PRECISION NANOSYSTEMS

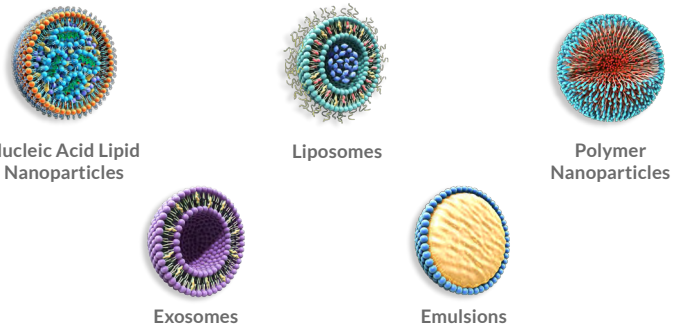
Create Transformative Medicines™

Scale Nanoparticle Formulation from Discovery to Commercialization

Nanomedicine from Concept to Clinic

Seamless Scaling for Nanomedicine Development

Nanomedicines represent the next paradigm in drug innovation with treatment modalities like gene therapy and targeted medicine, offering improved efficacy and reduced side effects. Nanoparticle formulations vary in particle size, payload and excipient characteristics opening up possibilities for difficult-to-deliver drugs and hard-to-treat targets.



Precision NanoSystems is a global leader in nanoparticle technologies, solutions and services for developing genomic medicines, including mRNA vaccines and therapeutics that define the future of medicine.

- NanoAssemblr® instruments with proprietary NxGen™ microfluidic mixers with scalable flow rates enable increased nanoparticle stability, efficacy, yield and quality, accelerating timelines to develop robust and reproducible formulations from discovery to commercial manufacturing.
- GenVoy-ILM™ off-the-shelf Research Use Only (RUO) lipid nanoparticle (LNP) delivery reagents accelerate discovery and proof-of-concept studies to clinical development.
- End-to-end biopharmaceutical services span nanomedicine formulation from discovery to commercialization, including proof-of-concept studies, optimization of formulation, lead candidate process development, analytical development, scale-up and technology transfer for cGMP production.

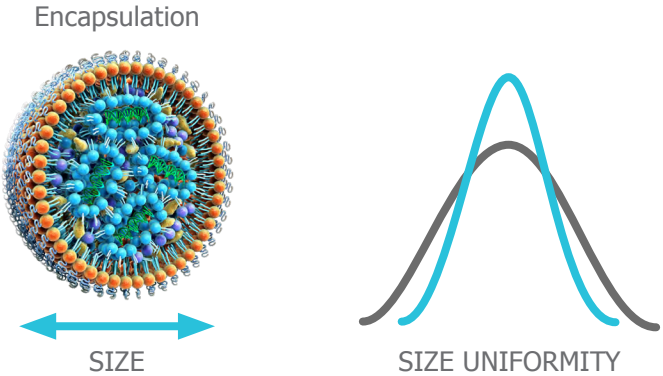
Scale Up with NxGen™ Mixers

NXGen™

Reproducible, homogeneous particle production scalable from lab to commercial manufacturing

The NxGen mixers at the heart of NanoAssemblr platforms use rapid, non-turbulent mixing to precisely control nanoparticle formation to reproducibly generate homogenous particles. NxGen is the only technology that shows proven scalability, starting from lab scale to commercial batch sizes, with the same mixer design and low hold-up volumes. This maintains nanoparticle characteristics across batches, ensuring low-risk process development and scaling with consistent results.

Critical Quality Attributes



- Test batches of up to 12 L/h
- Maintains consistent particle characteristics (size, PDI and encapsulation efficiency)
- Ensures biological activity is maintained
- Offers broad flow rate capacity of 1 mL/min to 200 mL/min
- Maintains architecture from lab scale to commercial manufacturing

NanoAssemblr® Platforms – Speed to Manufacturing

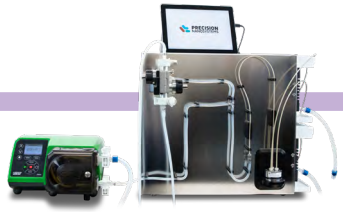
NanoAssemblr instruments offer rapid screening and drug discovery at the lab bench to large-scale manufacturing under cGMP conditions, providing robust and uniform LNP production at all scales through one single mixing element. Manufacturing conditions may be defined from early process development to production scale allowing seamless technology transfer, accelerating the clinical and commercial development of nanomedicine drug products.

