BIOELECTRONICS TO RESTORE ORGAN FUNCTION PAGE 8

THE U-M COULTER PARTNERSHIP PAGE 12

EMPOWERING NEURAL ENGINEERING PAGE 10
Progress in cancer research over the past ten years has helped scientists gain a greater understanding of cancer cell metabolism and how cancer cells interact—metabolically speaking—with neighboring cells in the tumor microenvironment in order to secure the nutrients they need to proliferate.

"Learning which conversations between cancer cells and their neighbors to interrupt could potentially point us to new targets for treatments that are more effective than those in use today," said Deepak Nagrath, associate professor, who joined the BME faculty in January 2017.

In ongoing work begun at Rice University, Nagrath takes a systems biology approach, combining a metabolic isotope tracing technique with a computational framework, together known as 13C-based metabolic flux analysis. He has conducted a number of studies to more fully understand the metabolism of cancer cells as well as their interactions with their immediate environment.

In work published in November 2016 in Cell Metabolism, Nagrath focused on glutamine, an amino acid for which many types of cancer cells have been shown to have a voracious appetite. He also focused on the related enzyme glutamine synthetase in the stroma, or the connective tissue that makes up the tumor microenvironment.

In ovarian cancer cells, Nagrath’s team found greater expression of genes that control glutamine production than in normal cells and that, when the cancer cells were put into a glutamine-deprived environment, surrounding cells known as cancer-associated fibroblasts (CAFs) began producing higher than normal levels of the amino acid.

Upon further investigation, the researchers observed an interesting dynamic between the cancer and stromal cells: The cancer cells appeared to barter with their neighbors. The cancer cells contributed two enzymes, lactate and glutamate, and in exchange, the neighboring CAFs used the enzymes to produce—and share—glutamine.

But when the team inhibited glutamine production by the neighboring CAFs using drugs or through depriving them of nutrients, the ovarian cancer cells stopped growing.

Precisely how ovarian and other types of cancer cells metabolically coax their neighbors to produce nutrients is still not fully known, but Nagrath’s latest work helps snap another important puzzle piece in place.

“We now know that targeting glutamine-producing enzymes in the tumor microenvironment slowed the growth of tumors," he said. "This suggests to us that using a combination of therapies, rather than just one, to simultaneously target glutamine production and metabolism within cancer cells as well as in their surrounding environment may help us improve treatment."
Yoshida, managing director of the U-M site, at <yoshidam@umich.edu>.

BME SCAFFOLD HELPS GROW 3-D LUNGS

A tiny biodegradable scaffold from the lab of BME Professor and Chair Lonnie Shea, PhD, provided a major leap forward for a three-dimensional lung model being developed in the Medical School. This is important progress toward future cell-based therapies and a tool for screening drugs, studying gene function, and examining complex diseases like asthma and lung cancer.

These “lungs in a dish” were a project led by Briana Dye, a PhD student in the lab of U-M organoid expert Jason Spence, PhD, from the Departments of Internal Medicine and Cell & Developmental Biology. When Dye reached out to Shea’s lab, she had made substantial progress turning human induced pluripotent stem cells into structures containing both bronchi and alveoli, but the tissue remained immature.

By embedding the stem cells in a porous PLG scaffold developed in Shea’s lab, the collaborators were able to generate structures that, when transplanted into mice, became vascularized, developed more mature airways, and contained mucus-producing cells, multiciliated cells and stem cells similar to those found in adult lungs.

The remaining hurdle — that the alveolar cell type didn’t grow in the transplants — is also something Shea’s lab can help address. The scaffolds can be refined, guided by a combination of computational modeling and a technology Shea co-developed, termed TRACER (Transcriptional Activity Cell aRray). TRACER can identify the signals required to stimulate alveolar development, which can then be incorporated into the scaffold.

COMPLEMENTARY NIH AWARD FOR PERIPHERAL NERVE MAPPING

Several BME researchers on the NSF hub are also recipients of a multi-investigator award to develop and test a novel microneedle array to map peripheral nerves and autonomic organ function. Supported by the NIH SPARC program, the project will develop two novel peripheral nerve electrodes in the Seymour/Yoon and Chestek labs then conduct animal evaluations in the lab of Tim Bruns, PhD.

Co-investigators include Cai, plus Paul Cederna, MD, and Stephen Kemp, PhD, of plastic surgery, and Sapan Ambani, MD, of urology.

BMES LEAD NSF TECH HUB TO MAP THE BRAIN

Several BME faculty are part of a new hub funded by the National Science Foundation to disseminate tools developed at U-M and partner institutions for mapping the brain’s circuitry. Called Multimodal Integrated Neural Technologies (MINT), it has been
U-M’s bicentennial is an ideal time for taking stock – of all that we have accomplished and all that we are now poised to do. Since arriving as department chair in 2014, my vision has been inspired by a single idea: for U-M BME to be a model of what’s possible.

