PRECISION NANOSYSTEMS

Create Transformative Medicines™

GenVoy-ILM™

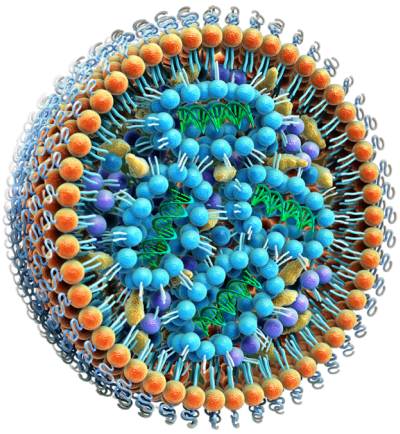
Power to Explore

For use with the NanoAssemblr® Platform

Explore RNA Medicine Development

RNA Medicine Drug Development Framework

Discovery		Early Pre-clinical		Late Pre-clinical	Clinical
Molecular Target Validation	A. RNA ID B. Excipient ID	RNA-LNP Development	RNA-LNP Optimization	RNA-LNP Candidate Selection	Clinical Development
Functionally confirm targets identified in silico using *in vitro* and *in vivo* models e.g. Yardeni et al Sci. Rep. 2018 Establish/confirm new epigenetic pathways by high-content screening e.g. Dejanovic et al Neuron 2018	A. *In vitro* and *in vivo* proof-of-concept e.g. Connolly et al J. Nucleic Acids 2018 B. GenVoy-ILM as a control/ reference standard to compare experimental formulations	Confirm encapsulation, establish acceptance criteria for physical characteristics, confirm *in vivo* efficacy of mRNA (Sequence and modifications). e.g. Connolly et al 2018	Develop downstream processes necessary for future GMP: Scale up supply, downstream processing and analytics.	Process and formulation parameters tested in system designed for GMP manufacturing	



Summary of Features

LNP ARE CLINICALLY VALIDATED

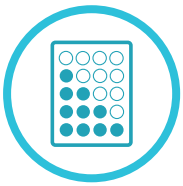
Lipid Nanoparticle (LNP) technology represents the most advanced non-viral RNA delivery technology and has been validated in the clinic for the delivery of siRNA (Onpattro®)

UNIQUE MECHANISM-OF-ACTION

RNA-LNP structurally resemble Low Density Lipoproteins (LDL) and can co-opt the endogenous uptake pathway of LDL to enter cells with high efficiency using receptor-mediated endocytosis

OPTIMIZED FOR NANOASSEMBLR PLATFORM

The NanoAssemblr uses NxGen™ microfluidic mixing technology for rapid, controlled and scalable manufacture of nanoparticles, including RNA-LNP made using GenVoy-ILM. LNP made with the NanoAssemblr platform exhibit a unique core structure that can improve potency. For more details, visit: precisionnanosystems.com/lnp-performance



ENABLE TARGET VALIDATION

GenVoy-ILM is an excellent tool for drug/biomarker target validation. The high transfection efficiency and low cytotoxicity exhibited by GenVoy-ILM LNP enables effective RNA-mediated gene silencing, gene expression and gene editing in primary cells, stem cells and difficult-to-transfect cells.

DEMONSTRATE THERAPEUTIC PERFORMANCE

GenVoy-ILM enables proof of concept for RNA medicines. For example, GenVoy-ILM LNP efficiently deliver RNA to hepatoyctes following intravenous administration and can be used as a positive control for the development of novel RNA Gene Therapies.

SUPPORT PROCESS DEVELOPMENT

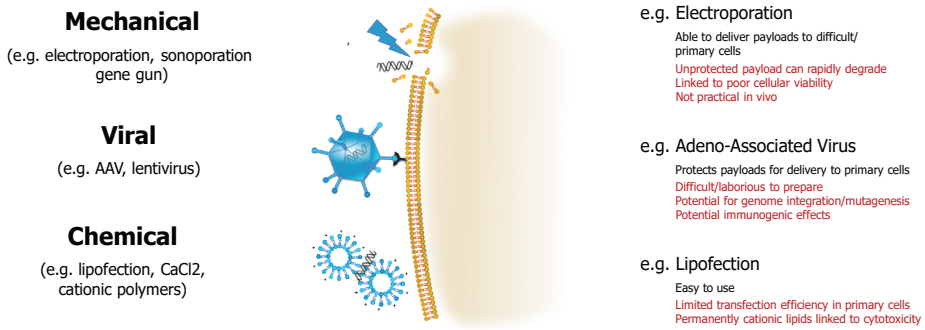
Scale-up manufacturing processes for RNA-LNP can be developed efficiently and proactively using GenVoy-ILM. GenVoy-ILM LNP can be used as a reference formulation at all scales of development to establish a NanoAssemblr manufacturing process that can be transferred to a GMP environment to support clinical development

