BIOMEDICAL ENGINEERING
UNIVERSITY OF MICHIGAN

Spring / Summer 2015

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Targeted Utrasound

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Photo: Brandon Baier

Message from the Chair

Lonnie Shea. Photo: Joseph Xu.

I've been spending a lot of time lately appreciating the value of being in the right place at the right time – and reflecting on what this could mean for translational research on campus.

In particular, the timing of my arrival as BME Chair last year couldn't have been better, with the department a formal entity of both the College of Engineering and the medical school, and our physician colleagues eager to collaborate and truly embracing what we as biomedical engineers have to offer.

Some of this, I think, represents the growing awareness of what our field has become. Once viewed as largely a purveyor of imaging and devices, BME is now being recognized for the role it also plays in areas like immune modulation, cell therapies, and drug delivery.

Perhaps nowhere is the potential greater for our current scope to impact medicine's future than in regenerative and restorative medicine.

This sense crystallized for me at a recent medical school retreat. Dean Woolliscroft asked his chairs to talk briefly about the developments most likely to shape their specialties – and 17 of the 22 in attendance said regenerative medicine.

Since then I've become the de facto head of a group exploring how we can harness expertise across BME, medicine, dentistry, pharmacy and related fields to create a world-class effort in this area at U-M.

Certainly the fit is a natural for me; this is my own area of research. It's also a fit for BME – it encompasses nearly everything we do. However, the truth is, without the structural and cultural changes that gave BME a seat at the medical school's table, this effort might not be taking shape as quickly or with such a broad, multidisciplinary and translational vision.

That's because its basis is the very synergy between medicine and engineering. This is what makes U-M an ideal place for this work. U-M is among the only places in the country with top rankings in the relevant medical and engineering departments. It is also uniquely strong in both regenerative medicine – growing cells, tissues and organs lost to disease or trauma – and restorative medicine – restoring function that has declined with age. Our research is broad and deep in realms both basic and translational.

Our group is discussing how to build bridges across groups and centers with individual specialties that, when combined, could supercharge efforts now underway, such as restoring sight or hearing; rebuilding damaged heart tissue; or reversing lost neurological function from spinal cord injury or diseases like Parkinson's, Alzheimer's and multiple sclerosis.

One idea we're exploring is a matchmaking board that could pair clinicians facing an intractable problem with those developing technologies with the potential to solve it. Another is developing a pipeline of enabling technologies that could guide promising new therapies along the pathway from bench to clinical trial. For example, we might have a group with an early-stage cell-based therapy that they want to take to the next level. We envision a hub that offers biomaterials expertise to help these cells survive a transplant; drug-delivery systems to stimulate their differentiation, growth, and function; small and large animal models for testing; and immunotherapy resources to prevent host rejection or control inflammation. And this would all be in the context of supportive cores in pathology/histology, imaging, systems biology, technology transfer, and so on.

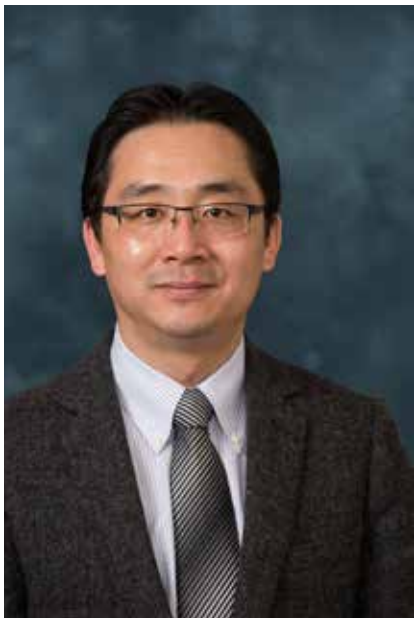
It's a grand vision, but one that U-M is uniquely positioned to realize. In many ways, it's similar in concept to the multidisciplinary approach taken by our cancer center. This center has made enormous advances by bringing to bear the best imaging, pharmaceuticals, surgery, and prevention education to improve patient outcomes. We envision a similar model for regenerative and restorative medicine. With the talent and momentum in place at U-M, I believe it's eminently within our reach.

Sincerely,

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

New BME Faculty: Xueding Wang

PHOTOACOUSTIC IMAGING



Xueding Wang

Associate Professor **Xueding Wang**, PhD, has transitioned his primary appointment to BME after 10 years in the Department of Radiology. His group is one of the world leaders in photoacoustic imaging, which applies laser pulses to target tissues then processes the resulting ultrasound waves to provide both chemical and histological information on the tissue.