It may sound bold, but I think we’re on our way. We’ve long had the foundation – top 10 engineering and medical schools, a joint department that grounds us in both, full-spectrum resources, and a robust culture of innovation and collaboration. By strategically layering in new expertise and support structures, we’re positioning ourselves to implement ideas we think the field will be motivated to emulate.

THE “INSTRUCTIONAL INCUBATOR”: A PIPELINE FOR EDUCATIONAL INNOVATION

One area that we are hoping to revolutionize is BME education. U-M BME already has a state-of-the-art curriculum that prepares students to add value to industry and academia from day one. But we want to take this preparation further.

This fall, we will implement a strategy to institutionalize, even accelerate, the kind of curricular innovation that has spawned recent additions such as the Clinical Observation and Needs Finding course, Medical Device Sandbox, Clinical Peer Mentors program, collaboration with U-M’s Clinical Simulation Center, and Master’s Concentration in Medical Product Development. Called an “instructional incubator,” the centerpiece is a novel course designed to guide graduate students and postdocs through the process of designing new classes. These classes will not only teach critical BME skills – from CAD to computational modeling – but do so in an experiential way that helps students integrate and apply information from the diverse disciplines they must study as biomedical engineers. Modules generated by the incubator will be piloted the following semester.
Our vision is a next-generation curriculum with continuous innovation built right in. The incubator features activities designed to keep the curriculum fresh and relevant – to reimagine existing classes and generate new ones that are responsive to the evolving needs of industry, the way students learn, and the latest developments in technology and medicine.

"IF YOU THINK ABOUT EACH CLASS AS A SEPARATE TILE – CIRCUITS, CELL BIOLOGY, ETC. – THE EXPERIENTIAL LEARNING CLASSES WE’RE INCUBATING WILL HELP ASSEMBLE THE TILES INTO A MOSAIC SO STUDENTS CAN SEE THE BIG PICTURE."

-Lonnie Shea

This concept was developed and is being led by Aileen Huang-Saad, whose research focus is engineering education research.

Aileen spearheaded development of the current design sequence and brings expertise in engineering education, industry design, and entrepreneurship.

MORE SUPPORT FOR DESIGN STUDENTS

The department is delighted to announce the creation of the new Mildred F. Denecke Scholarship, available to BME students engaged in the design curriculum.

TRAINING GRANTS COMPLEMENT CURRICULAR INNOVATION

The instructional incubator complements rich training opportunities in the department, including five BME-related training grants from the National Institutes of Health and Department of Education:

- Michigan Institutional Research and Academic Career Development Awards (IRACDA): Training Future Professors in Engineering and Physiology
- Cellular Biotechnology Training Program (CBTP)
- Microfluidics in Biomedical Sciences Training Program (MBSTP)
- Tissue Engineering and Regeneration (TEAM)
- Graduate Assistance in Areas of National Need (GAANN) Fellowships in BME

NEW FACULTY POSITIONED FOR BREAKTHROUGHS ACROSS MEDICINE

Since my arrival, the department has been fortunate to bring on 11 new faculty members with expertise that both reinforces the department’s traditional strengths and expands us into new areas. Indeed, it is both the growth of our faculty and their development that has led to a surge in our research funding – from just over $9 million in 2014 to $14.5 million in 2017.
Our new faculty bring expertise that is critical to key, large-scale initiatives at U-M, such as regenerative medicine, precision health, and big data (see diagram at right).

New faculty have also expanded our reach across the breadth of the Medical School – from allergy to arthritis, cardiovascular medicine to cancer, fibrosis to fertility and beyond. Such breadth allows us to lend our engineering tools to basic scientists, translational researchers, and clinicians across numerous disciplines and specialties.

Additionally, our faculty growth has allowed us to remain a powerhouse in neural engineering; to pioneer new imaging modalities; and to use tools like multi-scale modeling to optimize surgical plans, elucidate disease mechanisms, and inform the development of new drugs and immunotherapies. The BME Faculty Expertise diagram provides an overview of the many areas in which we work; most of our faculty cross multiple boundaries.