RNA Medicines Have the Power to Cure

RNA medicines can target the genetic underpinnings of disease. Synthetic RNA constructs can be designed to silence, express or edit genes. This powerful approach to medicine can be used to develop gene therapies, cell therapies, and vaccines to treat rare diseases, oncology and infectious disease where there is substantial unmet medical need.

The RNA Delivery Challenge

RNA is a polyanionic macromolecule that is susceptible to degradation in biological fluids and can not readily cross cell membranes to access the cellular machinery needed to mediate protein expression. Several technologies have been developed to overcome these challenges and enable RNA medicine. The advantages and disadvantages of these approaches are summarized in the figure below.



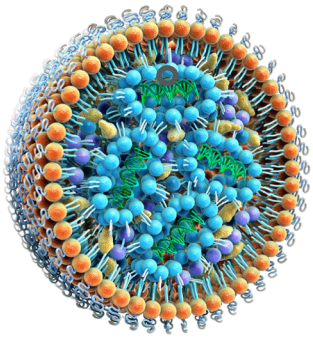
GenVoy-ILM Lowers Barriers to Developing RNA Medicines

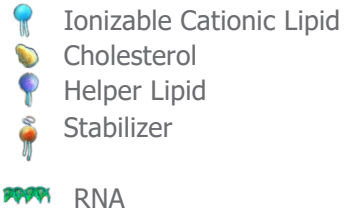
Lipid nanoparticles (LNP) are the most clinically advanced non-viral delivery technology and have been designed specifically to overcome the RNA delivery challenge. Onpattro® (patisiran) is a siRNA-LNP therapeutic approved to treat hereditary transthyretin amyloidosis.

GenVoy-ILM is a pre-optimized lipid mixture designed to encapsulate RNA – mRNA, gRNA, siRNA, miRNA, tRNA – in LNP. GenVoy-ILM is an effective tool to develop RNA medicines and can be used at various stages of drug development from discovery to late preclinical.

GenVoy-ILM is easy-to-use and effectively delivers RNA to cells with high efficiency and low toxicity.

GenVoy-ILM comprises 4 lipid components at defined ratios to prepare LNP engineered to efficiently encapsulate and deliver RNA. GenVoy-ILM has been optimized for use with the NanoAssemblr® platform.



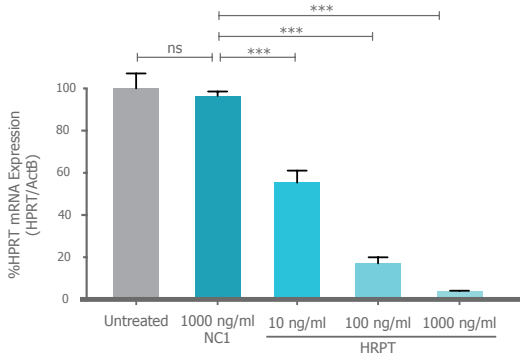


GenVoy-ILM as a Tool for the Development of RNA Medicines

Discover New Therapeutic Targets

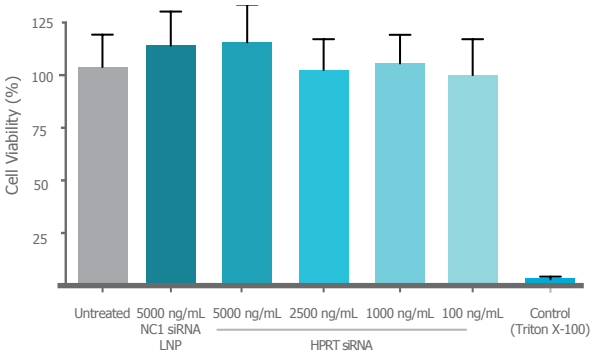
Discover new therapeutic targets and confirm mechanism-of-action in primary and difficult-to-transfect cells by using GenVoy-ILM LNP to efficiently deliver RNA with low cytotoxicity.

