# EXOSOME-mRNA BASED GENE THERAPY FOR REGENERATIVE MEDICINE AND CANCER TREATMENT

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## ABSTRACT

Nucleic acid (or gene) therapeutics including coding messenger RNA (mRNA) and DNA plasmids have great potential for regenerative medicine and disease treatment. The recent success of mRNA-based vaccines developed by Moderna and BNT for COVID-19 pandemic further promoted a strong interest in this frontier field. However, a major limiting factor is the ability to deliver well-defined amounts of these large and negatively charged biomolecules into target tissues and cells. A variety of nanocarrier techniques have been developed for *in vivo* gene delivery, including viral vectors and chemical methods (e.g. liposomal and polymeric nanoparticles, LNPs and PNPs). But viral vectors suffer from severe immunogenicity and high cost, while LNPs/PNPs exhibit poor efficacy in many medical applications other than vaccines and liver diseases. Recently, cell-secreted vesicles such as exosomes that encapsulate genetic and proteomic materials have emerged as promising therapeutic agents because they are biocompatible, can penetrate physiological barriers, and are much more affordable than cell- or virus-based therapies. But only a few cell types such as mesenchymal stem cells (MSCs) can secret high numbers of exosomes that exhibit some immunosuppressive activity and few functional native mRNA molecules are found in exosomes. Here we show the development of a new technology platform, nanochannel electroporation (NEP), for highly effective cell transfection and production of exosomes aplenty. The potential of cell secreted exosomes containing therapeutic mRNAs is demonstrated in a number of case studies for unmet medical needs including skin rejuvenation, revascularization, osteoarthritis (OA) treatment and bone repair, and solid tumor treatment.

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## About the Speaker

Dr. Lee is the Emeritus Helen C. Kurtz Professor of Chemical and Biomolecular Engineering at The Ohio State University (OSU) and a Jade Mountain Scholar at National Yang Ming Chiao Tung University (NYCU). He founded and served as the Director of NSF Nanoscale Science and Engineering Center for Affordable Nanoengineering of Polymer Biomedical Devices (CANPBD) at OSU. 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 nanobiotechnology, drug delivery, gene therapy, and liquid biopsy. He has more than 450 refereed journal publications, 35 patents and patent applications, and 14 book chapters. He was elected as the Fellow of 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.

**Drug repurposing: from big data to therapeutics**

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Of 71 anti-cancer drugs for solid tumors approved by the FDA between 2002 and 2014, the median gains in progression-free and overall survival are ~2 months. A review of 277 randomized controlled trials for systemic therapies for solid cancers published 2011-2015 show that only one third of these trials with statistically significant meet the meaningful overall survival benefit. These observations suggest two potential unmet clinical needs: (1) the existence of drug resistance (either intrinsic or acquired), and (2) the importance of patient stratification. In other words, it is imperative to implement a companion diagnostic biomarker along with drug discovery pipeline. To address these two questions, we have accessed several big data to identify compounds (old drugs) for anti-cancer drug discovery. Firstly, resistance to chemotherapy or targeted therapy, such as EGFR inhibitor, is a major problem for systemic lung cancer treatment. Such resistance may be explained by cancer stem-like cell (CSC) theory. By using the Connectivity Map dataset, we have identified phenothiazine-like antipsychotic drugs which may reverse the CSC-associated gene expression. Further, the in vitro and in vivo experiments have validated its anti-CSC effects. This study demonstrated a novel platform for screening potential anti-CSC drugs, which may overcome the drug resistance. Secondly, synthetic lethality (SL) has emerged as a novel anti-cancer strategy. SL is an interaction between two genes such that simultaneous perturbations of the two genes result in cell death or a dramatic decrease of cell viability, whereas a perturbation of either gene alone is not lethal. The successful application of SL concept in the drug development is the approval of olaparib (a PARP inhibitor) by FDA in 2014 for the treatment of advanced ovarian cancer with *BRCA1/2* mutations. We have first built a big data approach to simulate this clinical trial results. Then, we evaluated several old drugs, which have been used in oncology, and mapped their corresponding SL pairs. Finally, we have analyzed several big data to reveal potential drugs for COVID treatments. Examples will be illustrated. In conclusion, this systematic analysis strategy could rapidly place old drugs for clinical study.