**BME FACULTY ADDITIONS (SINCE 2014)**

- **Carlos Aguilar** | integrative genomics for muscle regeneration
- **Kelly Arnold** | computational immunology
- **Brendan Baker** | biomaterials & cellular microenvironments
- **Sriram Chandrasekaran** | transcriptional and metabolic modeling
- **Mohammad Fallahi-Sichani** | modeling of cancer signaling
- **Alberto Figueroa** | computational hemodynamics
- **Aileen Huang-Saad** | engineering education research
- **Scott Lempka** | neurostimulation for chronic pain
- **Deepak Nagrath** | modeling of cancer metabolism
- **Xueding Wang** | photoacoustic imaging
- **James Weiland** | bioelectronic retinal prostheses

**ENHANCED SUPPORT FOR INTERDISCIPLINARY WORK**

Working where fields overlap is the essence of BME – and it’s as exciting as it is challenging to stay at the cutting edge of multiple disciplines. To help meet this challenge, we’re implementing new structures and support mechanisms.

We’re grateful to have added three endowments to the department, each of which provides tangible support for
interdisciplinarity and additional freedom to innovate in this space. Not only has my own chair been endowed with a generous gift from William and Valerie Hall, we’ve also awarded two named professorships. Alberto Figueroa has become the Edward B. Diethrich M.D. Research Professor of Biomedical Engineering and Vascular Surgery, and Andy Putnam has been named the Robert C. Leland, Jr. and Donna D. Leland Professor of Biomedical Engineering and Cardiovascular Medicine. Our goal is to build on this momentum so that we can offer this invaluable means of support to additional ground-breaking researchers.

We are also helping to spearhead a new university-wide interdisciplinary structure. The Regenerative Medicine Collaborative, which I’m co-leading with David Kohn, Deneen Wellik, Lori Isom, and Paul Lee, has attracted more than 150 faculty members across campus, with more than 20 from BME.

This collaborative aims to harness U-M’s significant strength in regenerative medicine for large-scale, transformative projects. There are already numerous small teams with R01s and other grants; our goal is to facilitate the assembly of groups with the scope to tackle the grand biomedical challenges of our time. For example, we could envision experts in biology, stem cells, imaging, immunology, and biomaterials for cell transplantation coming together to tackle diabetes. The medical needs are vast and the opportunities seem endless.

We have just completed a call for project themes and are planning a kick-off symposium in the months ahead to share the group’s vision, explore thematic possibilities, and begin fostering research connections. Already it has been exhilarating to see the range of experts who are interested in collaborating on the big goals.

This is truly an exceptional time for biomedicine at the University of Michigan. Never before in 200 years have we had such a strong institutional alignment, with a physician-scientist as university president and Medical School dean; large-scale initiatives by the chief scientific officer at the Medical School and the newly appointed vice provost for biosciences; and strong support for BME in both the College of Engineering and Medical School. It is this environment, combined with the department’s enormous momentum, that makes U-M BME uniquely positioned to set new standards for what’s possible. I’m delighted to be part of this process.

Sincerely,

Lonnie D. Shea, PhD
William and Valerie Hall Chair of Biomedical Engineering, Professor, Biomedical Engineering

THE UNIVERSITY OF MICHIGAN RANKS #5 IN THE WORLD
for regenerative medicine-related citations. Our faculty have garnered $320 million from the NIH and submitted 120 patent filings in the past five years for research in this area.
The work of Assistant Professor Tim Bruns has been recognized with a highly competitive National Science Foundation Faculty Early Career Development (CAREER) Award. The five-year award will fund Bruns’ winning proposal, “Modeling dorsal root ganglia: Electrophysiology of microelectrode recording and stimulation.”

Bruns directs the U-M Peripheral Neural Engineering and Urodynamics (pNEURO) Lab, which develops bioelectronic interfaces with the peripheral nervous system to understand systems-level neurophysiology as well as to restore autonomic organ function. Dorsal root ganglia (DRG), which lie near the spinal cord and contain the cells of multiple, converging peripheral sensory nerves, have been an important focus of his research.

“Many peripheral nerves are small and hard to access, so when we’re trying to learn about these sensory systems, recording and decoding signals from the DRG can simplify the process while still giving us important clues about what’s happening,” Bruns says.

But electrodes used to record signals from or stimulate DRG have shortcomings that lessen the efficacy of current and potential therapies and slow research efforts. With the CAREER Award, Bruns will study and model the anatomy and behavior of neurons in the DRG to better understand how they interact with electrodes and, ultimately, improve upon existing technology.

**MAPPING DRG**

While many researchers have examined individual nerve cells in the DRG, Bruns is one of the first to study their arrangement, electrical behavior, and interactions at a systems level within the DRG.

In work recently published in *Journal of Neuroscience Methods*, Bruns and lab members found concentrations of nerve cells in different areas of the DRG and demonstrated a novel way to quantify their patterns and distribution.

Through collaborations with U-M Electrical Engineering and Computer Science faculty, his team is using the findings to develop improved microelectrodes, including a new, flexible, non-penetrating thin-film array that better matches the shape of the DRG and may reach more neurons with better long-term viability than current devices.