90% siRNA knockdown in 95% of cells



Enriched (>90%) E18 primary rat cortical neurons treated at DIV12 with siRNA-GenVoy LNP against HPRT. HPRT mRNA assayed by qPCR 48h post-treatment. *** P < 0.001

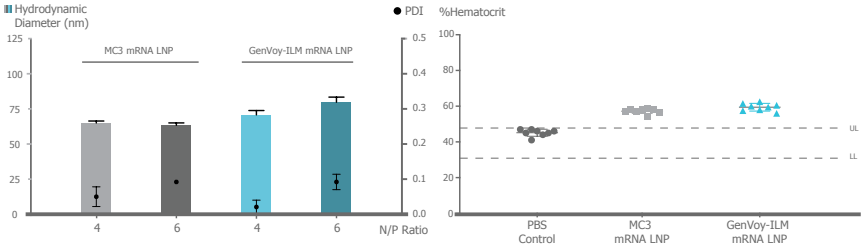
No observed cytotoxicity



Enriched (>90%) E18 primary rat cortical neurons treated at DIV7 with siRNA-GenVoy LNP against HPRT for 48h. Cell viability assayed using PrestoBlue.

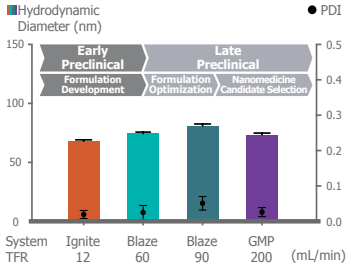
Benchmark Therapeutic Performance

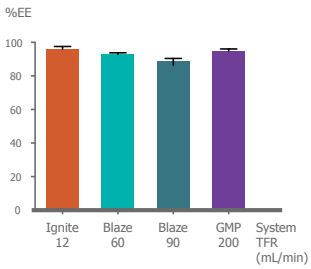
mRNA designed to express erythropoietin (EPO) was used as the basis for a model RNA Gene Therapy to treat anemia. The particle specifications of EPO mRNA-LNP prepared using GenVoy-ILM, and its therapeutic activity in an *in vivo* model of anemia, were used as a benchmark for development of novel EPO mRNA-LNP containing the ionizable cationic lipid MC3.



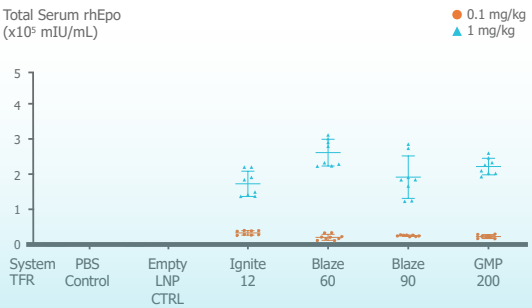
Develop Processes for Scale-Up Production

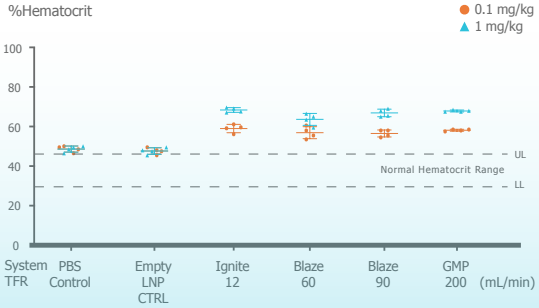
GenVoy-ILM was used to prepare reference RNA-LNP to support all scales of development and establish a process suitable for scale-up production of a model RNA Gene Therapy using the NanoAssemblr® platform.





Consistent size, homogneity, and encapsulation efficiency were achieved with EPO-mRNA formulated with Genvoy-ILM across all scales of development.





Increased expression of the encoded protein and resulting increase in erythropoiesis was consistent across all scales of development demonstrating the scalability of the formulation and process.

