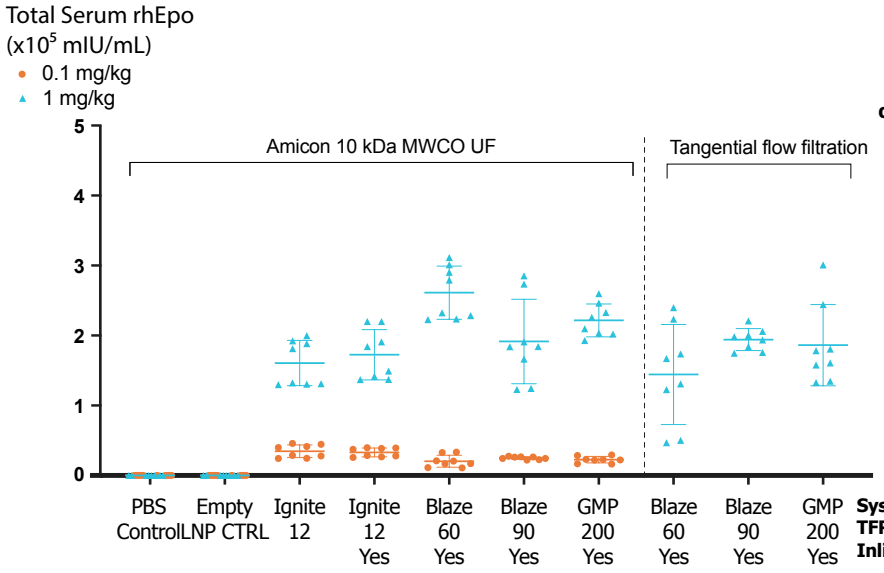
mRNA-LNP Have Equivalent Size, PDI and Encapsulation Across Scales

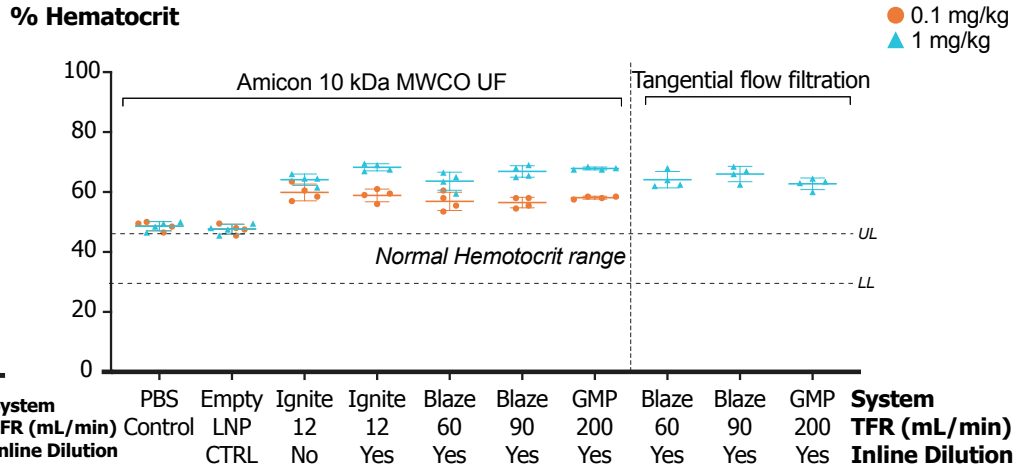




Epo-encoded mRNA-LNP using GenVoy-ILM had similar size (~70 nm), polydispersity (<0.1) and encapsulation efficiency (>90%) across all scales

mRNA-LNP Have Equivalent Protein Production and Therapeutic Activity Across Scales





Following i.v administration in mice, Epo-encoded mRNA-LNP using GenVoy-ILM had similar Epo levels in serum and hematocrit increase across all scales

Philosophy of our process: modeling GMP process at earlier scales

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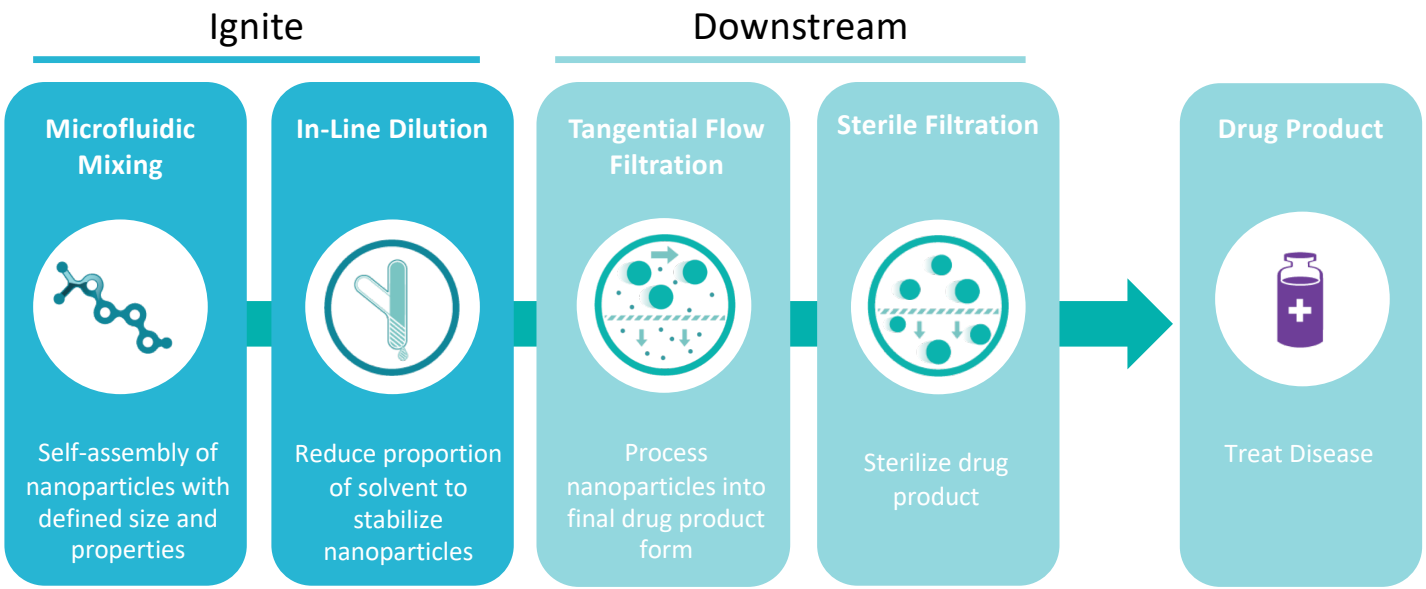

Reduce risk during transition from Research to Development and accelerate timelines to IND

Thank you for Listening!

If you have any additional questions, please reach out to your regional PNI representative, or send them to **info@precision-nano.com**

Or go to our website:
www.precisionnanosystems.com

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