**TOWARD RESTORED BLADDER FUNCTION**

In the case of bladder dysfunction, sensory neuron signals recorded from particular DRG can help researchers and clinicians learn more about the bladder’s state. The DRG also can serve as a target for nerve stimulation therapies, including closed-loop systems that provide electrostimulation when bladder pressure approaches a critical threshold.

Bruns’ team is studying the effectiveness of new algorithms to estimate bladder pressure from DRG signals and also has demonstrated the use of microelectrodes to monitor and modulate lower urinary tract behavior from DRG signals and DRG stimulation, both in animal models. These are the first long-term, behavioral experiments examining bladder function at DRG, providing a clearer path towards clinical relevance.

**IMPROVING SEXUAL DYSFUNCTION**

Some patients using existing bladder pacemakers to improve bladder function have reported improvements in sexual function, ...
too. Bruns and colleagues in the U-M Medical School believe neurostimulation may hold promise as a potential treatment for female sexual dysfunction (FSD). In pre-clinical research, his lab has found that peripheral nerve stimulation can increase vaginal blood flow, a proxy for assessing sexual arousal.

“...these are quality of life issues and incredibly important to patients, yet few researchers are working in these areas,” says Bruns. In collaboration with a urogynecologist in the U-M Medical School, Bruns recently conducted a patient survey to assess interest in neuromodulation for FSD. Over 700 respondents in Michigan completed the survey.

The team now is leading an active clinical study that runs through early 2018. All three women who have completed the study so far had significant improvement in the Female Sexual Function Index, an assessment tool to gauge key aspects of sexual function in women.

In a small, exploratory study of kidney neuromodulation to control blood glucose, researchers in Bruns’ lab have found that stimulation in particular ranges can prevent the organs from reabsorbing sugar and boost glucose excretion from the body. The early findings are laying a foundation for further work to develop potential non-pharmacologic approaches to treating diabetes.

"FSD may affect up to 40 percent of adult women; millions of men and women suffer from bladder control issues; and diabetes affects nearly 10 percent of the U.S. population," Bruns notes. "As we better understand how nerves control the ways in which our organs function and as we develop new interfaces for interacting with neurons, we’re finding more and more opportunities to improve quality of life for these, and other, patient populations – there’s so much we can do, especially when we work closely with clinicians."

---

**CONTROLLING BLOOD GLUCOSE**

In a small, exploratory study of kidney neuromodulation to control blood glucose, researchers in Bruns’ lab have found that stimulation in particular ranges can prevent the organs from reabsorbing sugar and boost glucose excretion from the body. The early findings are laying a foundation for further work to develop potential non-pharmacologic approaches to treating diabetes.

"FSD may affect up to 40 percent of adult women; millions of men and women suffer from bladder control issues; and diabetes affects nearly 10 percent of the U.S. population," Bruns notes. "As we better understand how nerves control the ways in which our organs function and as we develop new interfaces for interacting with neurons, we’re finding more and more opportunities to improve quality of life for these, and other, patient populations – there’s so much we can do, especially when we work closely with clinicians."

---

Bruns’ DRG work is funded by National Science Foundation CAREER Award 1653080, National Institutes of Health NIBIB SPARC grant U18EB021760, and Craig H. Neilson Foundation grant 314980.

For more information on the FSD clinical trial, visit [https://clinicaltrials.gov/ct2/show/NCT02692417](https://clinicaltrials.gov/ct2/show/NCT02692417) or contact Bruns at bruns@umich.edu
EMPOWERING NEURAL ENGINEERING

by Kim Roth

Some of the earliest neural engineering work in the field was—pun unintended—conducted at U-M, including the invention of the first silicon neural electrode by Kensall Wise, professor emeritus of BME and Electrical Engineering and Computer Science.

Today a cluster of innovative, accomplished faculty is driving the field forward, working side-by-side with clinicians in the U-M Medical School to focus on translational applications to improve the lives of patients.

BRAIN-MACHINE INTERFACES AND PROSTHETIC HAND CONTROL

Cynthia Chestek | Assistant Professor | Director, Cortical Neural Prosthetics Laboratory

Chestek’s lab works to restore natural movement to individuals who have lost the use of their hands, whether due to amputation, spinal cord injury or other cause of paralysis. Her work includes improving neural signal control of prosthetics and natural limbs through novel and improved brain-machine interfaces, functional electrical stimulation and assistive exoskeletons.

Toward that goal, Chestek and collaborators are developing new electrodes. She and Professor Euisik Yoon recently demonstrated an eight-micrometer carbon-fiber probe. Research to date has shown that the probes cause significantly less scarring and immune response than conventional larger electrodes.

