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Next-Gen LNP Enables Gene Delivery in iPSC-Derived Organoids

Qiuyan Ma, PhD[1]*, Brecca Ridenour[2], Jiwu Wang, PhD[2]
[1]OriGene Technology, Inc, Rockville, MD 20850, USA; [2]Allele Biotechnology and Pharmaceuticals, San Diego, CA 92121, USA

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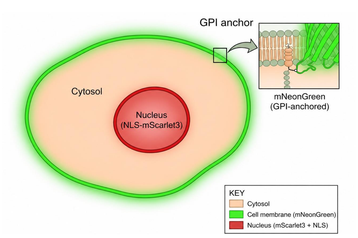
Background

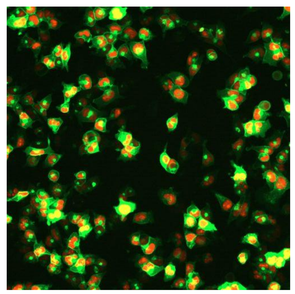
A major gap remains between efficient *in vitro* transfection (e.g., lipofectamine, PEI) and effective delivery in complex systems such as 3D organoids and in vivo models. While conventional reagents achieve high transfection efficiency in transformed cells, their performance is often limited in physiologically relevant systems, particularly iPSC-derived cells and 3D cultures.
Here, we introduce EZ-LNP, a novel ionizable lipid-based platform designed for instrument-free formulation and compatibility with both RNA and DNA payloads. Combined with proprietary iPSC technologies and application-specific differentiation kits, this platform enables efficient gene delivery across challenging 2D cultures, iPSC-derived organoids and Matrigel domes. EZ-LNP demonstrates robust delivery in challenging culture systems, with effective penetration into 3D structures.
Furthermore, through advanced mRNA design, this approach enables spatial, real-time functional monitoring in living iPSC organoids, bridging the gap between delivery and functional biology.

KEY ADVATNAGES

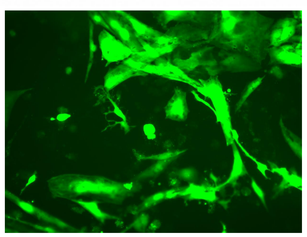
- ✓Instrument-free formulation (Add-Mix-Use)
- ✓Broad applicability across payloads, cell types and species
- ✓Compatible with various 3D cultures and organ-on-chip
- ✓Support live functional assays in organoids without fixation, staining
- ✓Proprietary mRNA design and iPSC reprogramming

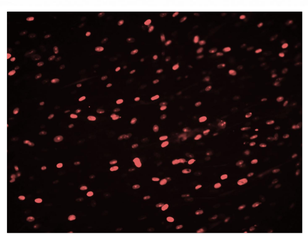
1 Efficient mRNA delivery in iPSC derived cells





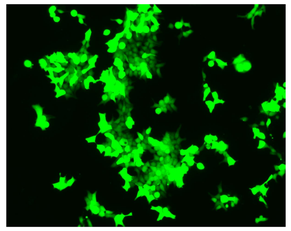
Brightness ↑ | Photostability | Monomer | Acid-resistant | Flexible mRNA

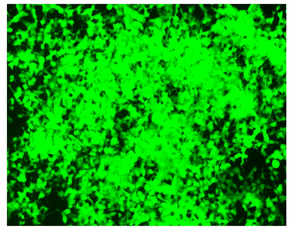


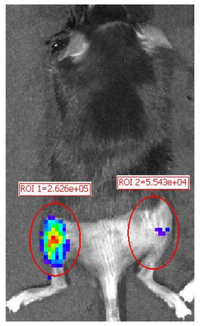


EZ-LNP-mediated mRNA delivery is effective across differentiated cell types and species.
Schemic of subcellular fluorescent tags used in this study (top, *left*). Merged fluorescent image of cells co-transfected with Nuclear mScarlet3 and GPI mNeonGreen (top, *right*). Human iPSC-derived endothelial cells were transfected using mWasabi mRNA, and canine fibroblasts were transfected with nuclear-localized mScarlet3 mRNA using LNP. Fluorescence images acquired 21 hours post-transfection, demonstrating efficient delivery, strong expression, and proper localization in cells (*bottom*).

2 DNA delivery achieved across *in vitro* to *in vivo* studies



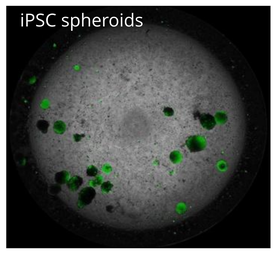


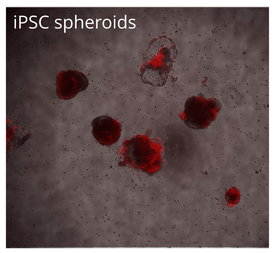


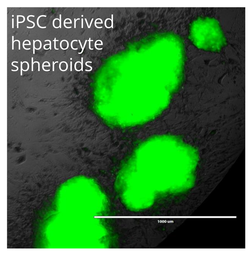
A low dose LNP-DNA (Luc) intramuscularly →

