Highly efficient and biocompatible delivery of RNA therapeutics using BioDrone™ platform technology

Jinhee Park, Yoonjin Baeg, Yoonjeong Kim, Yerim Kwon, Jieun Lee, Eun Hyang Jang, Sung-Soo Park, Seung Wook Oh
BioDrone Research Institute, MDimune Inc., Seoul, Republic of Korea

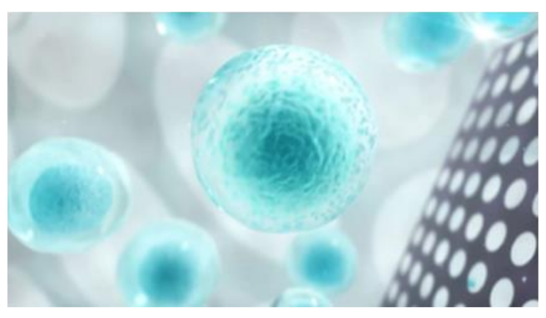
Introduction

Synthetic vehicles such as lipid nanoparticles (LNPs) and polymers commonly used for RNA delivery exhibit considerable safety concerns. Efficient delivery of RNA therapeutics to various non-hepatic tissues also remains the major challenge. Cell-derived vesicles (CDVs) produced by serial extrusion of diverse human cells are emerging as a novel delivery solution for RNA therapeutics due to their superior biocompatibility and capability to cross diverse tissue barriers. The unique scalability of CDVs also distinguishes them from any other existing vesicle technologies.

BioDrone™ Technology

Human cells

- Most biocompatible substance
- Excellent therapeutic potential
- Diverse manipulation available

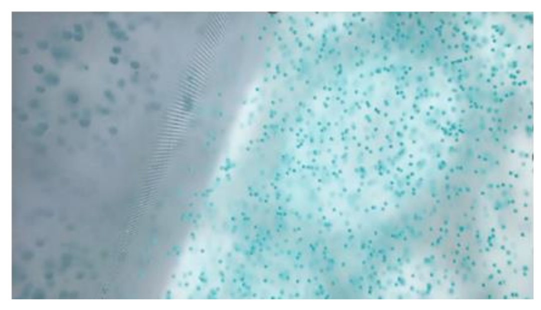


Extrusion

- Rapid process (1-2 hr)
- Highly scalable process
- Lower cost of goods

Nanovesicles (CDVs)

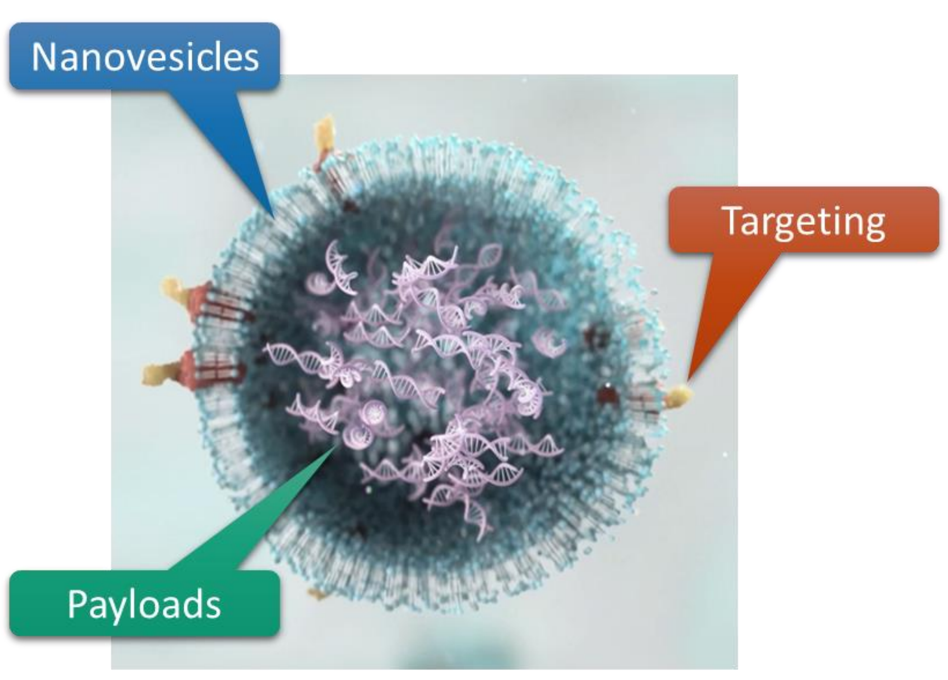
- Minimize safety issues
- Inherit cellular components
- Enhanced manufacturability