In a collaborative project with Parag Patil, MD, to develop a system for brain controlled functional electrical stimulation, Chestek and her students apply machine learning algorithms to neural signals recorded by 100-channel implanted arrays. Using Kalman filters and regression techniques, the objective is to understand the relationships between hand movements and their respective neuron firing rates.

In collaboration with Paul Cederna, MD, professor of surgery and chief of plastic surgery, Chestek’s lab has been conducting pre-clinical work on hand control using neural signals. One of the barriers to nerve-controlled prosthetic limbs has been the small signal.

The team’s work found muscle grafted to the ends of split nerves—a procedure Dr. Cederna performs on patients suffering from painful nerve growths following amputation—can amplify neural signals to the point they can control a prosthetic hand.

Chestek joined the BME faculty in 2012 and jokes that she will be here forever. “At U-M, we have a Top 10 engineering school and a Top 10 medical school — I came here for the very strong collaborations and, because of the doctors, I’ll never leave. I collaborate with a surgeon on every project. There’s a fertile group of clinicians here who are deeply invested in this technology and to bringing it to clinical practice.”

NEUROSTIMULATION FOR CHRONIC PAIN

Scott Lempka | Assistant Professor | Neuromodulation Laboratory

For the 25 million Americans and countless others around the globe who suffer from chronic pain, Lempka’s work holds great promise. Research in his lab focuses on neuromodulation for managing chronic pain and, although such techniques have been used for years, only about 50 percent of patients get relief.

In those who do, however, it’s often not enough to make a real impact on their quality of life.

To identify and better understand the specific mechanisms...
by which neurostimulation works, and why it works for some patients and not others, Lempka’s group takes an engineering approach to develop patient-specific computer models. The models are generated from quantitative and qualitative clinical data, obtained from CT, MRI and functional MRI imaging, and how patients respond to different stimulation parameters.

In recently published work, Lempka and colleagues describe a first-in-man clinical trial of deep brain stimulation for post-stroke pain that targets alternate pathways, specifically those related to emotions and behavior, rather than sensation. The areas targeted, the ventral striatum/anterior limb of the internal capsule, have been widely studied and safely used in treatment of obsessive compulsive disorder and refractory depression. Although pain intensity wasn’t significantly reduced in the study, participants’ reports of anxiety and depression related to the pain were.

"This tells us we should consider changing what we consider a success with these neurostimulation therapies. Rather than fixating on pain intensity, we should shift our focus to reducing pain-related suffering or disability,” says Lempka, who joined the BME faculty in January 2017 and is excited about further research. “Working with U-M’s clinical pain research groups and pain management specialists will help us not only better understand how neurostimulation works on pain but also to develop innovative and more effective patient-specific therapies.”


Weiland’s BioElectronic Vision Lab investigates the fundamental mechanisms underlying the ways in which implantable and wearable electronic systems interact with the natural visual system and other senses. He has demonstrated the feasibility of using MRI and fMRI in patients with the retinal prosthesis to better understand how the visual pathways in the brain respond to sight recovery and also how these pathways adapt to process other sensory input, including tactile input, in a phenomenon known as cross-modal activation.

In addition, Weiland and researchers in his lab are studying how these prosthetic systems affect the anatomy and functioning of the visual system over time in order to optimize existing and future devices. His lab is also developing a wearable, smart camera system that can work with the Argus or as a standalone assistive technology for the visually impaired.

Findings from these studies will lead to further refinements to the Argus II to enhance vision restoration. Involving Argus patients in evaluating design changes is a key aspect to his research program.

Weiland earned his MS and PhD degrees in BME and returned to campus to join the BME faculty in January 2017, after holding faculty appointments at Johns Hopkins University and University of Southern California.

"Ann Arbor has always been a second home for me,” Weiland says. "When an opportunity became available to join the BME department, it was difficult to not explore the possibility. The more I visited and talked with faculty and students in BME and Ophthalmology, the more the move made sense. The excellence of the engineering and medical schools was a strong attraction.”
A PIVOTAL PROGRAM HELPS CATAPULT PROMISING BIOMEDICAL TECHNOLOGIES FROM THE LAB TO THE MARKETPLACE

by Aimee Balle

The 1990s saw the rise of a new term that would reshape biomedical engineering and academic medicine in the years to come — “translational” research.

Driven by funders’ desire to bridge a gap between basic research and clinical application, it encouraged biomedical scientists to more directly impact human health by taking their work “bench to bedside.” In doing so, it suggested that the end-game for academics could just as reasonably be a high-impact journal article as a medical product poised for commercialization.

