2020 ANNUAL REVIEW

UNIVERSITY OF NOTRE DAME

Bioengineering GRADUATE PROGRAM

at the University of Notre Dame

Webber and Yoon receive CAREER Awards

Matthew J. Webber and **Sangpil Yoon** both received 2020 National Science Foundation Early Career Development (CAREER) Awards. The CAREER Award is one of the highest honors given by the U.S. government to young faculty members in engineering and science.

In his CAREER project, "Dissipative non-equilibrium supramolecular hydrogels using fuels," Webber is working to create a new material paradigm at the intersection of supramolecular chemistry and soft materials. He and his team will be studying materials and systems that exhibit transient states and enable properties of material formation in the presence of a fuel or light source, which will fall apart when the fuel is consumed or the light is turned off.

"It's exciting to think about the possibilities for a new class of materials inspired by nature, which activate in response to specific cues but exist only for a short time," said Webber. "Our first goal will be to understand more about the phase changes in these materials. What cues might influence precursor molecules to adopt a temporary structure? What types of intermolecular forces can be manipulated to activate such a structure? These are the engineering fundamentals we will be exploring."

Matthew J. Webber

Webber's CAREER proposal includes an educational objective which focuses on building several modules to enhance training in scientific communication for graduate students in the chemical and materials sciences.

He was also recently named a 2020 Polymeric Materials: Science and Engineering Young Investigator by the PMSE Division of the American Chemical Society.

Webber, a Notre Dame alum (B.S., CBE '06), joined the Department of Chemical and Biomolecular Engineering in 2016. His expertise encompasses supramolecular biomaterials, "smart" drug delivery and diagnostics, bio-inspired materials, and supramolecular chemistry. His work focuses on the development of novel materials, featuring bio-inspired properties or offering solutions for pressing problems in healthcare.

Yoon joined the University in 2018. His research centers around the development of diagnostic and therapeutic devices for cell engineering in cancer treatment, including personalized immunotherapies such as adoptive cell transfer (ACT). During ACT,

Matthew J. Webber and former Clare Boothe Luce Scholar Siena Mantooth (B.S., CBE '19), review test results in the Supramolecular Engineering Lab. Mantooth is now a biomedical engineering graduate student at North Carolina State University.

IN THIS ISSUE

From the Director

While this year has been a challenge for research and education, the events surrounding COVID-19 emphasize the vital role of bioengineering and biotechnology in society. Technologies and knowledge that have been developed over the last 20 years have allowed the world to advance toward diagnostics, therapeutics, and vaccines at an incredible pace.

Perhaps more than anything, the pandemic has highlighted the importance of communication skills in science and engineering. The ability to explain a complex scientific problem to a broad population of all ages has been and will be our most effective tool. Prevention, vaccines, and therapies can have no effect on a population that won't use them. This makes communication of the importance and effectiveness of these interventions essential.

Our laboratories and students have persevered throughout the uncertainty of these times. It has been gratifying to see the students, postdoctoral researchers, and faculty come together with building managers and Notre Dame Research to define workable plans to reopen all research facilities. Although the limits on lab occupancy and restricted building and office access have changed the rewarding interactions that are so important to being a Ph.D. student, it seems that we are adapting to those changes. Webcams set up in labs are allowing us to train new students through video conferencing, and meetings are sometimes interrupted by the curious cat or the whims of a finicky internet connection. But we continue.

We were happy to share the news that two assistant professors in our program, **Matthew J. Webber** and **Sangpil Yoon**, have received NSF CAREER awards this year. These awards follow their previous success with additional early career awards, including the 3M Innovator's award for Webber and a K99/R00 award for Yoon. Other faculty in the program have been awarded their first or continuing NIH, NSF, or DOD awards. While these awards are an acknowledgment of the creativity of our young faculty, we also appreciate that they provide the resources necessary to support our students.

Five students completed their Ph.D. degrees in 2019 or 2020. This milestone was bittersweet, as the closing of campus in the spring resulted in the cancellation of our Commencement Exercises and the traditional hooding ceremony. We hope that the students will be able to return for the delayed Commencement Ceremony over Memorial Day Weekend 2021. A special congratulations to **Tyler Curtis**, who was recognized by the Graduate School for his outstanding achievements (*see the highlight on page 7*).

Despite the present challenges, we look forward to the exciting research contributions of our students and faculty in the coming year.

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Webber and Yoon, cont.

