Center for Affordable Nanoengineering of Polymer Biomedical Devices

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PI: **L. James Lee**
Ohio State University

Economic, technological, and industrial competitiveness for the U.S. in the coming decades will largely hinge on advances in nano-, bio- and information technologies. Demand for products with nanoscale features and functions for industrial, information, and biomedical applications, presents significant career opportunities for future generations. However, the development of nanotechnology lags far behind the other two. Most nanotechnology research remains exploratory and commercialization is hindered by a great need for mass-producible, reliable, and affordable manufacturing processes that can lead to both new products and existing products with high value-added features. **This proposal seeks to develop polymer-based low-cost nanoengineering technology that can be used to produce nanofluidic devices and multifunctional polymer-nanoparticle-biomolecule nanostructures for the next generation medical diagnostic and therapeutic applications.**

Micro/nanofabrication methods from the electronics industry exist for producing miniature devices in silicon and glass. However, the properties of these materials (poor impact strength/toughness, poor biocompatibility) are inappropriate for many biomedical devices. In contrast, 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 polymers and biomolecules can offer tailored properties for various medical devices, but the ability to process them at the nanoscale is still largely underdeveloped.

To gain the full advantages of nanotechnology and integrate its benefits into useful polymer-based biomedical devices requires a breadth of high-level research with close collaboration among engineers, biomedical researchers, chemists and physicists. Although a number of multifaceted partnerships involving academia, government, national laboratories and industry have been recently established in the U.S., there is an urgent need to increase effort in this field because nanobiotechnology covers a very broad range of challenges and opportunities. Each center or program can only address a focused portion of these issues. We propose to establish a multi-institutional, interdisciplinary Center for Affordable Nanoengineering of Polymeric Biomedical Devices (CANPBD), with a broad-based research, education, and outreach program. The main center will be at The Ohio State University (OSU) with complementary partners at the University of Akron, Boston University, University of California at Berkeley, Johns Hopkins University, Florida A&M/Florida State University (a historically black university) and Purdue University. Collaborators include at least 20 companies in Ohio and the U.S., Battelle, the Cleveland Clinic Foundation, the National Cancer Institute, Oak Ridge National Laboratory, Wright Patterson Air Force Labs, and researchers in Asia, Australia and Europe. We also plan to coordinate our work closely with NSECs at the University of California at Los Angeles and the University of Illinois-Urbana (nanomanufacturing), the NSF STC at the University of North Carolina at Chapel Hill (environmentally responsible solvents), and the NSF ERCs at the University of Washington (biomaterials and biocompatibility) and the Georgia Institute of Technology (3D tissue models) because their research focus complements ours in several important areas. Our research goals partially overlap with those of the NSF STC at Cornell University (nanofluidics) and MIT's Center for Biomedical Engineering (molecular medicine), but the methodology proposed and the applications targeted are substantially different. We will also seek mutually beneficial collaboration with these centers in the future.

The **research vision** of the proposed center is to establish a series of non-cleanroom, affordable, environmentally and biologically benign nanoengineering techniques using biocompatible polymers, biomolecules, and nanoparticles as building blocks as well as nanofluidic surface transport as a mechanism to design, synthesize, and fabricate biomedical and therapeutic devices. The research plan is comprised of three thrust areas. In the *Nanomanufacturing Thrust Area*, we will combine 'top-down' fabrication and 'bottom-up' molecular self-assembly to produce well-defined passive and active nanostructures. Examples of novel nano-fabrication concepts that will use non-cleanroom, nanomanufacturing protocols include the integration of femtosecond-pulsed-laser-based solid freeform fabrication (SFF) and sacrificial template nano-lithography on a multi-axial magnetic suspension stage; surface force-guided dynamic self-assembly; and supercritical fluid-enhanced molding and bonding techniques. In the *Transport Phenomena Thrust Area*, the research will achieve design capabilities at the nanoscale by combining nanofluidic design, transport phenomena at the nanoscale, and multiphase transport structures with multiscale modeling and macroscalar property assessment. Biocompatibility issues will be addressed in the *Biocompatibility Thrust Area* in parallel with the development of new nanofluidic designs and devices. In addition to FDA toxicology tests, 3D 'nanofiber nests' seeded with cells and embedded with optical sensors will be produced as ex vivo models to provide rapid feedback on the influence of introduced nanoscale devices fabricated in the center on the resident cell population within this 'neotissue.' This will allow the simultaneous testing of biocompatibility and transport properties. Further device performance and biocompatibility will be evaluated through NIH-sponsored animal studies at OSU's College of Medicine/Public Health, College of Pharmacy, James Cancer Research Institute, and Davis Heart and Lung Institute, as well as through some collaborating companies and laboratories.

The **near-term goal** of the three closely linked research thrust areas is to design and fabricate polymer-based, 3D nanofluidic circuits for manipulating the shape, orientation and transport behavior of individual biomolecules in well-defined nanoscale flow fields (5-100 nm). Such novel circuits will offer a controlled, dynamic environment for both biomedical diagnostics that use enzymatic reactions and for molecular transport in therapeutic processes, resulting in significant improvements over existing methods. Test bed examples include a simple, handheld protein separation/diagnostic device; an electroosmotic flow (EOF)-based 'four-roll-mill' for high-speed dynamic hybridization and complexation; a nanoneedle cell patch for low-invasive delivery of genes and macromolecular medicines into cell walls by electrophoretic stretching of molecules through converging channels located in the nanoneedles; and biomolecular nanopumps as synthetic ion channels.

