BIOGRAPHICAL SKETCH

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NAME **L. James Lee, Ph.D.**	POSITION TITLE Helen C. Kurtz Professor of Chemical and Biomolecular Engineering
eRA COMMONS USER NAME lee.31	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
National Taiwan University, Taipei, Taiwan	B.S.	1972	Chemical Engineering
Case Western Reserve University, Cleveland, OH	GRA	1974-75	Macromolecular Science and Engineering
University of Minnesota, MPLS, MN	Ph.D.	1979	Chemical Engineering

A. Personal Statement

My research interest is to design and develop nanoscale biochips/devices for fundamental and therapeutic biomedical applications including cancer therapy and regenerative medicine. I have published extensively in this field and have been serving on the NIH Study Sections. I have an established history of research collaboration with many medical researchers and clinicians in the US. I have advised more than 70 PhD students and more than 100 postdoc researchers/research associates/visiting scholars in the past 37 years. I have also raised more than US$120M research grants from federal and local government agencies as well as industry, and have managed several large-scale interdisciplinary, cross-college research and education programs/centers at the Ohio State University (OSU) from 2002 to 2015. I have retired to an emeritus status on September 1, 2018, but remain active in research and student/postdoc training at OSU. I have collaborated closely with co-PIs in this proposal.

B. Positions and Honors

ACADEMIC EXPERIENCE

2018-present	Emeritus Helen C. Kurtz Professor, The Ohio State University
2000-2018	Helen C. Kurtz Professor, The Ohio State University
1990-2000	Professor, Chemical Engineering, The Ohio State University
1986-90	Associate Professor, Chemical Engineering, The Ohio State University
1982-86	Assistant Professor, Chemical Engineering, The Ohio State University

INDUSTRIAL AND GOVERNMENTAL EXPERIENCE

1979-82	Senior Research Engineer, 1979-82 The General Tire & Rubber Company (GenCorp), Akron, Ohio
Summer1988	Structural Materials Branch -Air Force Wright Patterson Materials Laboratory, Dayton, Ohio

AWARDS AND HONORS

2016	Lifetime Achievement Award, Society of Advanced Molding Technology
2010	International Award, Society of Plastics Engineers
2010	OSU, College of Engineering Lumley Interdisciplinary Research Award
2008	Engineering/Technology Award, Society of Plastics Engineers
2008	Malcolm E. Pruitt Award, Council of Chemical Research
2006	Fellow, American Institute for Medical and Biological Engineering

2005,01,95,91,88,85	OSU, College of Engineering Research Award
2002	OSU, College of Engineering Scott Senior Faculty Award
2002	OSU, College of Engineering Lumley Interdisciplinary Research Award
2001	Fellow, Society of Plastics Engineers
2000	OSU Technology Partnership Alliance Award
2000	OSU Distinguished Scholar Award
2000, 1996	OSU, College of Engineering Annual Research Accomplishment Award
1989	OSU, College of Engineering Harrison Faculty Award for Excellence in Engineering Education
1987	Central Ohio AIChE Section, Innovation in Chemical Engineering
1986-2011	15 Best Paper Awards in Society of Plastics Engineers, Society of Plastics Industry Annual Conferences and American Association of Pharmaceutical Scientist Annual Conferences
2002-2007	Director of NSF Integrated Graduate Education and Research Training (IGERT) Program on Molecular Engineering of Micro-Devices
2004-2015	Director of NSF Nanoscale Science and Engineering Center for Affordable Nanoengineering of Polymer Biomedical Devices (CANPBD)
2005-2012	Director of Ohio Center for Affordable Multifunctional Polymer Nanomaterials and Devices (CMPND)