This cutting-edge technique allows deep-tissue imaging with the high sensitivity of optical methods and high spatial resolution of ultrasound. It produces a 2D map of tissues that Wang calls a physiochemical spectrogram. "One dimension is the optical wavelength; the other is the ultrasound frequency," he says. "By using a tunable laser with different optical wavelengths, we can quantify a tissue's chemical components – such as its lipid, collagen, water, or blood content. The ultrasound dimension tells you how each component is distributed. Every tissue has a unique 2D signature, which can be used for very accurate tissue characterization or disease diagnosis."

Wang views photoacoustic imaging as a platform technology that can be used alongside traditional ultrasound imaging for a variety of applications. He and his team are now working with the U-M Office of Technology Transfer on an international patent.

One potential application is cancer diagnosis. By harnessing the technology's ability to probe cancer biomarkers like the blood content and oxygenation of tissue, Wang and his collaborators are testing a photoacoustic imaging system for breast cancer. He sees additional diagnostic potential in fatty liver disease and liver fibrosis by quantifying the size and distribution of fat clusters and collagen fibers in the organ. He's also been imaging inflammatory arthritis – even attaching gold nanoparticles to anti-rheumatic drugs to visualize their uptake by inflamed joint tissues.

Wang hopes his transition to BME will help take his work even further. As a joint department, BME can give him the same access to patients for clinical research that he had in radiology, as well as a pool of talented engineering students for his lab. Wang says he's excited to teach BME courses and to mentor incoming medical-track BME faculty in areas from the structure of U-M's health system to the medical school tenure process.

CELLULAR BIOTECHNOLOGY TRAINING PROGRAM
UNIVERSITY OF MICHIGAN

BME TAKES THE REINS IN DEVELOPING FUTURE BIOTECH LEADERS

by Aimee Balfe

If you're seeking a who's who of biotech education, a great place to start is the roughly 20 U.S. universities that are home to an NIH Biotechnology Training Program. Funded by the National Institute of General Medical Sciences (NIGMS), the program aims to develop a cadre of highly trained biotechnology PhDs prepared to make tomorrow's breakthroughs in molecular genetics, cell culture technologies, drug development, biomaterials, microbiology, tissue engineering and related areas.

U-M's program, the Cellular Biotechnology Training Program (CBTP), got its start in the late 1980s and has been shepherded all these years by faculty from the Department of Microbiology & Immunology. Until last summer, that is, when the reins were turned over to BME Associate Professor **Andy Putnam**, PhD.

Putnam, whose research explores how the physical and chemical properties of the extracellular matrix affect tissue development, was a CBTP trainee himself in the late 1990s.

The program has been tweaked a bit since he was first associated with it – it now incorporates an industry internship and offers a Rackham certificate, for example – but its key activities are just as relevant now as they were then. They include a core biotechnology course, monthly student dinner meetings, mentoring lunches with industry leaders, and an annual symposium.

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Zhen Xu's Histotripsy Lab: On Track for Translation

by Aimee Balfe

By now regular readers of this magazine are familiar with histotripsy, the groundbreaking therapy developed at U-M BME that uses high-intensity ultrasound pulses to treat soft-tissue conditions quickly, painlessly, non-invasively, and with unprecedented precision. It does this through cavitation, creating microbubbles that disrupt cell structures and break unwanted soft tissue into an acellular slurry that is readily eliminated from the body. Through spinoff company HistoSonics, a device is now in clinical trials for histotripsy's first human application -- treating benign prostatic hyperplasia. But its developers think this is just the start.

Zhen Xu. Photo: Joseph Xu.

One of them is BME Assistant Professor **Zhen Xu**, PhD, who was in on the ground floor of histotripsy's development. She's now built a flourishing lab dedicated to not only clarifying its underlying mechanisms but extending its range of applications – some of which are closing in on clinical trials themselves.

And she's not just reaching for low-lying fruit either. She's going where the need is great and where angels fear to tread.

TREATING NEWBORNS WITH CONGENITAL HEART DISEASE

The idea of using a new technology on any human is daunting. Planning to use it on fragile newborns might make anyone flinch – but not Xu.

She was working on histotripsy as a graduate student when the development team was approached by pediatric cardiologist Achi Ludomirsky, MD, who wondered whether the procedure could be used on newborns with hypoplastic left heart syndrome (HLHS). Though a relatively rare condition, it's one that is fatal without treatment. Xu's advisor and histotripsy co-developer Charles Cain, PhD, challenged Xu to see what she could do.

"He told me to 'figure out how to punch a hole in a heart non-invasively,'" she says.

This challenge actually represents the first stage in treating babies born with HLHS. The left side of their heart is underdeveloped, compromising their ability to pump oxygen-rich blood to the rest of their body. But having a perforation between the heart's two upper chambers, or atria, creates a flow channel so the right side of the heart can temporarily pump for both sides. This buys the infants time to become strong enough for heart reconstruction surgery.

Fast forward just under 15 years, and Xu has met this challenge – and more.