Non-viral Delivery via Nanovesicles

- Highly biocompatible with low toxicity and immunogenicity
- Nanosized vesicles crossing various cellular and tissue barriers
- Easily scalable fitting cGMP applications

BioDrone™ technology was named one of the 3 finalists in Advanced Drug Delivery category in 2023 Edison Award

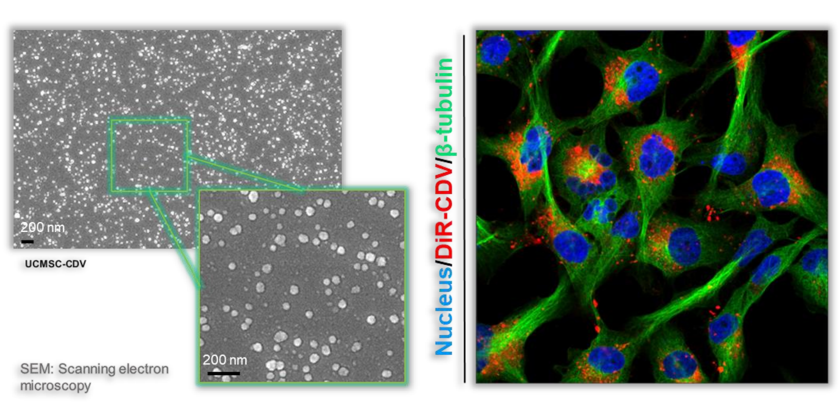


Tissue-specific Targeting

- Precision targeting toward the brain, tumor, and other challenging tissues
- Tissue-specific ligands attached to surface
- Robust engineering enabled via unique anchor proteins

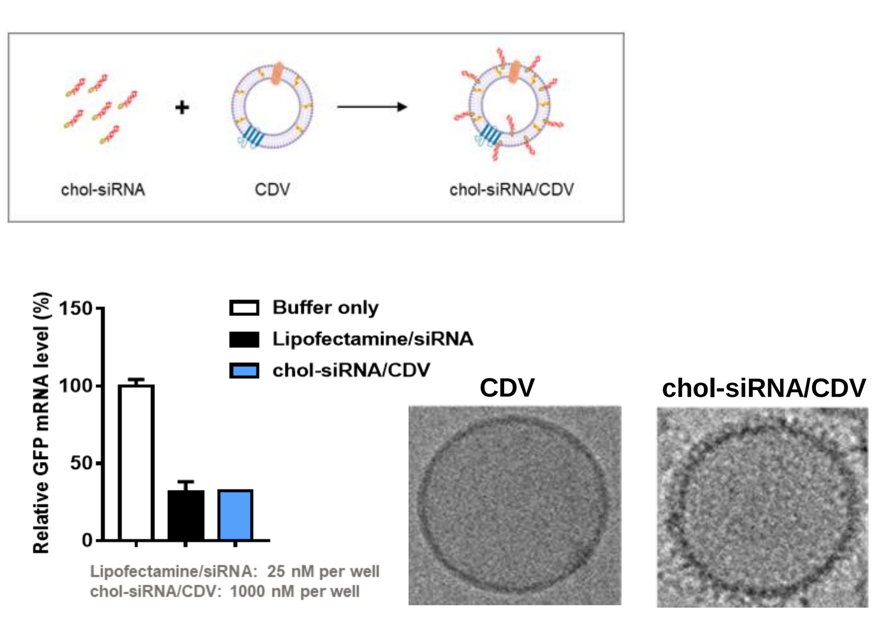
Flexible Payload Design

- Nucleic acids (RNA/DNA), protein cargo
- Therapeutics loaded on or inside the vesicles
- Membrane structure providing protection from rapid degradation