Perhaps no program at U-M played a greater role in institutionalizing this approach within the College of Engineering (CoE) and Medical School than the Coulter Translational Research Partnership Program.

Launching a Program — and a Mindset

The process began in 2005, when then-BME Department Chair Matthew O’Donnell led a successful pitch to the Wallace H. Coulter Foundation for its $5 million Translational Research Partnership Award in Biomedical Engineering.

O’Donnell’s enthusiasm spread quickly among the faculty and was sustained by his successor, Douglas Noll. In its first five-year funding cycle, the U-M Coulter Program supported 19 projects ranging from engineered ACL replacements to optical detection of pancreatic cancer to custom, 3D-printed biodegradable scaffolds for skeletal reconstruction and bone regeneration. The work yielded four start-up companies that garnered $25 million in funding.

But just as importantly, the award provided a mechanism for cooperative work that was reinforced in 2012 when Biomedical Engineering became a joint department of both entities.

ENDOWMENT AND ENHANCED SUPPORT

The program’s success also positioned U-M for an even larger award — $10 million from the Coulter Foundation that was matched by the CoE and Medical School, yielding a $20 million endowment to support translational projects in biomedicine. U-M was one of only six universities nationwide to receive this award.

That was in 2011. Since the endowment, the Coulter Program has funded another 30 projects (see examples) and has ramped up its coaching in an effort to ensure the technologies it supports stand the best chance of making it to market through a license to an established company or start-up.

“The award supported research teams co-led by engineers and clinicians in developing promising health-related technologies that could be translated from the lab to the clinic via the marketplace. It offered individual project grants within a coaching framework designed to help participants think early-on about their technology’s path to commercialization.

“I was personally very excited about Coulter,” says O’Donnell. “It allowed me to marry my two loves, industry and academics. I thought how wonderful, especially for our junior faculty, to be exposed to a world where you don’t just write papers; you put out a device…that people will actually use in the clinic.”

O’Donnell’s enthusiasm spread quickly among the faculty and was sustained by his successor, Douglas Noll. In its first five-year funding cycle, the U-M Coulter Program supported 19 projects ranging from engineered ACL replacements to optical detection of pancreatic cancer to custom, 3D-printed biodegradable scaffolds for skeletal reconstruction and bone regeneration. The work yielded four start-up companies that garnered $25 million in funding.

But just as importantly, the award provided a mechanism for cooperative translational research between the CoE and Medical School — an approach that was reinforced in 2012 when Biomedical Engineering became a joint department of both entities.

This happens even before funding decisions are made. Coulter has recently launched a program for its finalists, called the Coulter College Commercializing Innovation planning program, or C3i. It provides expert analyses of each project’s regulatory and competitive landscape, as well as market research in which target users evaluate the proposed product. The program also leads each team through eight weeks of structured homework guided by industry mentors matched to their project.

The result of this work is a “blueprint report” for each project that systematically examines its potential market; likely challenges; characteristics necessary to be sustainably adopted; as well as the research, intellectual property, and other milestones that must be met to make the product attractive to investors.

“By the time we go through this process, both Coulter and the teams have a clear sense of their project’s commercialization potential,” says Marten. This robust planning also means that the winning teams are able to hit the ground running, using their funds to implement the strategy they developed, and pressure-tested, through C3i.

Of course, all of this is possible because of Coulter’s reach and deep connections. “We have relationships with top industry executives, medical device serial entrepreneurs, regulatory specialists, and venture capitalists — many of whom are on our oversight committee — so we can provide expert mentoring to help faculty reach their hand-off goals.”
The projects funded since the endowment have yielded 7 start-ups, $30 million in outside investment and one license to industry. But Marten believes that with U-M’s talent pool, its culture of collaboration and innovation, and the resources provided by the Coulter Program, Tech Transfer, MICHR and others, there is even more success to come.

**HISTOSONICS**

*Non-Invasive Precision Surgery*

One of the earliest Coulter-supported projects involves histotripsy, a non-invasive surgical technique that uses the mechanical, not thermal, properties of focused ultrasound to precisely destroy target tissue without damaging surrounding structures. Coulter catalyzed a team of academics and businesspeople that launched a start-up around the technology and supported an intellectual property analysis that helped attract venture capital. The company, HistoSonics, has since secured more than $25 million in funding, developed a prototype device, conducted first-in-human clinical trials for enlarged prostates, and is now pursuing additional applications, such as liver cancer.