Though compelling from a technical standpoint, the project's real lure for Xu was that current treatments are harsh and often unsuccessful. "They involve threading a catheter into a blood vessel all the way to the baby's heart, then inflating a balloon that pushes a knife through the heart wall and atrial septum," she says. "It's quite violent, and there's high morbidity and mortality associated with the procedure in these very sick babies."

She hoped that the precise, noninvasive procedure they were developing could help these children. In fact, despite the obvious challenge of targeting a tiny structure in a critical organ in a fragile patient, the procedure was a good candidate for histotripsy because of its acoustic path.

"You can place an ultrasound imaging probe on a baby's belly, just under the ribcage, and see the atrial septum very nicely," says Xu. "So we felt we could use our therapy probe to create a perforation, perhaps in just a few minutes."

After a series of promising tissue and animal studies, Xu, Cain and current pediatric cardiology collaborator Gabe Owens,

PhD, MD, set their sights on translation. This would involve developing an appropriate clinical histotripsy system, and gathering feasibility and safety data to present to the Food and Drug Administration (FDA).

For the latter, Xu's team turned first to piglets. But pigs are not a perfect model. As four-legged animals, their hearts are oriented differently than ours, and the acoustic path to the atrial septum is obstructed by ribs and lung. Ultrasound not only has difficulty propagating through air in the lungs, but the lungs' smallest air pockets actually seed the cavitation process, creating unwanted treatment zones.

> "[The FDA's] feedback was great. They said… we're well on our way to submitting the application for our first clinical trial."

The clearer path is to the piglets' lower heart chambers and the ventricular septum. It is still a more challenging path than in humans, but even so Xu's team found they could create a perforation in the ventricular septum despite some rib and lung obstruction within 20 minutes and, just as importantly, with no apparent side effects.

One side effect they were checking for was whether the fractionated tissue might get into the bloodstream and create blockages in the vessels of the brain. However, because tissue treated with histotripsy is so thoroughly broken down, histology and imaging studies showed that no such blockages occurred. After recovering and monitoring the piglets for a month, her team found no other adverse effects, either.

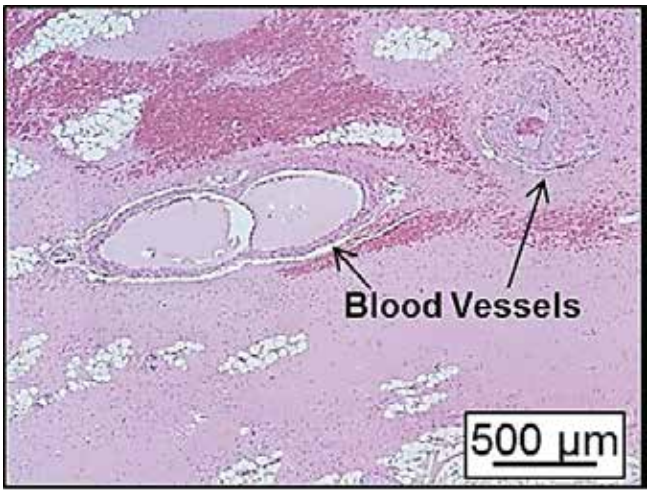
The lab's next model was a higher-fidelity one. Using ultrasound and CT imaging data for newborns, Xu and her team 3D printed a human baby torso. By filling it with a 3D-printed rib cage, foam lungs and piglet heart tissue, they created an anatomically correct system for testing their targeting accuracy.

This model was also critical to helping them design their clinical system. The other essential piece, of course, was funding. Because HLHS affects so few newborns – an estimated 2 to 3 per 10,000 live births in the U.S. – it's an orphan disease. This means its target population is too small to warrant investment by large funders like the National Institutes of Health. But the team was able to secure funding from The Hartwell Foundation and combine it with cost sharing by the university, the College of Engineering, and the pediatrics department to drive the project forward.

With development and regulatory support from HistoSonics and hard work by BME PhD students-turned-project-engineers Ryan Miller and Kuang-Wei Lin, they were able to produce a sleek mobile unit that integrates imaging, therapy and high-precision positioning functions on a single cart. It is based on HistoSonics' VortxRX system and can be wheeled easily between rooms for treatment.

With all this in place, Xu's team met with the FDA in January, presenting their data along with videos of their system in action to learn what the FDA still wanted to see. "Their feedback was great," says Xu, "They said our supporting data is strong and we're well on our way to submitting the application for our first clinical trial."

There are things the team wants to do next, such as testing their new system on piglets' atrial septums, which involve more critical structures than the ventricular septums, and doing further studies on their 3D baby models. But their progress thus far, says Xu, really validates the technology. "There is a much higher standard for treatment safety and efficacy with this application," she says. "So if we can do this successfully, it shows that histotripsy is a genuine platform technology."



Histology shows histotripsy selectively preserve the vessels while completely fractionating the porcine liver tissue surrounding it.