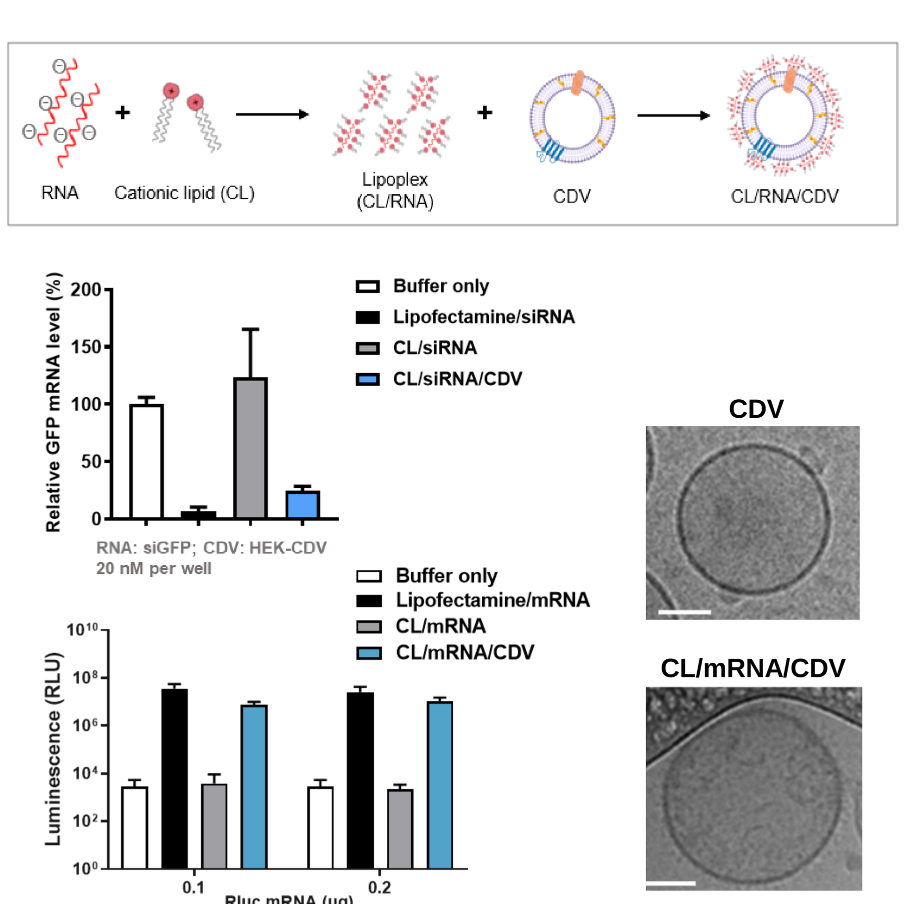


RNA Therapeutics Loading

1. Integration of Lipid-conjugated RNAs

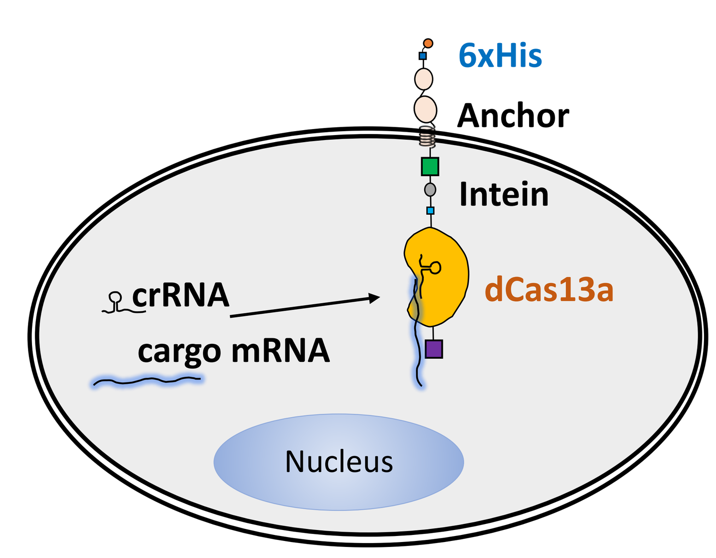


2. Complexation with Cationic Reagents

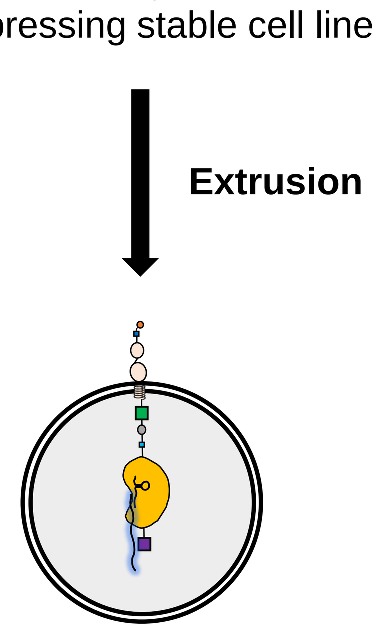


3. Encapsulation by Genetic Engineering

- Engineered cells express RNA binding motifs fused to anchor proteins of CDVs.
- RNA therapeutics enriched in CDVs upon extrusion