For the full story of GenVoy-ILM EPO mRNA-LNP as a model RNA Gene Therapy to treat anemia, visit: precisionnanosystems.com/mRNA-case-study

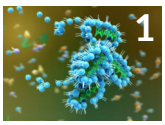
Lipid Nanoparticles (LNP) are the Most Clinically Advanced Non-Viral Delivery Technology

GenVoy has been optimized for use with the NanoAssemblr™ platform

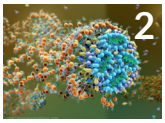
Your RNA | GenVoy-ILM™ | NanoAssemblr® Process | Homogeneous LNPs

The RNA chemistry, the lipid composition and the manufacturing process affect characteristics of the resultant LNP.

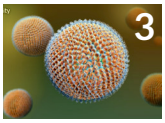
LNP co-opt endogenous uptake mechanisms to efficiently deliver RNA to cells *in vitro* and *in vivo*



GenVoy-ILM contains an ionizable cationic lipid, which at low pH mediates efficient encapsulation of the anionic RNA in a lipid core



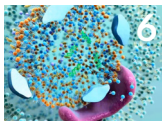
The RNA-lipid core is surrounded by helper lipids, cholesterol and stabilizers to form the RNA-LNP



Once formed, RNA-LNP are neutral at physiological pH which eliminates a main source of toxicity present in other materials used in RNA delivery systems

RNA-LNP mimic low density lipoproteins (LDL) and are then taken up by most cell types through receptor-mediated endocytosis

Once in the endosome, ionizable lipids in RNA-LNP respond to low pH and become cationic



The cationic lipids in the RNA-LNP interact with anionic lipids in the endosome to disrupt the endosomal membrane and release the RNA into the cytoplasm

GenVoy Users are Transforming Medicine

To view over 200 publications, visit precisionnanosystems.com/resource-center

Molecular Target Validation

The Hornstein Lab used high content image analysis to identify mir-124 as a potential target due to its role in control of mitochondria localization and function

Yardeni et al Sci. Rep. 2018

RNA Identification

Genetech designed siRNA sequences to know down regulatory proteins in rat cortical neurons and restore neuron spine density

Dejanovic et al Neuron 2018

RNA-LNP Optimization

Alexion demonstrated that an mRNA LNP could achieve expression of SerpinA1 in two target tissues which could benefit patients suffering from AAT deficiency

Connolly et al J. Nucleic Acids 2018

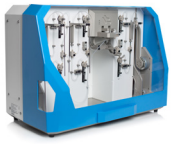
RNA-LNP Selection

The Heuser group showed that leukemia specific siRNAs could be formulated into LNPs and demonstrated prolonged survival of mice bearing patient derived leukemia cells

Jyotsana et al Leukemia 2018

Ordering Information

REAGENTS		PRODUCT CODE	INCLUDES
	**GenVoy-ILM™**	NWW0041 NWW0042	2 mL ionizable lipid mix 5 mL ionizable lipid mix
	GenVoy-ILM™ with dye (644/665 nm ex/em)	NWW0039 NWW0040	2 mL ionizable lipid mix 5 mL ionizable lipid mix
PNI Formulation Buffer		NWW0043	20 mL formulation buffer

INSTRUMENT AND CARTRIDGES		PRODUCT CODE	INCLUDES
	**NanoAssemblr® Ignite™**	NIN0001	1 Instrument 2 Sample Switch arms 2 Cartridge adapters 1 year warranty
NxGen Ignite Cartridges		NIN0061 NIN0062	100 pack 200 pack
NxGen Ignite Cartridges with Dilution		NIN0063 NIN0064	50 pack 100 pack
	**NanoAssemblr® NxGen™ Blaze™**	NIB0055	1 Instrument 1 Control Laptop Parts required for installation and training 1 year warranty
	NanoAssemblr® NxGen™ Blaze+™	NIB0056	
NxGen 400 Blaze Cartridge		NIB0062	1 cartridge
NxGen 500 Blaze Cartridge		NIB0064	
NxGen 400D Blaze Cartridge		NIB0063	
NxGen 500D Blaze Cartridge		NIB0065	

About Precision NanoSystems

Precision NanoSystems (PNI) a global leader of innovative solutions for the discovery, development, and manufacture of nanomedicine based gene and cell therapies, small molecule and protein based drugs, rapidly taking ideas to patients.

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