**SLIT-STENT**

*Lacrimal Drainage Device*

One of Coulter’s more recent projects aims to help patients with excessive tearing. Traditional treatment involves creating and temporarily stenting a new drainage canal. But current stents don’t drain, so symptoms persist until the stent is removed months later. The Coulter program connected U-M oculoplastic surgeon Alon Kahana, MD, with Jeffrey Plott, a PhD student in ME/BME Professor Albert Shih’s lab. Plott solved the problem in a single day by cutting slits at key places in an existing lacrimal stent to create a patentable new “Slit-Stent” concept. The Coulter team, Kahana, and Plott are now collaborating with a leading manufacturer of lacrimal stents to modify one of their existing FDA-approved stents to create the Slit-Stent. The manufacturer has committed to running this product through its FDA-validated pre-clinical testing processes, which is required for an investigational device exemption (IDE) that U-M will file with the FDA. With the IDE in place, Coulter will fund a Slit-Stent clinical trial at U-M in late 2017 to generate the proof-of-concept data needed for a licensing arrangement.

**NEUROMAMEND**

*Surgical Tool to Treat Neuromas*

While working on a way to amplify nerve signals for prosthetic limb control, a U-M team that included BME Assistant Professor Cindy Chestek, PhD, and Plastic Surgery Section Chair and BME Professor Paul Cederna, MD, discovered a technique to treat neuromas. Neuromas are disorganized bundles of nerves that form when a nerve is severed; amputees suffer greatly from them, and they’re notoriously difficult to treat. However, Cederna developed a manual surgical procedure to wrap the severed nerves in a “cap” of harvested muscle tissue to relieve the pain. To make the procedure widely available, he sought a way to make it less time- and skill-intensive. Coulter funded development of a surgical device prototype that automates the procedure and allows surgeons to harvest the muscle, grab the nerve, and slide the muscle over the nerve in as little as five minutes. With support from Coulter, the team was able to demonstrate the functionality of the device in animal studies and secure a licensing agreement with Michigan-based RLS International. RLS will finalize development, and it hopes to file for FDA approval and bring the tool to market within two years.
CONTINUED FROM NEWS NOTES PAGE 3

Others at U-M are developing ultra-small, ultra-precise electrodes, as well as carbon wire electrodes that can sense chemical activity and measure neurotransmitters.

Euisik Yoon is the MINT project lead. Other U-M BME co-investigators include Cynthia Chestek, PhD; James Weiland, PhD; Kensall Wise, PhD; and John Seymour, PhD. Additional collaborators are from the California Institute of Technology and New York University.

To follow the long, winding connections among neurons, a technique called “Brainbow” labels each neuron a random color. This allows researchers to visualize individual neurons and their random color. This allows researchers to visualize individual neurons and their random color. Credit: Dawen Cai, Cai Lab

Probes like this one, which stimulate neurons with light and then record activity with electrodes, are just one facet of the technology suite that can help neuroscientists map circuits in the brain. Photo: Fan Wu, Yoon Lab, University of Michigan

awarded as a five-year, $7.75 million NSF NeuroNex Technology Hub.

The grant aims to encourage researchers around the world to use these technologies as a toolkit to generate new breakthroughs in the structural and functional mapping of the brain, ultimately paving the way to better understand and treat brain diseases.

One example of the tools developed at U-M is a neural probe conceived in the lab of BME and EECS Professor Euisik Yoon, PhD, and made in U-M’s Lurie Nanofabrication Facility. It uses light from micro LEDs to stimulate specific neurons in genetically modified mice and then records the response from other neurons with electrodes.

Another is a technique called “Brainbow,” developed by Dawen Cai, PhD, in cell and developmental biology, in which genetically modified brain cells produce fluorescent tags, labeling each cell a random color. This allows researchers to visualize individual neurons and their connections.

Others at U-M are developing ultra-small, ultra-precise electrodes, as well as carbon wire electrodes that can sense chemical activity and measure neurotransmitters.

Euisik Yoon is the MINT project lead. Other U-M BME co-investigators include Cynthia Chestek, PhD; James Weiland, PhD; Kensall Wise, PhD; and John Seymour, PhD. Additional collaborators are from the California Institute of Technology and New York University.

FAN’S NANOWIRE LASER HAS BME SENSING APPLICATIONS

A nanowire laser developed in the lab of BME Professor Xudong (Sherman) Fan, PhD, has the potential to detect cancer and other abnormal cells by their generally higher-than-normal refractive indices.

The device is a 204-nm diameter, 15-μm long cadmium sulfide wire that acts as an optical cavity. When excited with an external light source, the nanowire lases at a wavelength that depends on the surrounding’s refractive index. Testing the sensor in mixtures of ethanol and toluene, Fan and his colleagues found that changing the relative concentration changed the refractive index. The sensor could identify differences in the index as small as 1.4 × 10⁻³.

Additionally, they found that lasing intensity can serve as a proxy for a liquid’s refractive index. Though offering coarser resolution, intensity measurements wouldn’t require an interferometer to analyze wavelengths.