C. Contribution to Science (>400 referred journal publications, >15,000 citations)

1. Non-viral Gene Delivery by Nanochannel Electroporation- The ability to deliver precise amounts of biomolecules and nanofabricated probes into living cells offers tremendous opportunities for biological studies and therapeutic applications. It may also play a key role in the non-viral generation of engineered stem cells and induce pluripotent stem cells with high efficiency and non-carcinogenic properties. Currently-available transfection approaches are heavily dependent upon diffusion- and endocytosis-based mechanisms, which results in highly stochastic transfection. We have overcome this problem by developing a new technology, nanochannel electroporation (NEP) allowing transfection of many small sized and delicate cells with precise control over dose and timing. Cell mortality from NEP is virtually zero. We show dose control effects on a variety of transfection agents such as oligonucleic acids, molecular beacon, quantum dots and efficient delivery of large DNA directly into the nucleus using nanoparticle “bullets.” Dosage controlled delivery to multiple cells is not achievable with any existing techniques. NEP also leads to mass secretion of extracellular vesicles containing functional RNAs from transfected cells.

- P. E. Boukany, A. Morss, W-C Liao, B. Henslee, X. Zhang, B. Yu, X. Wang, Y. Wu, H.C. Jung, L. Li, K. Gao, X. Hu, X. Zhao, O. Hemminger, W. Lu, G. Lafyatis and **L.J. Lee**, “Nanochannel Electroporation Delivers Precise Amounts of Biomolecules into Living Cells”, **Nature Nanotechnology**, 6, 747-754 (2011), research highlight in **Nature Methods**, 8, 996-997 (2011).
- D. Gallego-Perez, L. Chiang, J. Shih, J. Ma, S. Kim, X. Zhao, X. Wang, P. Mao, K.J. Kwak, Y. Wu, L. Wu, G. Lafyatis, D.J. Hansford, I. Nakano, and **L.J. Lee**, “On-Chip Clonal Analysis of Glioma-Stem-Cell Motility and Therapy Resistance”, **Nano Letters**, 16(9), 5326-5332 (2016).
- D. Gallego-Perez, D. Pal, S. Ghatak, V. Malkoc, N. Higuita-Castro, S. Gnyawali, L. Chang, W-C Liao3, J. Shi, M. Sinha, K. Singh, E. Steen, A. Sunyecz, R. Stewart, J. Moore, T. Ziebro, R.G. Northcutt, M. Homsy, P. Bertani, W. Lu, S. Roy, S. Khanna, C. Rink, V.B. Sundaresan, J.J. Otero, **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).
- Z. Yang, J. Shi, J. Xie, Y. Chen, J. Sun, T. Liu, Y. Zhao, X. Zhao, X. Wang, Y. Ma, V. Malkoc, C-L Chiang, Y. Fu, K.Joo Kwak, Y. Fan, C. Kang, C. Yin, J. Rhee, P. Bertani, J. Otero, W. Lu, A.S. Lee, W. Jiang, L. Teng, B.Y.S. Kim and L.J. Lee, “Large-Scale Generation of Functional mRNA Containing Exosomes via Cellular Nanoporation”, **Nature Biomedical Engineering**, 4, 69-83 (2020).

2. Targeted Delivery by Lipoplex Nanoparticles- The high mortality rates for many cancers can be attributed to late diagnosis, high recurrence rates, metastasis, and limited effectiveness of current therapeutic modalities. Although the aforementioned issues have been studied extensively, there is no current technology platform that allows for simultaneous detection, therapy and prognosis determination. MicroRNA (miRNA) dysregulation has been implicated in HCC development. These miRNAs regulate a network of tumor promoting and tumor suppressor genes that are critical for tumor cell survival, epithelial-to-mesenchymal and mesenchymal-to-epithelial transition (EMT/MET), escaping the host immune system, resistance to therapy, and angiogenesis.

Modulating tumor cells and its microenvironment with miRNA replacement (MRT) and anti-miRNA therapy (AMT) can potentially inhibit tumor growth and sensitize tumor cells to existing therapy. A critical barrier to the clinical development of MRT/AMT is that oligonucleotides are sensitive to nucleases, subject to renal and reticuloendothelial system (RES) clearance with minimum membrane permeability. Delivery systems based on targeted lipid nanoparticles can potentially address these problems. My team has made significant contribution in this area.