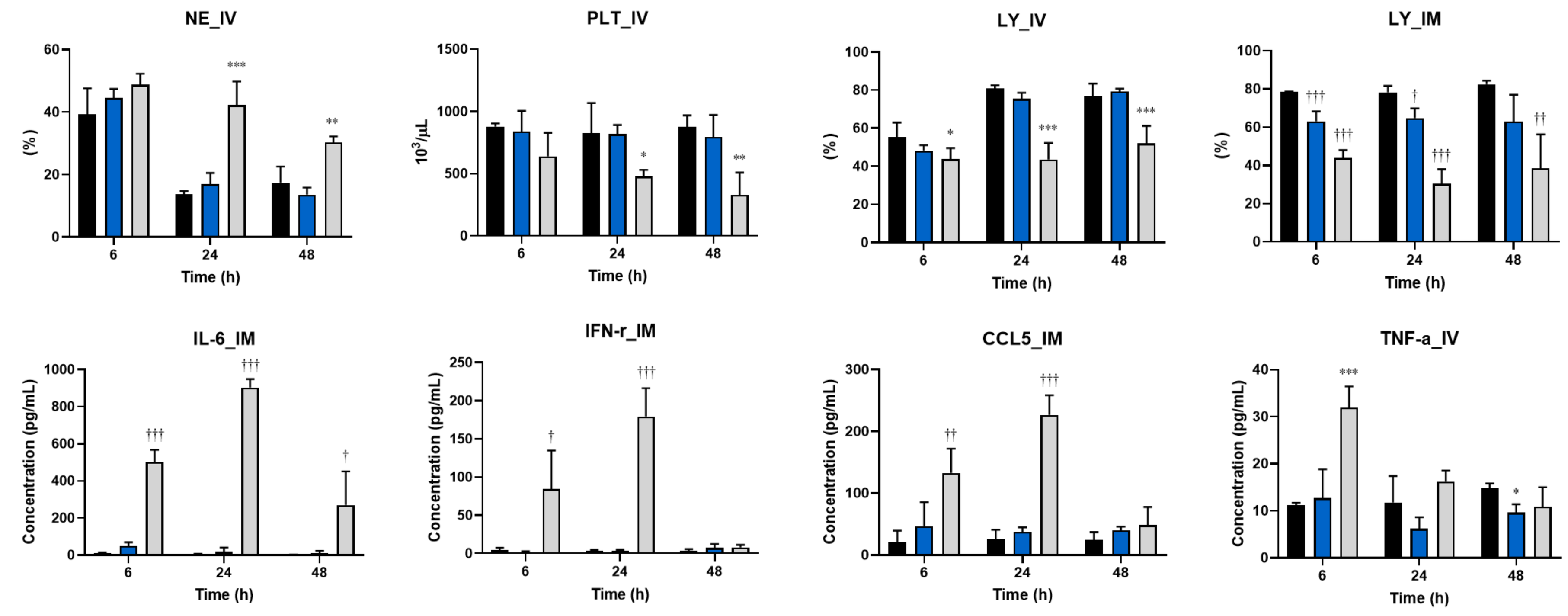
Anchor-dCas13, cargo mRNA and crRNA expressing stable cell line