The instruments have been cited in >500 respected scientific journals and used in drug development by top pharma companies including Daiichi-Sankyo, Entos, Sirnaomics and more!

Spark™
25–250 uL

Ignite™ and Ignite+™
Up to 60 mL

Blaze™ and Blaze+™
Up to 10 L



GMP System
Up to 50 L

Accelerate LNP Development

Reliable, small-scale formulations needed to streamline discovery of revolutionary new medicines are rapidly achievable with Spark. Its quick formulation time provides an efficient systematic approach to finding and developing lead genomic medicine candidates. Ignite and Ignite+ allow for optimization of crucial factors at initial stages and with the NanoAssemblr Blaze and Blaze+, process development can be conducted on both the upstream and downstream portions. This streamlined development from material preparation to buffer exchange, filtering and analytics ensures that a program is ready to quickly accelerate towards the clinic.

Traditional drug development timeline		Estimated time savings using Precision NanoSystems' technology
2–3 years	**DRUG DISCOVERY**	4 Month Acceleration with Spark for rapid composition and formulation and by using Ignite for modeling clinical manufacturing process at early stages
3–5 years	**PRECLINICAL**	8 Month Acceleration with faster process optimization and scale-up by selecting the right lead formulations for GMP manufacturing
5–7 years	**LATE PRECLINICAL**	

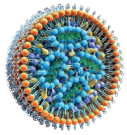
Sirnaomics Case Study

> *The scalability and reproducibility of Precision NanoSystems' NanoAssemblr platform allowed us to move into GMP manufacturing with greater control over the process and increased precision in the final product compared to our previous macromixing process, allowing acceleration of our time to commercialization.*

David Evans, Ph.D., CSO, Sirnaomics

October 2018
Proof of concept study Benchtop purchase

June 2019
Formulation development and scale-up initiated



November 2019
License and Supply Agreement executed

December 2019
Tech transfer of formulation and GMP System to CMO

December 2019
GMP Manufacturing run

January 2020
Engineering batch run

Low-Risk Scalable Process

From discovery to clinic, the NxGen architecture produces uniform and reproducible high-quality LNPs, reducing the risk of scaling processes. The critical quality attributes (CQAs) and critical process parameters (CPPs) of the LNPs serve as the foundation for the development, design, monitoring, control and life-cycle management of production processes. NanoAssemblr instruments and the Biopharmaceutical Services team make it possible to identify the CQAs, develop drug product specifications and establish CPPs for downstream processing, such as tangential flow filtration (TFF) and sterile filtration.

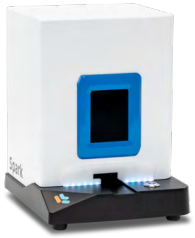
CRITICAL QUALITY ATTRIBUTES

- Concentration
- Particle size
- Polydispersity
- Nucleic acid loading levels
- Chemical stability
- Physical stability

CRITICAL PROCESS PARAMETERS

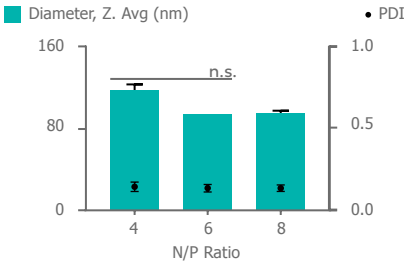
- Flow rate ratio
- Total flow rate

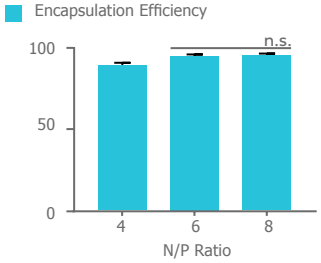
Drug Discovery and Screening with NanoAssemblr® Spark™

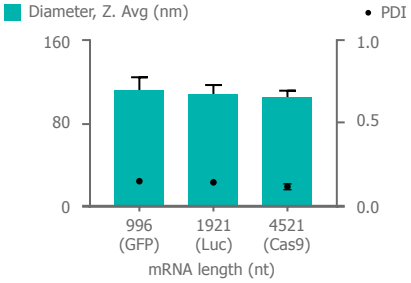


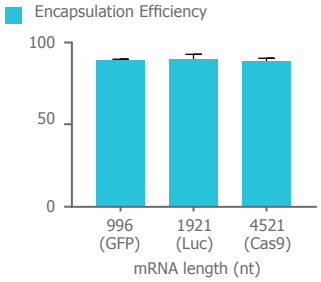
The Spark instrument overcomes the challenges of traditional techniques for the controlled and reproducible manufacturing of LNPs at low volumes. It can also help establish CQAs, such as cargo sizing and the ratio between the positively charged lipid amine groups (N) and the negatively charged nucleic acid phosphate groups (P) or N/P ratio.

