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Award Abstract # 1562468

Continuous-Flow Microfluidic Nanomanufacturing of Nanomedicines

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ABSTRACT

Nanoparticle-enabled drugs hold enormous potential for improving human health, allowing drug designers to tailor the delivery of therapeutic compounds to specific tissues or cells, and optimize the uptake of drugs into those cells. In particular, the use of lipid vesicles or liposomes as nanoscale drug carriers has resulted in significant advances toward the treatment of a range of cancers. However, the transition of liposomal nanomedicines from the lab to the clinic remains constrained by the lack of nanomanufacturing methods capable of scaling across the full production range. This award will investigate continuous-flow microfluidics technology as a unique scalable approach to bridge this gap. This technology will leverage chemical and physical phenomena across multiple size scales within a continuous-flow microfluidic system, resulting in nanoparticle self-assembly, passive and active drug loading, nanoparticle functionalization, and drug purification and concentration. Individual fluidic modules will be developed and optimized, and sequential modules will be combined in a single continuous-flow nanofactory. The multidisciplinary project will integrate contributions from high school students through graduate researchers, and result in development of a new nanomedicines designed for the treatment of recurrent pediatric neuroblastoma, a high-risk cancer with dismal clinical outcomes.

Current techniques for liposomal drug synthesis must be re-engineered at each production scale, introducing manufacturing costs and engineering challenges that present significant barriers to the development of new liposomal drugs. Overcoming this gap is fundamentally a nanomanufacturing challenge. We will develop a multistage microfluidic flow focusing technology as a highly scalable method supporting the full production of liposomal nanomedicines in a continuous-flow process. The studies will yield new insights into the underlying multiscale physics for each processing stage, resulting in improved understanding of the chemophysical processes involved in liposome self-assembly, drug loading, and targeting agent attachment within the microfluidic system. The work will also result in new solutions to the key engineering challenges associated with coupling diverse continuous-flow microfluidic modules for advanced functionalized nanoparticle manufacturing. Performance of the technology will be evaluated using a novel nanomedicine test-bed. Specifically, the award will demonstrate a targeted polypharmaceutical comprising of an amphipathic chemotherapeutic (doxorubicin) together with a lipophilic tyrosine kinase inhibitor (erlotinib) for the treatment of pediatric neuroblastoma. Using this test-bed, a combination of scale-up and scale-out will be explored to provide a unified framework for multi-scale liposomal drug synthesis, vastly increasing the speed and reducing the complexity of nanomedicine manufacturing.

PUBLICATIONS PRODUCED AS A RESULT OF THIS RESEARCH

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Zhu Chen, Jung Yeon Han, Laura Shumate, and Don L. DeVoe "High Throughput Nanoliposome Formation Using 3D Printed Micro uidic Flow Focusing Chips" *Advanced Materials Technology* , 2019 , p.1800511 10.1002/admt.201800511

J.Y. Han, D.L. DeVoe "Metamolding: a modular approach toward large scale micropatterning and microfluidics" *24th International Conference on Miniaturized Systems for Chemistry and Life Sciences* , 2020

J.Y. Han, S. Warshawsky, D.L. DeVoe "Direct laser writing in thermoplastic microchannels by in situ photopolymerization" *24th International Conference on Miniaturized Systems for Chemistry and Life Sciences (MicroTAS 2020)* , 2020

Jung Yeon Han, Beqir Krasniqi, Jung Kim, Melissa Keckley, Don L. DeVoe "Miniaturization of Hydrocyclones by High Resolution 3D Printing for Rapid Microparticle Separation" *Advanced Materials Technology* , v.1901105 , 2020 10.1002/admt.201901105

PROJECT OUTCOMES REPORT

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Nanoparticle-enabled drugs based on liposomes hold enormous potential for improving human health, allowing drug designers to optimize transport, kinetics, dynamics, biodistribution, and specificity of therapeutic compounds. However, the transition of liposomal nanomedicines from the lab bench to clinical use has been constrained by the lack of nanomanufacturing methods capable of scaling across the full production range. Through this NSF project we have developed a scalable continuous-flow microfluidic technology supporting high throughput synthesis of complex liposomal nanomedicines. The platform takes advantage of microfluidic hydrodynamic flow focusing as a highly efficient technique for forming liposomes of tunable size, while allowing controllable surface attachment of poly(ethylene glycol) (PEG) or other polymers to the liposome surface to modify nanoparticle behavior in vivo. The technology allows multiple types of drugs with different properties to be automatically loaded into the liposomes together with attachment of antibodies to the liposomes to support cell- and tissue-targeted delivery. We have also demonstrated techniques for the isolation of drug-laden nanoparticles to remove free drug molecules, targeting agents, and residual solvent as an important step toward allowing the resulting nanomedicines to be directly used as therapeutics without further processing. Significantly, several related approaches to microfluidic-enabled process scale-up to increase production throughput were developed to enhance nanomanufacturing productivity without altering the physical processes involved in self-assembly of functional nanoparticles, enabling the generation of fully functional nanomedicines at rates sufficient for pilot-scale production. Furthermore, we have demonstrated that multiple microfluidic devices operating in parallel can serve to provide sufficient throughput for large-scale agile nanomedicine manufacture. Finally, the project has resulted in a new microscale hydrocyclone technology with unique potential for both nanoliposome synthesis and continuous-flow nanoparticle purification that may impact a wide range of applications beyond the liposomal nanomedicines at the heart of the current project.

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