Anchor-dCas13/mRNA/CDV

Safety

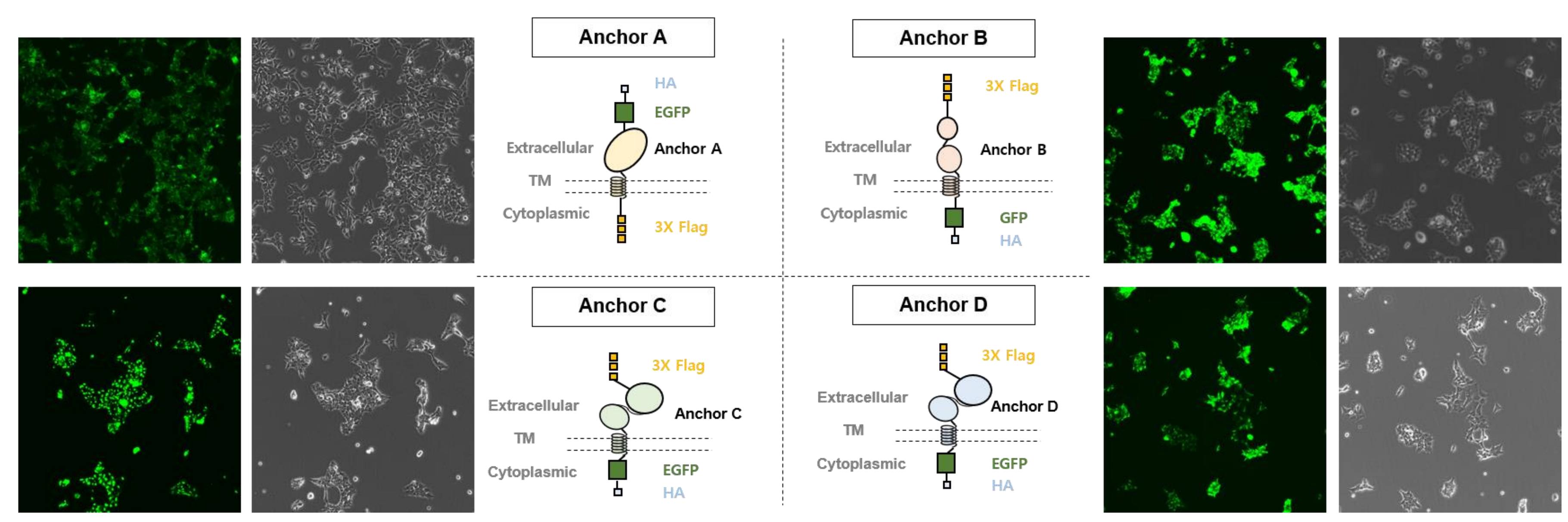
CDVs vs. LNPs (Hematology and Cytokine Analysis)



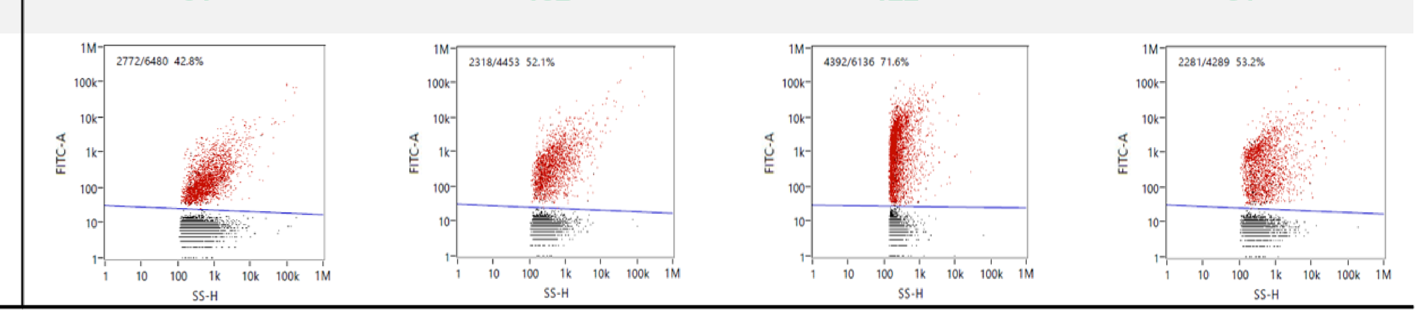
- 0.3 mpk mRNA delivered by LNPs or CDVs via i.m and i.v. routes
- LNPs showed increase in neutrophils (NE), monocytes, and basophils; reduction in lymphocytes (LY), platelets (PLT), and reticulocytes; increase in IL-6, IL-10, IFN-γ, CCL5, and TNF-α.
- No changes were observed in CDVs.