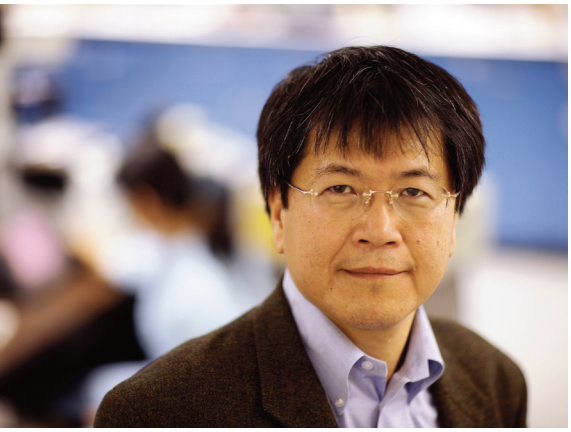
Sangpil Yoon

a patient's T cells are removed, engineered to better recognize cancer cells, then returned to the blood stream.

Yoon's CAREER project, titled "The next generation intracellular delivery device for immunotherapy: The integration between ultrasonic transducer and microfluidic chip (UXuChip)," proposes the development of a novel intracellular delivery device that would provide a more reliable technique to reinfuse a patient's T cells once they have been reengineered. This new device would improve molecule delivery efficiency while also maintaining T cell anti-tumor activity.

Yoon will also be developing educational activities for postdoctoral researchers, graduate students, undergraduates and high school students highlighting ultrasound imaging, microfluidic chip development and cancer therapies.

Chang Receives AES Lifetime Achievement Award



Hsueh-Chia Chang, the Bayer Professor of Chemical and Biomolecular Engineering, has received the AES Lifetime Achievement Award. Bestowed annually by the AES Electrophoresis Society, the award honors exceptional career contributions to the fields of electrophoresis, electrokinetics, and related areas.

Chang is known for his creative contributions across several disciplines within micro/nanofluidics, including reaction engineering, control, fluid mechanics, soft materials and biosensing. He has integrated his broad knowledge into commercialization-ready molecular diagnostic technologies. Three start-ups have licensed his technologies.

A Notre Dame faculty member since 1987, Chang serves as director for the University's Center for Microfluidics and Medical Diagnostics. During his tenure at Notre Dame, he has mentored approximately 60 doctoral candidates and postdoctoral scholars.

He is a fellow of the American Physical Society (APS) and has received many awards throughout his career, including the APS François Frenkiel Award for Fluid Mechanics, the Presidential Young Investigator Award from the National Science Foundation, and a Distinguished Visiting Fellow Award from the Royal Society of Engineering in the United Kingdom.

The author of "Electrokinetically Driven Microfluidics and Nanofluidics,"published by Cambridge University, Chang has also authored more than 270 journal publications in top fluid physics, microfluidics, and biosensing journals. In addition, he has served in an editorial capacity on a number of scientific journals, recently stepping down after 12 years of service as the founding and chief editor of *Biomicrofluidics,* now the highest ranked original journal in the ISI Fluids & Plasma Physics category.

About the ND Bioengineering Graduate Program

The Bioengineering Graduate Program at Notre Dame is an interdisciplinary Ph.D. program based in the College of Engineering. It encompasses faculty from across the University with expertise in biomaterials, cancer, computational and systems biology, drug delivery and therapeutics, environmental science, genomics/DNA/RNA, health robotics and technology, imaging, mechanobiology and physical effects on cells, orthopaedics, regenerative medicine, rehabilitation and motor control, and sensors and diagnostics.

Cutting diagnoses time with liquid biopsy option

Early detection of a disease, whether it be cancer or any number of illnesses, can make a huge difference in the outcome. A team of researchers led by bioengineering faculty is working to cut the time it takes to identify disease biomarkers. The new timeline — 30 minutes instead of 13 hours — uses very small sample sizes to offer a novel liquid biopsy option.

The difference is an integrated microfluidics platform developed at Notre Dame that uses extracellular vesicles (EVs) containing microRNAs (miRNAs) as biomarkers for early-stage disease diagnosis.