- Y. Wu, M. Crawford, B. Yu, Y. Mao, S. Nana-Sinkam and **L.J. Lee**, "MicroRNA Delivery by Cationic Lipoplexes for Lung Cancer Therapy", **Molecular Pharmaceutics**, 8, 1381-1389 (2011).
- B. Yu, S-H Hsu, C. Zhou, X. Wang, M. Cavanaugh Terp, Y. Wu, L. Teng, Y. Mao, F. Wang, W. Xue, S.T. Jacob, K. Ghoshal, R.J. Lee and **L.J. Lee**, "Novel Lipid Nanoparticle Design for Delivery of Small Interfering RNA to Liver and Liver Tumor", **Biomaterials**, 33, 5924-5934 (2012).
- B. Yu, Y. Mao, L. Bai, S. May, A. Ramanunni, Y. Jin, X. Mo, C. Carolyn, K.K. Chan, D. Jarjoura, G. Marcucci, R.J. Lee, J.C. Byrd, **L.J. Lee** and N. Muthusamy, "Liposomal Targeted Delivery Overcomes Off-target Immunostimulatory Effects of RNA Oligonucleotide", **Blood**, 121, 136-147 (2013).
- X. Huang, S. Schwind, B. Yu, R. Santhanam, H. Wang, P. Hoellerbauer, A. Mims, R. Klisovic, A.R. Walker, K.K. Chan, W. Blum, D. Perrotti, J.C. Byrd, C.D. Bloomfield, M.A. Caligiuri, R.J. Lee, R. Garzon, N. Muthusamy, **L.J. Lee** and G. Marcucci, "Targeted Delivery of microRNA-29b by Transferrin Conjugated Anionic Lipopolyplex Nanoparticles: A Novel Therapeutic Strategy in Acute Myeloid Leukemia", **Clinical Cancer Research**, 19(9), 2275-2292 (2013).

3. Tethered Lipoplex Nanoparticle Biochips for Extracellular Vesicles Based Circulating RNA Biomarkers- Biomolecules such as miRNAs, lncRNAs, mRNAs and protein antigens can be useful as biomarkers for cancer and other diseases. Recent studies show that they are excreted by cells in the form of extracellular vesicles (EVs) including exosomes and can be detected in the blood. Our group has been actively engaged in establishing EVs as potential noninvasive biomarkers. EVs are known mobile elements that function as escape routes for proteins and RNAs from one cell (site of origin) to distant locations. Many studies have revealed that EVs cross talk and/or influence major disease-related pathways, such as hypoxia-driven EMT, angiogenesis, and metastasis, involving many cell types within the tumor microenvironment. However, existing methods based on next generation sequencing (NGS), hybridization microarrays, and qRT-PCR have limited sensitivity and require tedious and expensive sample preparation and detection procedures. They also need several hundred microliters of blood for EV analysis. This necessitates the sacrifice of animals in murine studies, and making it impractical for tumor monitoring in murine tumor model therapy trials. To address these issues, my lab has developed "tethered lipid nanoparticle (TLN)" technology that can be used for ultra-sensitive detection of miRNAs, lncRNA, mRNA and protein antigen targets in EVs. Analysis can be performed using only 20 µL of blood from a patient or mouse with minimal sample preparation requirement. This would enable "non-lethal" monitoring of tumor load in mice. We believe that serum/plasma EV miRNA/mRNA/membrane protein profiles can serve as detection, surveillance and prognostic biomarkers that can be used for early disease diagnosis and to monitor and predict disease response to therapy.

