Demonstration of Safety and Therapeutic Effect of Cell-derived Vesicles in Retinal Degeneration

Hui-Chong Lau[1], Eun Hyang Jang[1], Yvette Wooff[2,3], Adrian V. Cioanc[2,3], Riccardo Natoli[2,3], Sung-Soo Park[1], and Seung Wook Oh[1]
[1]BioDrone Research Institute, MDimune Inc., Seoul, Korea, [2]Clear Vision Research, Eccles Institute of Neuroscience, John Curtin School of Medical Research, College of Health and Medicine, The Australian National University, Acton, ACT 2601, [3]School of Medicine and Psychology, College of Health and Medicine, The Australian National University, Acton, ACT 2601

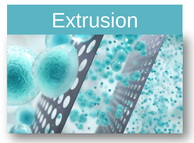
Introduction

Age-related macular degeneration (AMD) is the leading cause of blindness in developed countries. Despite the expansion of ophthalmic drugs, the effective treatment for AMD remains a major obstacle. Several studies have demonstrated that targeting multiple miRNAs provides effective therapeutic protection against AMD. However, the toxicity of synthetic lipid nanoparticles was apparent preventing their use as therapeutic carriers in human applications. Thus, more natural delivery options, such as cell-derived vesicles (CDVs) need to be investigated. Previously, we have reported the immunomodulatory capacity of CDVs in several inflammatory or degenerative diseases. Here, we assessed the safety and therapeutic potential of CDVs by examining retinal function in an AMD mouse model. Our results demonstrate the potential of CDVs as a novel therapeutic for slowing the progression of AMD. Additionally, we present our strategy to augment therapeutic effects by delivering miRNAs that are known for retinal protection on CDVs.

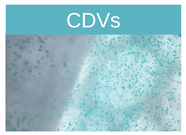
What is BioDrone™ Technology

BioDrone™ is an innovative drug delivery platform that relies on the proprietary extrusion method to obtain tiny vesicles from cells. Cells are passed through membrane filters with narrow pore sizes and revascularize into tiny nanovesicles or known as CDVs. With superior productivity and versatility, this technology has garnered increasing attention as a drug delivery vehicle. This extrusion technology generates nanosized vesicles in far greater numbers than naturally obtained extracellular vesicles (EVs).

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



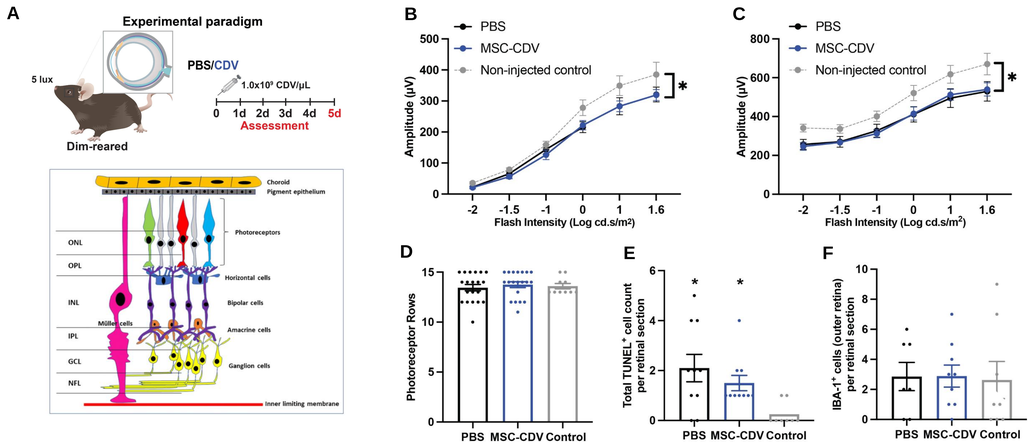
- Rapid process (1~2 h)
- Highly scalable process
- Lower cost of goods



- Minimize safety issues
- Inherit cellular components
- Enhanced manufacturability