In this study, LNPs encapsulating three different length mRNAs were examined with results showing no change in encapsulation efficiency. This shows that large cargos can be encapsulated in the LNPs, without impacting formulation characteristics. Further testing was performed to determine the effective N/P ratio, where three ratios were formulated and examined. At 6:1 and 8:1 ratios there is a similar polydispersity index and encapsulation efficiency, suggesting that an asymptotic limit has been reached, definining a key CQA.



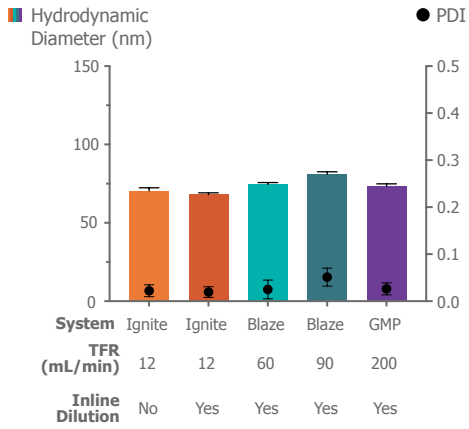


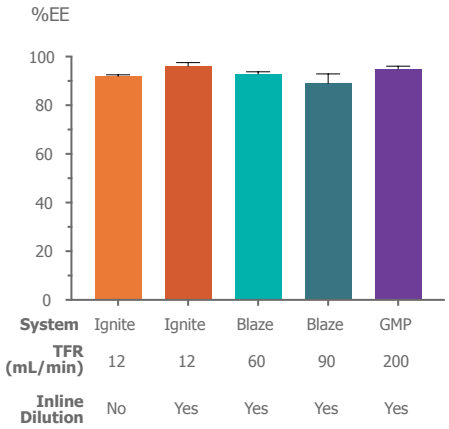


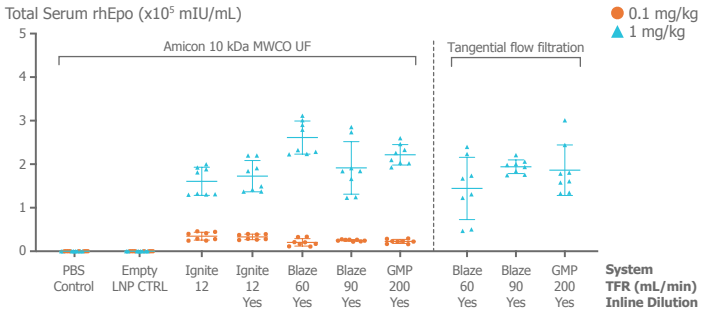


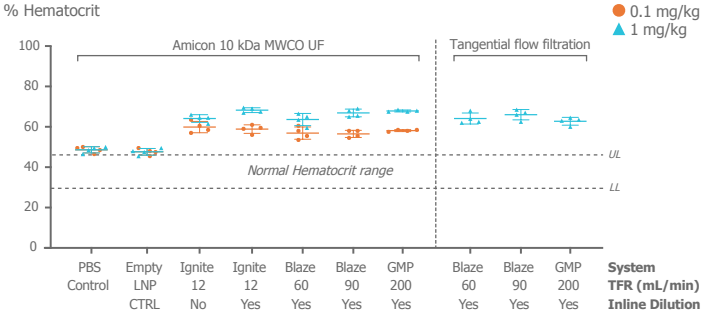
Critical Quality Attributes (CQAs) Maintained from Ignite™ to GMP System

In a recent study, Precision NanoSystems created an mRNA-LNP that encodes for the EPO gene, a potential model for the treatment of patients with anemia, as RNA and LNP delivery systems can eliminate the need for cell culture, making therapeutic development easier. The EPO RNA-LNPs were scaled up using the NanoAssemblr instruments (Ignite, Blaze and GMP System) and critical quality attributes were examined to quantify particles across platforms in terms of size, polydispersity and encapsulation efficiency. No significant difference was found between the lab and clinical manufacturing scales.