- Y. Wu, K.J. Kwak, K. Agarwal, A. Marras, C. Wang, Y. Mao, X. Huang, J. Ma, B. Yu, R.J. Lee, A. Vachani, G. Marcucci, J.C. Byrd, N. Muthusamy, K. Huang, C.E. Castro, M. Paulaitis, S.P. Nana-Sinkam and **L.J. Lee**, "Detection of Extracellular RNAs in Cancer and Viral Infection by Tethered Cationic Lipoplex Nanoparticles", **Analytical Chemistry**, 85(23), 11265-11274 (2013).
- **L.J. Lee**, Z. Yang, M. Rahman, J. Ma, K.J. Kwak, J. McElory, K. Shilo, C. Goparaju, L. Yu, W. Rom, T-K Kim, X. Wu, Y. He, K. Wang, H.I. Pass and S.P. Nana-Sinkam, "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).
- S. Baldwin, C. Deighan, E. Bandeira, K. J. Kwak, M. Rahman, P. Nana-Sinkam, **L. J. Lee**, and M. E. Paulaitis, "Analyzing the miRNA Content of Extracellular Vesicles by Fluorescence Nanoparticle Tracking," **Nanomedicine: Nanotechnology**, **Biology**, **and Medicine**, 13(2),765-770 (2017).
- Hu, Y. Sheng, K.J. Kwak and **L.J. Lee**, "A Signal-amplifiable Biochip Quantifies Extracellular RNAs for Early Cancer Detection", **Nature Communication**, 8(1),1683 (2017).

4. Cell Based Drug Delivery- Cell-based therapeutic strategy has been proposed as a tissue engineering application for several decades. Primary or cell line with certain product secretion can be used as "seed" cell for therapeutic function. Alternative resource of cells is from gene recombination-mediated methods. As most tissue or cellular transplants, the cellular grafts are subject to immunorejection in the absence of chronic immunosuppression. For cell-based device applications *in vivo*, the device must provide proper cell

immunoprotection with minimal inflammatory response. Furthermore, the device should possess controllable degradation characteristics such that the implant does not need to be removed after use via invasive second surgery. My lab has conducted considerable research in this area.

- X. Zhang, H. He and **L.J. Lee**, "A Biodegradable, Immunoprotective, Dual Nanoporous Capsule for Cell-Based Therapies", **Biomaterials,** 29, 4253-4259 (2008).
- H. He, V. Grignol, V. Karpa, C. Yen, K. Laperle, X. Zhang, N.B. Jones, M.I. Liang, G.B. Lesinski, W. Ho, W.E. Carson, III and **L.J. Lee**, "Use of a Nanoporous Biodegradable Miniature Device to Regulate Cytokine Release for Cancer Treatment", **Journal of Controlled Release**, 151, 239-245 (2011).
- F. Yang, X. Zhang, A. Maiseyeu, G. Michai, R. Yasmeen, D. DiSilvestro, K.S., Maurya, M. Periasamy, V. Bergdall, C. Sen, S. Roy, **L. J. Lee**, S. Rajagopalan, and O. Ziouzenkova, "The Prolonged Survival of Fibroblasts with Forced Lipid Catabolism in Visceral Fat Following Encapsulation in Alginate-poly-L-lysine", **Biomaterials**, 33(22), 5638-5649 (2012).
- H. He, E. Luedke, X. Zhang, B. Yu, A. Schmitt, B. McClarren, V. Grignol, W.E. Carson III and **L.J. Lee**, "A Nanoporous Cell-Therapy Device with Controllable Biodegradation for Long-Term Drug Release", **Journal of Controlled Release**, 165(3), 226-233 (2013).