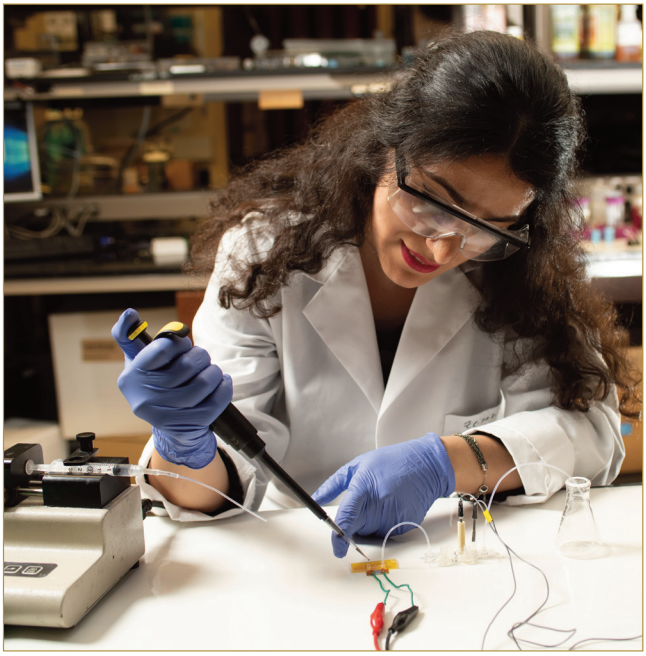
"Extracellular vesicles contribute to intercellular communication, especially during specific cellular processes such as coagulation or immune responses," said **Hsueh-Chia Chang**, co-lead of the study and Bayer Professor of Chemical and Biomolecular Engineering. "We are learning that EVs and the microRNA they carry play an important role in disease proliferation. If we can detect them accurately, quickly, and cost-effectively, they could very well be the key to early cancer detection."

Cells secrete EVs, which are easily isolated in bodily fluids such as blood, saliva, and even breastmilk.

Chang's team has developed a viable screening tool that significantly improves the inefficiencies of more conventional methods of EV-miRNA analysis.

"What we've developed is essentially a microfluidic chip that takes a small amount of blood plasma and analyzes it for a target EV microRNA in about 30 minutes," said **David B. Go**, Rooney Family Collegiate Professor of Engineering and a co-lead on the study. "By using a mechanical piezoelectric device to break open the EVs and an electrical device to detect the microRNA, we remove all the inefficiencies associated with purification, extraction, and RNA detection using PCR-based approaches — and it's a lot faster."

Their study, published in 2019 in *Nature Communications Biology*, details the screening tool and its performance. The Notre Dame team worked with cancer researchers from the University of Southern California, including **Reginald Hill**, assistant professor of medicine at the Keck School of Medicine and the Lawrence J. Ellison Institute for Transformative Medicine, and **Bangyan Stiles**, professor in the USC School of Pharmacy, to test the new device with both human and mouse liver cancer samples, demonstrating its clinical potential.



Zeinab Ramshani, a postdoctoral researcher in chemical and biomolecular engineering, tests the liquid biopsy device.

One of the most exciting aspects of the device is that it can be easily extended for other RNA and DNA biomarkers and, potentially, proteins. The team is also exploring other early-detection challenges such as preeclampsia and pancreatic cancer. As they continue to develop the technology, the team aims to offer a liquid biopsy diagnostic device that is simple, rapid, user-friendly, and capable of detecting biomarkers from clinical samples as early in the disease process as possible.

"Such a device could profoundly change how we approach health care and provide a better quality of life," Chang said. "We believe we are well on our way."

Co-authors on the study included **Satyajyoti Senapati**, research assistant professor of chemical and biomolecular engineering; **Zeinab Ramshani**, a postdoctoral researcher in chemical and biomolecular engineering; and **Chenguang Zhang**, engineering graduate student, all at Notre Dame.