Further evaluation of *in vivo* data showed that hematocrit and serum EPO levels are consistent across batches indicating that particles have the same biological effect *in vivo* regardless of the manufacturing platform. This study's data validates that Precision NanoSystems' technologies enable developers to de-risk the scaling process by ensuring consistent CQAs of LNPs as they scale from the lab to larger scales.

Critical Process Parameters (CPPs) Maintained from Ignite To GMP System

Downstream processing time, flow rate ratio, total flow rate and tangential flow filtration are critical parameters during scale-up. The Ignite+ can manufacture RNA-LNPs at flow rates of up to 200 mL/min and batch sizes of up to 60 mL. This capacity allows for small-scale evaluation of RNA-LNPs using the same CPPs used in large-scale cGMP production.

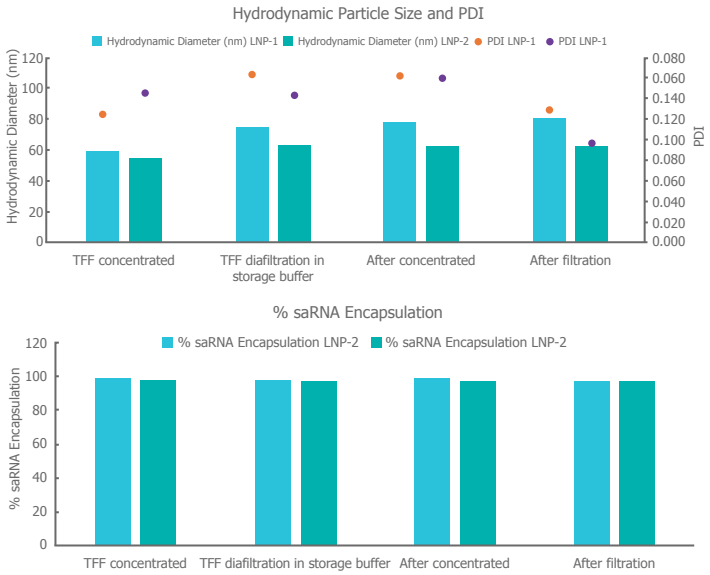
Late preclinical studies can be conducted efficiently with the NanoAssemblr Blaze using a process that mimics clinical scale implementation. Furthermore, the Blaze+ upgrade enables the formulation of volumes ranging from 20 mL to 10 L, allowing for late preclinical experiments and process development activities (downstream filtration and analytical protocols).

Analyze Formulations Early for Downstream Process Parameters

CPPs for the TFF process, such as filter material and construction, shear rate and target transmembrane pressure, must all be determined and optimized for LNP formulations as the transition to TFF is an essential activity and should be de-risked early in process development.

> The ability of the Ignite and Blaze to formulate at clinically relevant flow rates and millilitre volumes allows early testing of multiple formulations economically.

When developing a saRNA-LNP COVID-19 vaccine, Precision NanoSystems demonstrated the significance of early testing of formulations for downstream process parameters. An important step for this therapeutic is in-line dilution and buffer exchanges to remove the ethanol from the formulation and prepare for storage in the final cryo-buffer. While both formulations (LNP1 and LNP2) produced similar CQAs initially (particle size, polydispersity, and encapsulation efficiency) at different flow rates and scales (Ignite, Blaze, GMP), following the TFF processing LNP1 showed a significant increase in size, while LNP2 maintained these characteristics. This study demonstrates that some formulations are sensitive to downstream processes, and identifying those CPPs early by testing formulations at a smaller scale can save time, materials, and de-risk the scale-up process.



Commercialization and Manufacturing Made Easy

Precision NanoSystems will help bring novel drugs to market

The NanoAssemblr GMP System has a touchscreen interface, saved recipes and a single-use fluid path and together with our partners Pall and Cytiva, provides an end-to-end manufacturing workflow for clinical and commercial nanomedicine production. This versatile solution for commercial manufacturing provides the ability to scale up and scale out at a range of facilities.

Biopharmaceutical Services

Collaborate to advance future therapies

The Biopharmaceutical Services team at Precision NanoSystems provides a one-stop-shop solution to deliver exceptional lipid formulations and nanoparticle development expertise for success in different applications while reducing the risk of failure and delays. Avoid delays and losing control over process know how by working with one vendor. The Biopharmaceutical Services team enables end-to-end LNP formulation services combined with analytical capabilities from proof-of-concept studies to preclinical to clinical transition with credible expertise and proven success.

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