GenVoy-ILM™

Power to Explore

For use with the NanoAssemblr® Platform
Explore RNA Medicine Development

RNA Medicine Drug Development Framework

<table>
<thead>
<tr>
<th>Discovery</th>
<th>Early Pre-clinical</th>
<th>Late Pre-clinical</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular Target Validation</td>
<td>A. RNA ID</td>
<td>RNA-LNP Development</td>
<td>RNA-LNP Optimization</td>
</tr>
<tr>
<td>B. Excipient ID</td>
<td>B. GenVoy-ILM as a control/reference standard to compare experimental formulations</td>
<td>Develop downstream processes necessary for future GMP Scale up supply, downstream processing and analytics.</td>
<td>Process and formulation parameters tested in system designed for GMP manufacturing.</td>
</tr>
</tbody>
</table>

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.
- e.g. Connolly et al 2018

Confirm encapsulation, establish acceptance criteria for physical characteristics, confirm in vivo efficacy of mRNA (Sequence and modifications).

**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 hepatocytes 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

[Graph showing knockdown efficiency across different conditions]

No observed cytotoxicity

[Graph showing cell viability across different conditions]

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

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, homogeneity, 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 NanoAssembr™ platform

Your RNA + GenVoy-ILM™ + NanoAssembr® 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**

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

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

3. 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

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

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

6. 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


**RNA Identification**

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


**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

Connell 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

<table>
<thead>
<tr>
<th>Product Code</th>
<th>INCLUDES</th>
</tr>
</thead>
<tbody>
<tr>
<td>NWW0041</td>
<td>2 mL ionizable lipid mix</td>
</tr>
<tr>
<td>NWW0042</td>
<td>5 mL ionizable lipid mix</td>
</tr>
<tr>
<td>NWW0039</td>
<td>2 mL ionizable lipid mix</td>
</tr>
<tr>
<td>NWW0040</td>
<td>5 mL ionizable lipid mix</td>
</tr>
</tbody>
</table>

**GenVoy-ILM™**

**GenVoy-ILM™ with dye (644/665 nm ex/em)**

**PNI Formulation Buffer**

<table>
<thead>
<tr>
<th>Product Code</th>
<th>INCLUDES</th>
</tr>
</thead>
<tbody>
<tr>
<td>NWW0043</td>
<td>20 mL formulation buffer</td>
</tr>
</tbody>
</table>

#### INSTRUMENT AND CARTRIDGES

<table>
<thead>
<tr>
<th>Product Code</th>
<th>INCLUDES</th>
</tr>
</thead>
</table>
| NIN0001      | 1 Instrument  
|              | 2 Sample Switch arms  
|              | 2 Cartridge adapters  
|              | 1 year warranty |

**NanoAssemblr® Ignite™**

**NxGen Ignite Cartridges**

<table>
<thead>
<tr>
<th>Product Code</th>
<th>INCLUDES</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIN0061</td>
<td>100 pack</td>
</tr>
<tr>
<td>NIN0062</td>
<td>200 pack</td>
</tr>
</tbody>
</table>

**NxGen Ignite Cartridges with Dilution**

<table>
<thead>
<tr>
<th>Product Code</th>
<th>INCLUDES</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIN0063</td>
<td>50 pack</td>
</tr>
<tr>
<td>NIN0064</td>
<td>100 pack</td>
</tr>
</tbody>
</table>

**NanoAssemblr® NxGen™ Blaze™**

**NanoAssemblr® NxGen™ Blaze+™**

**NxGen 400 Blaze Cartridge**

<table>
<thead>
<tr>
<th>Product Code</th>
<th>INCLUDES</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIB0062</td>
<td>1 cartridge</td>
</tr>
</tbody>
</table>

**NxGen 500 Blaze Cartridge**

<table>
<thead>
<tr>
<th>Product Code</th>
<th>INCLUDES</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIB0064</td>
<td></td>
</tr>
</tbody>
</table>

**NxGen 400D Blaze Cartridge**

<table>
<thead>
<tr>
<th>Product Code</th>
<th>INCLUDES</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIB0063</td>
<td></td>
</tr>
</tbody>
</table>

**NxGen 500D Blaze Cartridge**

<table>
<thead>
<tr>
<th>Product Code</th>
<th>INCLUDES</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIB0065</td>
<td></td>
</tr>
</tbody>
</table>

### About Precision NanoSystems

Precision NanoSystems (PNI) is 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.

---

Precision NanoSystems Inc.  
50 - 655 West Kent Ave. N.  
Vancouver, BC, V6P 6T7  
Canada

Precision NanoSystems Europe:  
Two Snowhill Road  
Birmingham, UK.  B4 6WR

Precision NanoSystems Inc.  
395 Oyster Point Boulevard, Suite 145  
South San Francisco, CA, 94080  
USA

Precision NanoSystems APAC:  
10 Anson Road #12-#14  
International Plaza  
Singapore 079903  

For Research Use or Further Manufacturing. Not for direct administration into humans.

Copyright © Precision NanoSystems Inc. 2020 All rights reserved. Create Transformative Medicines™ and NanoAssemblr® are trademarks of Precision NanoSystems Inc.