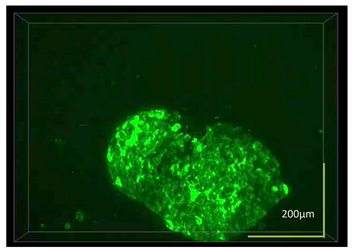
LNP enables efficient, sustainable, dose-dependent DNA delivery from *in vitro* to *in vivo* systems. HEK293T cells transfected with GFP pDNA showed durable expression for >17 days (*left*). *In vivo,* low-dose luciferase pDNA delivery demonstrates effective transgene expression (*right*), indicating translatability of the platform, with minimal immunogenicity and toxicity (data not shown).

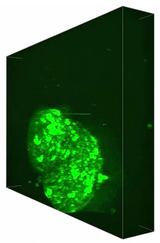
3 Deep mRNA Delivery in 3D Spheroids and Organ-on-Chip

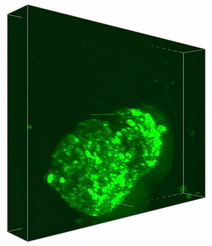




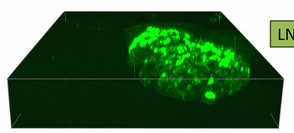




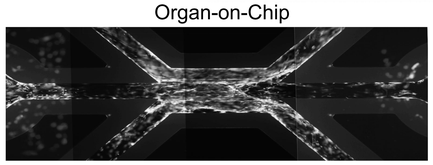




Organ-on-Chip



LNP-RNA →

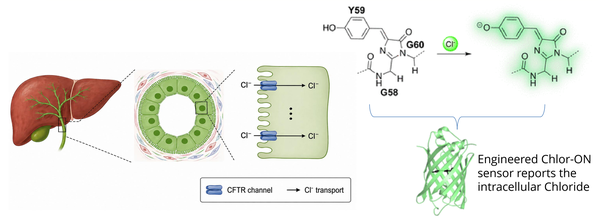


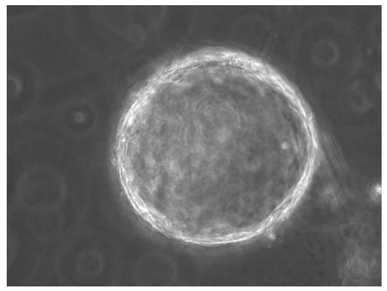
Human Primary Retinal endothelial, pericyte, and astrocyte

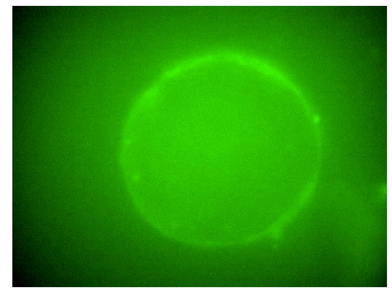
EZ-LNP enables highly effective mRNA delivery in multiple 3D models and micro-physiological systems'. Heterogenous iPSC spheroids and iPSC-derived hepatocyte spheroids (*top,* **Scale bar**: 1000 µm) were transfected with membrane-anchored mNeonGreen, nuclear mScarlet3 and membrane-anchored mNeonGreen, respectively. Z-stack reconstruction (*mid,* **Scale bar**: 200 µm) further reveals internal distribution of fluorescence within spheroid structures.
The LNP-RNA was also introduced into the culture medium and perfused into the microfluidic channel to transfect the organ-on-chip with a heterogenous human retinal cells. (*bottom*)

For more details about OriGene's gene delivery solutions , visit our booth **#0811** | Download the e-poster | Access to the product page

4 EZ-LNP enables functional assays in live organoids







EZ-LNP-mediated gene delivery enables functional biosensor monitoring in live iPSC-derived cholangiocyte organoids. A schematic illustrates liver, cholangiocytes, and the Chlor-ON sensor for monitoring chloride transport. Cholangiocyte cysts cultured in Matrigel domes were transfected with Chlor-ON mRNA(100 ng/µL), an engineered fluorescent Cl^- indicator, using EZ-LNP. Fluorescence images/videos were acquired in live status, enabling real-time functional readout in 3D organoids.

EZ-LNP overcomes key limitations of existing gene delivery

Challenges	Lipoplexes	Conventional LNP	⭐ EZ-LNP
Workflow	✔	⚠	✔
iPSC / Difficult Cells	⚠	✘	✔
3D Culture	⚠ Surface only	✘	✔ Penetrates
In Vivo (pDNA)	✘	✘	✔
Application Scope	2D	In vivo	2D →3D organoid→in vivo

TAKE-HOME MESSAGE

Ez-LNP enables gene delivery in iPSC systems from 2D cultures to 3D organoids and in vivo, unlocking functional assays in physiologically relevant models.

APPLICATIONS

- Organoid-based functional assays
- Live-cell imaging and biosensor studies
- CRISPR & mRNA screening in physiologically relevant models