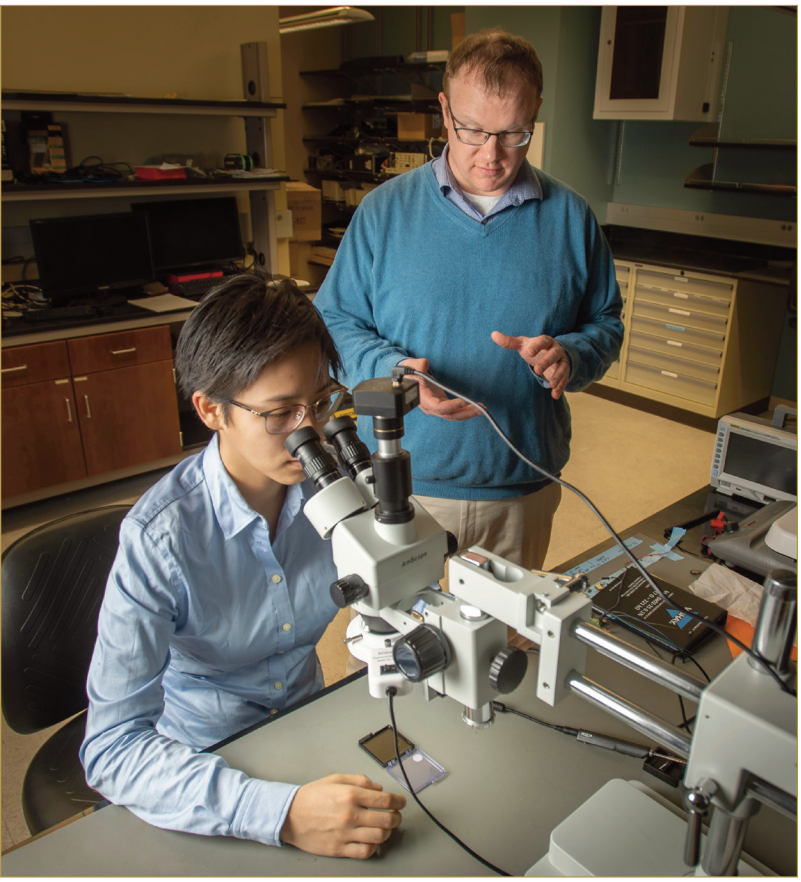
The National Institutes of Health, C. Moschetto Discovery Fund, and Notre Dame's Advanced Diagnostics and Therapeutics initiative funded the study in collaboration with the Center for Microfluidics and Medical Diagnostics at Notre Dame and the Harper Cancer Research Institute.

Smart clips offer new approach to breast cancer treatment

Breast cancer is the second most common cancer in American women, and the second leading cause of cancer deaths in women. It claimed the lives of more than 41,000 women in the United States in 2019 and changed the lives of 3.5 million breast cancer survivors.

A research team led by **Thomas O'Sullivan**, assistant professor of electrical engineering and an expert in biomedical optical sensing and imaging, is working to revolutionize breast cancer treatment by developing the first "smart" breast marker clip. The three-year project is funded in part by the Department of Defense's Breast Cancer Research Program.

About the size of a sesame seed, breast marker clips are commonly placed in the body during a biopsy, where breast tissue was removed. The biologically safe clip "marks" the biopsy area and can beseen on post-biopsy mammograms to more quickly identify the affected tissue.



Funded by the Department of Defense's Breast Cancer Research Program, graduate student Alicia Wei, seated, and Assistant Professor Thomas O'Sullivan are working to develop a "smart" breast clip to aid in the detection and monitoring of the disease.

"Since marker clips are routinely introduced in breast tumors, we began to envision ways to create 'smart' versions of the markers that could provide that information in near real-time so they could be used to optimize treatment at the earliest possible opportunity."

The team is developing a wireless, low-power, light-based sensor the size of standard breast marker clips. However, instead of simply marking the place of the abnormal tissue, the sensor continuously measures the composition of the surrounding breast tissue — without potentially toxic contrast agents or ionizing radiation — and relays it to a handheld device, similar to a glucose monitor.

Information obtained from the smart clip would allow physicians to quickly access and respond to the data regarding the regression or progression of the disease and personalize treatment for each patient based on the data received from the smart clip.

The clip could also be used to monitor benign breast lesions that are at high risk of becoming cancerous. This would decrease the number of mammograms and scans employing radioactive tracers that a woman would typically undergo for her physician to obtain comparable information about a lesion.

In a related project, which is funded by the Breast Cancer Alliance, O'Sullivan and his team are developing microimplants that can sense information and deliver light-based photodynamic therapy to nearby cancerous cells. Light from the implants excite an injected drug, making it toxic to the tumor.

The team includes **Alicia Wei**, astudent in the Bioengineering Graduate Program; **Siyuan Zhang**, the Nancy Dee Associate Professor of Cancer Research at the Mike and Josie Harper Cancer Research Institute and associate professor of biological sciences at Notre Dame; and **Joshua R. Smith**, the Milton and Delia Zeutschel Professor in Entrepreneurial Excellence and director of the Sensor Systems Laboratory at the University of Washington.