The **ultimate goal** is to design and assemble a nanofactory based on the integration of nanofluidic circuits, synthetic chemistry and biological complexation. Nanofluidics in conjunction with externally tunable surface forces at the nanoscale will be used to overcome the Brownian motion and relaxation forces of biomolecules and nanoparticles, so they can be caged in the fluid or near the solid surface with a desirable shape and orientation, and moved along a pre-specified 'assembly line' in channel-like networks with controlled velocity and displacement. Together with synthetic chemistry and biological complexation, this nanofactory platform will allow continuous production of well-defined, multifunctional 3D biomimetic nanostructures and devices through polymer-biomolecule and polymer-nanoparticle-biomolecule conjugation. Such biologically active nanoscale structures and devices may greatly enhance clinical realization of extensive genomics and proteomics research results for the treatment of cancers, chronic, infectious, parasitological and central nervous diseases, and vaccine delivery. A test bed example is the formation of virus-like polymer-DNA conjugates.

Our **education and outreach vision** is to integrate the latest research developments into a practical student curriculum that imparts multidisciplinary skills and global awareness to both graduate and undergraduate students. The key education elements include a series of new courses to introduce nanoengineering of biomedical devices and related topics; an interdisciplinary curriculum offering an undergraduate minor and a graduate certificate; internships and visits to industry and national laboratories in the U.S. and abroad; and web-based dissemination. To promote technology transfer and commercialization, the proposed center will serve as an incubator of SBIR/STTR and NIST-ATP proposals prepared by teams of faculty, students and companies. The recruitment and retention of minorities and women will be emphasized through close collaboration with minority institutes such as FAMU/FSU. Undergraduate students will participate in research via senior honors theses and targeted REU support. Outreach activities include web-based science modules for K-12 students nationwide; workshops and short courses for high school science teachers and industrial researchers; and on-site research projects and workshops for middle school and high school students supervised by graduate students.

The center will be linked closely with a newly established research facility, the Ohio MicroMD Laboratory at OSU. MicroMD represents an ongoing $27M investment from the State of Ohio and OSU. It is designed to integrate micro/nanofabrication to support a broad range of activities, including MEMS/NEMS applications and polymer synthesis/processing. The bioprocessing line is fully enabled for production of biological components and reagents. The organization of CANPBD includes the Director and an Executive Committee, the Education Director and an Education/Outreach Committee, an Industrial Advisory Board (IAB), a Steering Committee, and a Medical and Ethical Evaluation Board (MEEB). Faculty participants will be invited to submit collaborative proposals for fellowships that will be competitively evaluated by the Executive Committee in consultation with the IAB and the MEEB. Each fellow will be linked with an interdisciplinary advisory team, comprised of a primary advisor, co-advisor(s), and an industry mentor. Both internal and external (IAB and an External Evaluation Team) assessments will be carried out annually for program monitoring and improvement. The evaluation plan will incorporate both formative and summative evaluation to determine any modifications needed to improve project effectiveness and to determine the degree to which objectives are being achieved.

A research team of 38 faculty (5 from underrepresented groups) from the seven partner universities is assembled for this collaborative effort. The team includes many well-established senior faculty (3 members of the National Academy of Science or Engineering, 2 Distinguished University Professors at OSU, 7 Chaired Professors, 3 Department Chairs, the Associate Dean for Medicine and Public Health and the Assistant Dean of the College of Engineering at OSU, and 4 winners of the prestigious OSU Distinguished Scholar Award) and high quality younger faculty (5 Assistant Professors and 13 Associate Professors). Their affiliations and expertise are given in the List of Participants and their roles are discussed in the proposal. Equally important is the availability of sophisticated research equipment and facilities housed at OSU and partner universities. Collectively, the above labs feature over $50M in state-of-the-art equipment in synthesis and characterization, manufacturing, and device/sensor fabrication and testing. Additional infrastructure exists in the form of a recently funded NSF IGERT (Integrative Graduate Education and Research Traineeship) program, involving many faculty from OSU and FAMU/FSU in the proposed center, on the theme 'Molecular Engineering of Microdevices' (MEMD). This topic is highly complementary to the center's focus. The IGERT program will partially support thirty outstanding domestic Ph.D. students over the next five years and will develop a series of interdisciplinary courses on nanotechnology. Cost sharing will be made available to the proposed center through an additional > $3M cash contribution and > $8M in-kind contribution.

The **intellectual merit of the proposed activities in research** is to revolutionize medical diagnosis and medicine by establishing (1) an affordable multiscale synthesis and fabrication protocol leading to a nanofactory for nanofluidic and polymer therapeutic devices; (2) a multiscale modeling approach to achieve science-based material and process optimization, and virtual device and process analysis at the nanoscale; and (3) a comprehensive biocompatibility study to ensure that the materials used and the devices developed follow regulatory policy and are relevant to the targeted biomedical applications.

The **intellectual merit of the proposed activities in education and outreach** is to (1) establish an interdisciplinary curriculum and training program to help students and industrial researchers develop skills needed to establish/adapt to careers in the burgeoning field of nanoengineering of biomedical devices; and (2) enhance the competitiveness of U.S. industry and promote awareness of this area of research among a broad spectrum of K-12 students and the general public.

The **broader impacts of the proposed activities** are to (1) realize the commercialization of nanoengineered biomedical devices through affordable manufacturing methods and novel design, (2) extend research results from medical/biology applications to homeland security, environmental protection, and food industry toxicology, (3) establish new products and new industries to create high-paying jobs in the U.S., and (4) train the 21st century workforce in economically important and critical high-tech fields.