Nanobiotechnology in Vesicular mRNA Based Disease Therapy and Diagnosis

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Abstract

Gene therapeutics including coding messenger RNA (mRNA) and DNA plasmids, and non-coding small interfering RNA (siRNA) and microRNA (miRNA) have great potential for unmet medical needs such as regenerative medicine and cancer treatment. However, a major challenge is the ability to deliver those large biomolecules into target tissues and cells. Many cell transfection techniques have been developed, including viral vectors and nanoparticles (e.g. liposomes). But they suffer from severe immunogenicity, poor efficacy, and/or high cost. Recently, cell and cell-secreted vesicles such as exosomes that encapsulate genetic and proteomic materials have emerged as promising new therapeutics. Here, we introduce a new technology platform, nanochannel electroporation (NEP) for highly effective cell transfection and vesicle secretion. The potential of transfected cells and their secreted extracellular vesicles (EVs) containing therapeutic mRNA is demonstrated in a number of frontier medical fields including non-viral generation of induced endothelial cells (iECs) for wound healing, therapeutic neutrophils for rheumatoid arthritis (RA) treatment, umbilical cord MSC secretome for acute respiratory distress syndrome (ARDS) treatment, as well as mRNA containing therapeutic exosomes for skin rejuvenation, revascularization, and gliomas and pancreatic cancer treatment. Liquid biopsy is a minimal invasive early detection method that has the potential to reduce mortality rates of many major diseases such as cancer and virus infection. Current detection of soluble proteins in body fluids suffers from high false positive rate and limited application range. Given their role in fundamental tumor biology, EV mRNAs have emerged as potential biomarkers for cancer detection. The current methods for EV analysis use either PCR, next generation sequencing and/or hybridization microarray to identify RNA targets, or LC-MS and ELISA to identify protein targets. These technologies can only provide averaged information from total RNA/protein from all EVs. Since EVs in body fluids come from various cell sources, these analyses cannot provide high sensitivity and specificity in liquid biopsy. We have developed a facile nano-engineered biochip technology to detect target mRNAs and their proteins in individual EVs for superior diagnosis potential of cancer and infectious diseases.

Relevant Recent Publications

- P. E. Boukany, et.al. and **L.J. Lee**, “Nanochannel Electroporation Delivers Precise Amounts of Biomolecules into Living Cells”, **Nature Nanotechnology**, 6, 747-754 (2011).
- **L.J. Lee**, et.al., “Extracellular mRNA Detected by Tethered Lipoplex Nanoparticle Biochip for Biomarker Development in Lung Cancer”, **American Journal of Respiratory and Critical Care Medicine**, 193(12), 1431-1433 (2016).
- J. Hu, et.al. and **L.J. Lee**, “A Signal-amplifiable Biochip Quantifies Extracellular RNAs for Early Cancer Detection", **Nature Communication**, 8(1), 1683 (2017).
- D. Gallego-Perez, et.al., **L.J. Lee** and C.K. Sen, "Topical Tissue Nano-transfection Mediates Non-viral Stroma Reprogramming and Rescue", **Nature Nanotechnology**, :10.1038/nnano.2017.134 (2017).
- M.S. Pavlyukov, et.al., **L.J. Lee** and I. Nakano, “Apoptotic Cell-Derived Extracellular Vesicles Promote Malignancy of Glioblastoma Via Intercellular Transfer of Splicing Factors”, **Cancer Cell**, 34(1):119-135 (2018).
- Z. Yang, et.al. and **L.J. Lee**, “Large-Scale Generation of Functional mRNA Containing Exosomes via Cellular Nanoporation”, **Nature Biomedical Engineering**, 4, 69-83 (2020).

About the Speaker

Dr. Lee is the Emeritus Helen C. Kurtz Professor of Chemical and Biomolecular Engineering at The Ohio State University (OSU). He founded and served as the Director of NSF Nanoscale Science and Engineering Center for Affordable Nanoengineering of Polymer Biomedical Devices (CANPBD) at OSU from 2004 to 2015. He received a BS degree in chemical engineering from National Taiwan University and a Ph.D. degree in chemical engineering from University of Minnesota. His research interest includes bio-micro/nanotechnology, biomaterials, liquid biopsy, and cell/exosome based gene therapy. He has >450 refereed journal publications, 35 patents and patent applications, and 14 book chapters. He was elected as the Fellow of the American Institute for Medical and Biological Engineering in 2006. Dr. Lee received the 2008 Malcolm E. Pruitt Award from Council of Chemical Research, 2010 International Award from the Society of Plastic Engineers, and 2016 Lifetime Achievement Award from the Society of Advanced Molding Technology.