Student Spotlights

Laura Alderfer is on track to receive her doctorate in bioengineering from the University in May 2022. She is a member of the Hanjaya-Putra Lab studying stem cell morphogenesis and molecular therapeutics.

Alderfer has been focusing on the use of hydrogels to control endothelial cell behavior with the goal of creating lymphatic vessels for use in transplant therapies. By controlling the mechanical and biochemical environment of 3D cellular models, Alderfer simulates different scenarios in the body to study how changes impact lymphatic vessel formation and remodeling.

She is growing lymphatic vessels that could eventually be transplanted into a patient to treat lymphedema, myocardial infarction, and possibly neurological degeneration. Her work could also provide more information on how lymphatic vessels develop, and that information could be used to screen pharmaceutical effects that are hard to study in traditional small animal models.

Prior to COVID-19, Alderfer was set to move to Finland — part of her fellowships from the Fulbright Foundation and the American-Scandinavian Foundation — and work with Dr. Kari Alitalo to study disease mechanisms in lymphatic vessels. Alitalo discovered VEGF-C, one of the main signaling molecules involved in lymphatic vessel formation. Later this year, she hopes to be able to travel to the Alitalo lab and begin her work using their specialized mouse models in conjunction with the hydrogels she has developed. "The mouse model studies would be the next step in developing hydrogel based lymphatic vessels as a practical transplantation option," she said. "I am eager to work with the researchers in Finland and form new collaborations."

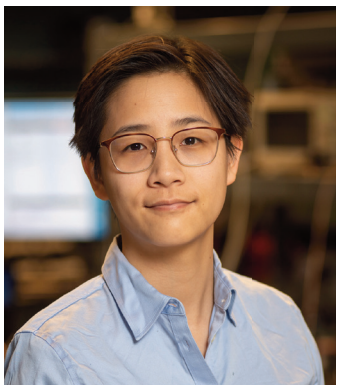
Alderfer's two fellowship opportunities are among the many valuable experiences she has found at Notre Dame. "I really appreciate the collegiality of the Bioengineering Graduate Program, the numerous collaborations, and the many avenues for professional development," she said. "Working with the Grants and Fellowships Office has been especially beneficial as I learned how to find potential grants and write compelling project statements."

Alderfer received her bachelor's degree in biomedical engineering from the Rochester Institute of Technology in 2017. Her adviser is Assistant Professor Donny Hanjaya-Putra.

Alicia Y. Wei is pursuing her doctorate in bioengineering. As a member of the O'Sullivan Research Group, she spends a large part of her time in the Biomedical Photonics Laboratory. Recently, Wei's work in the lab garnered her a fellowship from the Indiana Clinical and Translational Sciences Institute (CTSI).

"Our team focuses on expanding the technology we've developed — an ultrafast and portable imager that uses light to determine the composition of tumors — to quickly and noninvasively image cancer," said Wei. "As part of my fellowship, I've been working with our collaborators at the Saint Joseph Regional Medical Center to create and validate user friendly protocols and image analysis methods that will take our lab based technology to the clinical setting so it can be used to monitor a tumor's response to treatment and, hopefully, decrease the number of breast cancer biopsies performed."

In a separate project, Wei has been running simulations on the design of a new implantable light sensor that can also monitor cancer. She has been using her understanding of the standard biopsy process, the work flow of breast imaging procedures, and, from collaborators, knowledge of what clinicians need to see when they look at imaged tumors. She will be presenting her findings at the 2021 Translational Science ACTS Conference in March.



"I'm about halfway through my time here," said Wei. "As with most graduate programs, it has its ups and downs. You have to learn when to ask for help from the people around you, and I appreciate that the Bioengineering Graduate Program offers a multidisciplinary platform to collaborate with labs in different fields. I've been able to continue learning more about topics, such as biophotonics, that I did not expect before entering the program."

Wei received her bachelor's degrees (B.A. in mathematics and B.S. in neuroscience) from the University of Rochester in 2018 and is on track to receive her doctorate in bioengineering in 2025. Her adviser is Assistant Professor Thomas O'Sullivan.

Alumni Spotlights

Tyler Curtis came to Notre Dame from Michigan Technological University in 2014. Having completed his bachelor's degree, he entered the Bioengineering Graduate Program with an excellent academic record and strong recommendations from his undergraduate instructors. He also came with extensive research experience at Michigan Tech, as well as at the Mayo Clinic in Rochester, Minn.