5. Polymer Based Micro/Nanofluidics Biochips- Micro/nanotechnology is initiated from the electronics industry. It has been extended to micro-electro-mechanic system (MEMS) and nano-electro-mechanic system (NEMS) for producing miniature devices based on silicon and semi-conductor materials. However, the use of these hard materials alone is inappropriate for many biomedical devices. Soft polymeric materials possess many attractive properties such as high toughness and recyclability. Some possess excellent biocompatibility, are biodegradable, and can provide various biofunctionalities. Proper combinations of micro/nanoelectronics, polymers, and biomolecules can lead to new and affordable medical devices. My team has established a series of non-cleanroom and cleanroom manufacturing techniques using biocompatible polymers, biomolecules, and nanoparticles as building blocks as well as micro/nanofluidics as a mechanism to design, synthesize, and fabricate biomedical and therapeutic devices. In addition to drug/gene delivery devices and cell-based constructs described earlier, we have also developed various biosensors/chips using advanced micro/nanofluidics concepts for medical diagnostics.

- S. Lai, S. Wang, **L.J. Lee**, S.T. Yang and M.J. Madou, "Design of a Compact Disk-like Microfluidic Platform for Enzyme-Linked Immunosorbent Assay", **Analytical Chemistry**, 76(7), 1832-1837 (2004).
- Y-J. Juang, S. Wang, X. Hu and **L.J. Lee**, "Dynamics of Single Polymers in a Stagnation Flow Induced by Electrokinetics", **Physical Review Letters**, 93, 268105 (2004).
- J. Guan and **L.J. Lee**, "Generating Highly Ordered and Stretched DNA Arrays", **Proceedings of National Academy of Science**, 102(51), 18321-18325 (2005).
- S. Wang, X. Zhang, W. Wang, and **L.J. Lee**, "Semi-continuous Flow Electroporation Chip for High Throughput Transfection on Mammalian Cells", **Analytical Chemistry**, 81, 4414-4421 (2009).

D. Relevant Research Support

Ongoing

UG3 TR002884-01 **(MPI:** Reategui/**Lee**/Kim/Wang**)** 09/10/2019-06/30/2021
Microfluidics array based sorting, isolation, and RNA analysis in single extracellular vesicles

R21 AR075318 **(MPI:** Jarjour/**Lee)** 07/01/2019-06/30/2021
Nucleic acids loaded neutrophils as therapeutics in Lupus

U01 CA213330 **(MPI:** Nana-Sinkam/**Lee)** 03/20/2017-03/19/2022
Extracellular vesicles in small cell lung cancer early detection

R01 CA190740-02 **(Co-I: Lee with MPI:** Croce/Nana-Sinkam**)** 08/01/2015-07/31/2020
Molecular Mechanisms of Cachexia in Lung Cancer

R33 CA225380-01 **(MPI: Lee**/Fleisher**)** 09/30/2017-09/30/2020
Molecular Beacon Based Extracellular mRNA and Protein Detection for Early Cancer Diagnosis

Completed

R21 NS099869 **(Co-I: Lee with PI:** Gallego-Perez**)** 09/01/2016-08/31/2018
Nanotechnology-based Non-viral Derivation of Induced Endothelium for Ischemic Disorders

R21 EB017539 **(MPI: Lee/**Otero**)** 08/01/2013-07/31/2016
Large scale of nanochannel electroporation (NEP) for cell reprogramming

R21 CA179403 **(MPI: Lee/**Nana-Sinkam**)** 09/17/2013-08/31/2016
Plasma RNA based early lung cancer detection by tethered cationic lipoplex assay

R21 CA185707 **(MPI: Lee**/Ghoshal/Schmidt**)** 04/01/2014-03/31/2016
Tethered cationic lipoplex nanoparticle assay for liver cancer detection and surveillance

R21 CA152969 **(MPI: Lee**/Ghoshal/Jacob/Lee R) 03/01/2011-02/28/2013
Delivery of Anti-miR Oligos in Lipid Nanoparticles to Hepatocellular Cancer

EEC-0914790 **(PI: Lee)** 09/01/2004-09/31/2015
NSF Div. of Engineering, Education, and Centers
This project, “Center for Affordable Nanoengineering of Polymer Biomedical Devices (CANPBD),” is aimed at development of affordable polymer-based nanocomposite materials and nanofluidics devices for biomedical applications.