Fan says the technology could conduct sensing at the scale of individual cells, as cells have been shown to readily internalize nanowires. Full article at aip.scitation.org/doi/10.1063/1.4995456

NOLL & FESSLER TO IMPROVE FMRI

BME Professors Doug Noll, PhD, and Jeffrey Fessler, PhD, are co-PIs on a new NIH R01 grant entitled “Fast Functional MRI with Sparse Sampling and Model-Based Reconstruction.” It will develop new ultrafast imaging methods for functional MRI to improve its robustness and sensitivity as well as broadening the scope of applications.

SHIKANOV WINS PILOT AWARD TO TEST OVARIAN TISSUE CONSTRUCT

BME Assistant Professor Ariella Shikanov, PhD, received a pilot project award from the California National Primate Research Center. It is designed to determine whether an implant her lab has developed that encapsulates donor ovarian tissue in an immunoisolating hydrogel can restore ovarian endocrine function and puberty in adolescent nonhuman primates with premature ovarian insufficiency (POI). Shikanov is interested in the longevity of graft function along with the dynamics of the recipient’s immune response to single and repeat transplantation. She hopes this research will be a stepping stone to restoring endocrine function in young women with POI.

MILDRED F. DENECKE SCHOLARSHIP FUND

The department gratefully announces the creation of the Mildred F. Denecke Scholarship Fund. The fund was endowed with a gift from Mildred F. Denecke (BSE Phys ’49) to provide need-based support for BME students focused on the design program. Denecke is an exceptionally loyal alumna who has been a longtime supporter of the Michigan Engineering Fund and the Class of 1949E Scholarship Fund in the CoE in addition to numerous other units and programs across the U-M campus.
This summer Girgis explored the fundamental mechanisms by which microRNAs regulate cells. He worked in the lab of Andrew Grimson at Cornell University as part of a National Science Foundation internship.

**BURNS’ SUMMER NEUROSURGERY INTERNSHIP**

Courtney Burns (BSE BME ’19) completed the Ramnath Student Fellowship, an intensive month-long shadowing internship in the Michigan Medicine Department of Neurosurgery. Burns observed in the operating room, attended departmental research presentations, and gained experience identifying clinical needs. She and co-fellow Kristen Raue created a video documentary of the experience, which can be requested by emailing <cjburns@umich.edu>, subject: Ramnath Fellowship Documentary Viewing.

**BMES WITH SWE IN INDIA**

Four U-M BME students – Melissa Cadena, Brooke Huisman, Aparna Sarkar, and Betsy Strehl – were part of a 10-member delegation of Society of Women Engineers (SWE) traveling to Walchandnagar, India, this May. The group organized an engineering outreach camp, working with over 80 high school students on design-build-test challenges. They also met with local teachers to learn more about Indian culture and share information about American universities. Following the camp, SWE members traveled, met with U-M alumni, and volunteered with Teach for India. A blog chronicling their trip is at <swe.engin.umich.edu/blog>.

**OSTROWSKI EXPLORES CONCEPT-GENERATION IN DESIGN**

Anastasia Ostrowski (BSE BME ’16, MSE BME ’17) conducted her thesis research on a topic especially relevant to BME’s design sequence: how to facilitate concept-generation in design. Using student interviews and design-class observations, Ostrowski explored how students think about idea generation, how instructors discuss the concept, and how students approach the task. Her research offers strategies to enhance this phase of the design process before students’ “inner critics” engage. Ostrowski’s thesis advisors included engineering education experts Aileen Huang-Saad from BME and Shanna Daly from ME.

---

Ashish Kamath (BSE BME ’19) works in the lab of Daniel Leventhal, MD, PhD, assistant professor of neurology and BME, investigating the firing patterns of neurons in the motor thalamus. On a project led by neuroscience PhD student Matt Gaidica, Kamath helped identify how this brain region is engaged in different actions of a motor task. They are currently working toward controlling the electrical excitability of specific groups of neurons in the motor thalamus using optogenetics. Their goal is to show how activity from other areas of the brain integrates within the motor thalamus to produce movement. Kamath’s work will be featured during a poster session at the 2017 Society for Neuroscience annual meeting in Washington, DC.

**GIRGIS WINS AACR AWARD, NSF INTERNSHIP**

Alexander Girgis (BSE BME ’18) won the third place Gary J. Miller Prize for undergraduate research at the American Association for Cancer Research conference this spring for research on how signaling interactions between pancreatic cancer cells and the immune system may stimulate metastasis. This work was done in the lab of Timothy Frankel in the U-M Department of Surgery.

At the Golden Temple in Amritsar, India.