Curtis's career at Notre Dame was equally as productive. His research as a bioengineering graduate student focused on novel imaging methodologies using a technique called photon counting spectral computed tomography, a new approach to X-ray imaging that enables molecular imaging.

Curtis's dissertation research focused on "material decomposition," which is the critical computational process for converting acquired X-ray spectral information into material identification and quantification. He demonstrated the capability to simultaneously quantify multiple coincident tissue and contrast agent compositions, which is not possible with current clinical molecular imaging modalties.

He also produced a number of key publications and presentations, authored two peer-reviewed journal papers, and co-authored an additional five publications, all of which have proven highly impactful in this rapidly evolving field.

In addition to receiving the Shaheen Award in Engineering from the Graduate School in 2020, Curtis received a Martell Family Ph.D. Fellowship for the 2018-19 academic year and was honored with an Outstanding Graduate Student Teacher Award from the Kaneb Center for Teaching and Learning in 2017.

Curtis completed his Ph.D. in fall 2019 and works as a systems engineer in Advanced Technologies at GE Healthcare.

"Diagnostic imaging is one of the most powerful techniques we have for clinical intervention," said Curtis. "Thanks to the combination of skills I garnered as an undergraduate and graduate student, the tutelage of gifted professors, and the opportunities I had to work on cutting-edge research at Notre Dame, I hope to take what I have learned and apply it to help develop the next generation of clinical imaging systems."

Alumni news spotlights

We love to hear from our alumni. Please send information about new positions, honors, awards, and more to Professor **Glen Niebur** at **gniebur@nd.edu.**

Funding agencies:

NIH, NSF, American Heart Association, ARMI, Breast Cancer Alliance, Craig H. Neilsen Foundation, CDMRP BCHP, DARPA, Juvenile Diabetes Research Foundation, Kelly Cares Foundation, Naughton Foundation, Walther Cancer Foundation

Awards:

Laura Alderfer — Fulbright Fellowship and American-Scandinavian Foundation Fellowship

Hsueh-Chia Chang — AES Lifetime Achievement Award

Alicia Wei — Indiana CTSI Predoctoral Fellowship

Commercialization and corporate partners:

Cubed Laboratories, Happe Spine LLC, IBM, Johnson & Johnson, Mars Bioimaging, Merck, Spinesmith LLC

1	National Science Foundation GRF
3	Fulbright Fellowships

7 Countries

22 Students
- 14 Women
- 10 Men

3 Engineering Departments

11 Laboratories

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Participating Faculty

Biomaterials
- Donny Hanjaya-Putra
- Maria Holland
- Ryan Roeder
- Joshua Shrout
- Matthew J. Webber

Cancer
- Hsueh-Chia Chang
- Glen Niebur
- Ryan Roeder
- Sharon Stack
- Sangpil Yoon

Computational Biology and Bioinformatics
- Tijana Milenkovic

Drug Delivery/Therapeutics
- Basar Bilgicer
- Hsueh-Chia Chang
- Donny Hanjaya-Putra
- Ryan Roeder
- Matthew J. Webber
- Sangpil Yoon

Environmental Science
- Robert Nerenburg
- Joshua Shrout

Genomics, DNA, RNA
- Gregory Timp

Health Robotics and Technology
- James Schmiedeler
- Patrick Wensing

Imaging
- Paul Bohn
- Danny Chen
- Scott Howard
- Thomas O'Sullivan
- Ryan Roeder
- Sangpil Yoon

Mechanobiology and Physical Effects on Cells
- Donny Hanjaya-Putra
- Maria Holland
- Glen Niebur
- Sangpil Yoon
- Pinar Zorlutuna

Orthopaedics
- Glen Niebur
- Matt Ravosa
- Ryan Roeder
- Joshua Shrout

Regenerative Medicine
- Donny Hanjaya-Putra
- Glen Niebur
- Gregory Timp
- Matthew J. Webber
- Sangpil Yoon
- Jeremiah Zartman
- Pinar Zorlutuna

Rehabilitation and Motor Control
- James Schmiedeler
- Patrick Wensing

Sensors and Diagnostics
- Basar Bilgicer
- Paul Bohn
- Hsueh-Chia Chang
- David Go
- Thomas O'Sullivan
- Joshua Shrout
- Bradley Smith
- Sangpil Yoon