Targeted Delivery

Identification & validation of CDV anchors

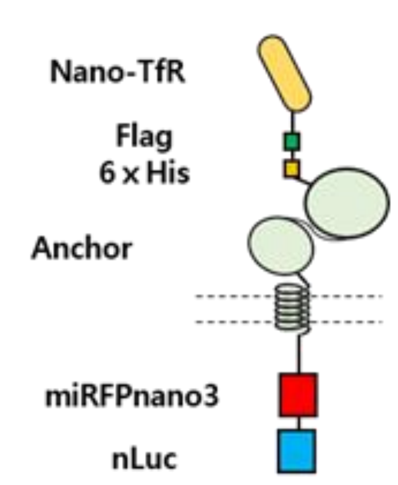


Subcellular origin	Plasma membrane		Lysosome	
Gene name	Anchor A	Anchor B	Anchor C	Anchor D
Percentage of GFP (+) particles (corrected ratio)	42	51	66	52
GFP quantification (GFP ng/ µg protein)	0.40	2.13	0.75	0.88
GFP/CDV* *in GFP positive CDVs	31	152	122	51



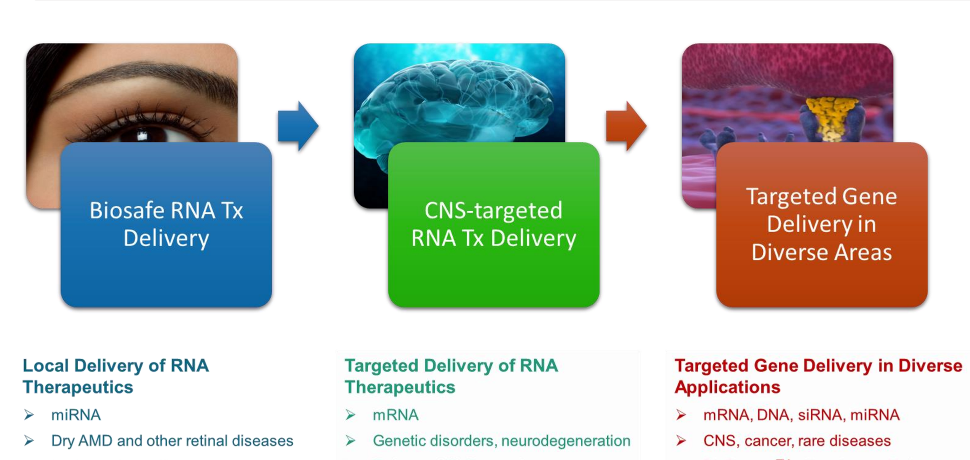
- Ligands with high affinity against target tissues can be decorated on CDV surfaces via robust anchor proteins.
- CNS targeting strategy – peptides, antibodies, or nanobodies against common targets (transferrin receptor, insulin receptor, low-density lipoprotein (LDL) receptor, etc.)

In vivo validation of CNS targeting



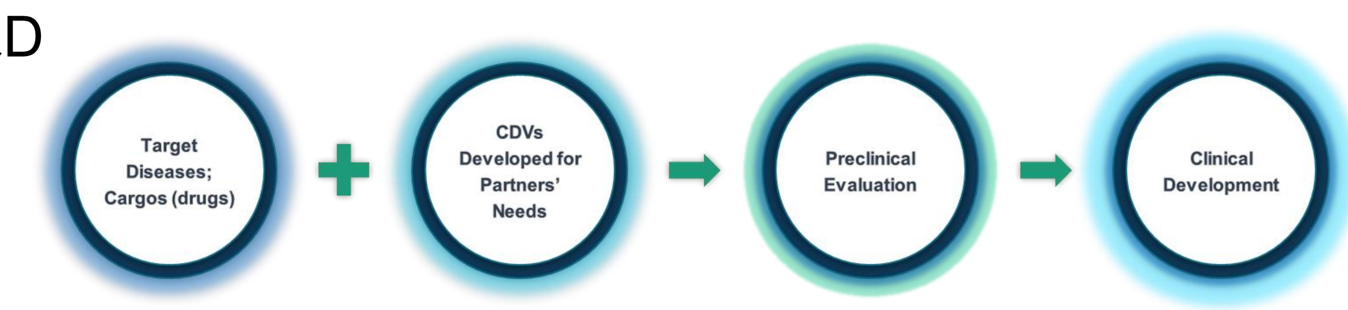
- >10x enhanced penetration across the blood-brain-barrier (BBB) was observed.
- CNS-targeted CDVs can be used to deliver mRNA and siRNA therapeutics for various CNS disorders.

Partnering Opportunities



With proven safety and versatility, the BioDrone™ technology will expedite the development of various RNA-based therapeutics for CNS disorders, rare diseases, and many other debilitating human diseases.

We're open for R&D collaboration, co-development, and standard licensing agreement.



For partnering information: bd@mdimune.com; swoh@mdimune.com