Safety of CDVs

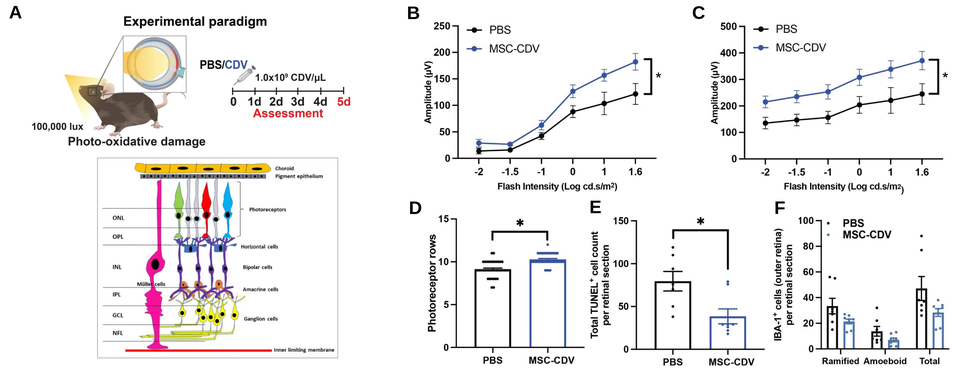
UCMSC-CDVs were injected into C57Bl/6J mice using intravitreal injection at a dose of 1.0x10^9 CDVs/μL. Following 5 days under standard housing conditions (12 h light/dark cycle with free access to food and water), retinal function and morphology were assessed using electroretinography (ERG) and immunohistochemistry (cell death; TUNEL, and inflammation; IBA1), respectively.



Schematic diagram of *in vivo* safety evaluation of CDVs in the mouse retina (A). UCMSC-CDVs do not confer any toxicity compared to controls, as measured by retinal function (B: a-wave for photoreceptor function; C: b-wave for second-order neuron function), cell death (D: the number of photoreceptor rows; E: TUNEL assay), and inflammation (F: IBA1+ cells).

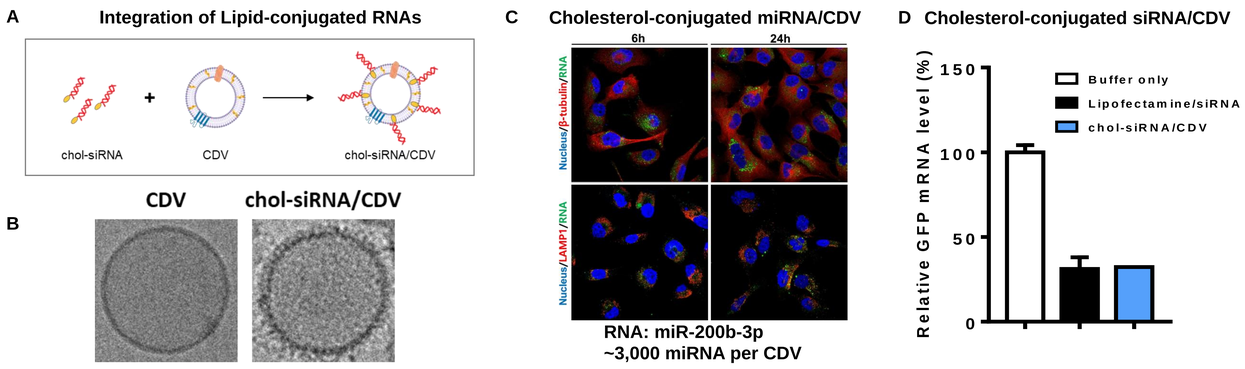
Protection Effect of CDVs

In vivo efficacy of UCMSC-CDVs were evaluated by administering intravitreal injection of CDVs at a dose of 1.0x10^9 CDVs/μL into C57Bl/6J mice subjected to photo-oxidative damage (100k lux) for 5 days. Following the oxidative damage, retinal function and morphology were evaluated using ERG and immunohistochemistry (cell death; TUNEL, and inflammation; IBA1), respectively.



Schematic diagram of *in vivo* protection effect of UCMSC-CDVs in the mouse AMD model (A). UCMSC-CDVs drastically improved retinal function (B: a-wave for photoreceptor function; C: b-wave for second-order neuron function), significantly reduced cell death (D: the number of photoreceptor rows; E: TUNEL assay), and improved inflammation (F: IBA1+ cells).

RNA Therapeutics Loading



Schematic diagram of cholesterol conjugated siRNA/CDVs (A) and the morphology of chol-siRNA-loaded CDVs by Cryo-TEM (B). RNA delivery by CDVs showed efficient cellular uptake (C) and gene silencing (D) at *in vitro* level.

Partnering Opportunities

Local Delivery of RNA Therapeutics
- miRNA
- Dry AMD and other retinal diseases
- In vivo safety, efficacy

Targeted Delivery of RNA Therapeutics
- mRNA
- Genetic disorders, neurodegeneration
- Enhanced CNS targeting

Targeted Gene Delivery in Diverse Applications
- mRNA, DNA, siRNA, miRNA
- CNS, cancer, rare diseases
- BioDrones™ tailored to multiple targets

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