MOVING TO FETUSES

As if work on fragile newborns weren't harrowing enough, it is actually a stepping stone to a more daring target – fetuses. "Ultimately our aim is to be able to create a perforation in the ventricular septum of these babies in utero to improve blood flow to that underdeveloped left ventricle," she says. "Our hope is that blood flow may act as a stimulant for the development of this chamber."

This would require her team to be able to make millimeter or even submillimeter perforations in the fetal heart – inside the mother's belly with all kinds of tissues in between. Though it

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These general activities are open to anyone interested in participating in them; but the program throws its full support behind six new trainees a year, and each student can receive funding for up to two years. The result is a vibrant little U-M cellular biotech network, with 12 active trainees and as many as 25 to 30 program alumni on campus at any given time. There's also a larger network of nearly 150 former trainees, many of whom are now leaders in industry and academia and in a position to connect the current crop of students and graduates with internships and jobs.

There is also a backbone of some 60 faculty supporters, including 19 from BME, who guide students' research and participate in CBTP events.

While each aspect of the program has its benefits, a critical overarching one is the exposure to colleagues from complementary disciplines. "The CBTP was one of the forerunners on this campus for multidisciplinary science," says Putnam. "It's all the rage now, but this program was doing it 25 years ago." The CBTP spans 10 different departments, so trainees routinely have opportunities for cross-fertilization.

In particular, the monthly dinner meetings allow students to share their research with a supportive multidisciplinary audience of peers. They can troubleshoot technical problems, share tips on securing internships, and gain insight into how their research might be viewed and impacted by others' specialties.

Putnam saw the value of this as a trainee himself. "As a graduate student doing PhD research, you can be pretty isolated," he says. "Your lab colleagues probably have a similar skill set and knowledge base, so it's important to broaden that. I remember as a student having trouble with some molecular biology techniques; I shared my troubleshooting efforts at one of our trainee meetings, and by the end I had invitations to visit three or four labs to learn their approaches. The program really helps participants access the diversity of this vast U-M campus."

Even more important than sharing specific techniques, he says, is the opportunity to view your research through another lens and see its broader potential. "Right now we have a student studying the molecular processes the body uses to correct DNA errors that arise during cell division," says Putnam. "If you wanted to use this knowledge to one day develop a therapy to correct error-prone DNA replication – say, in tumor cells – you'd need to test it. The molecular biologists or biological chemists working on the enzymes of DNA repair might be focused on the molecular mechanisms at play, but the person next to them who's working on 3D tissue models of tumor growth and invasion may have an ideal system to test a potential therapeutic. Still another person might be developing a relevant cancer drug, and across the room could be a chemist who is working on a conjugate that can target that drug to tumor cells." The potential synergies are endless.

Longer term, these interactions prepare students to work more effectively in the biotech industry. "Students are exposed to people from different disciplines from the minute they start this program until the minute they graduate, and that's important preparation for what industry is going to be like," says Putnam. "I know from my own experience in process development, I didn't spend my time talking with other engineers – we all knew the same things. The people we had questions for were the biologists, chemists, people in manufacturing, and people designing clinical trials. You need to be capable of communicating with a diverse audience in biotech, and the CBTP prepares you for that."

Putnam sees value in the program's other offerings, as well. The core course exposes students to the fundamental science of biotechnology, its key players, case studies, and commercialization issues from intellectual property to market potential to regulatory affairs. The monthly mentoring lunches connect students with visiting professionals who share insights on what it takes to get a job and succeed in industry. And the annual symposium gives students a chance to showcase their research progress.

But the internship piece is, for Putnam, what sets this training program apart. In his role as Associate Chair for Graduate Education, he's seen firsthand how hungry BME graduate students are for industry experience. It's even more essential, he says, for bioscience PhDs who are graduating faster than academia can absorb them. Because this program is deliberate about requiring such experience and has the cachet and network to open doors to not only regional biotech companies but also the significant number concentrated on the coasts, CBTP trainees have a track record of securing strong, enriching internships.

However Putnam feels there is potential to deepen the program's connection to industry – and that's ultimately what motivated him to take the helm. It's a classic win-win, he says. In the short term, students gain insight and seasoning through their exposure to industry projects and professionals. In turn, companies gain access to talent with deeper skills and experience than they get with traditional undergraduate interns. But the more sweeping benefit is that opening the lines of communication produces graduates with the qualities that biotech companies truly want in their people.

"As we develop a workforce that is better and better suited for their needs," says Putnam. "I think industry will look to the CBTP even more than it already does as a go-to source for highly skilled people. That's my goal for this program."

The U-M Cellular Biotechnology Training Program is funded by the NIGMS with additional support from the College of Engineering, Medical School, Office of the Vice President for Research, and Rackham Graduate School.

Master's in Medical Product Development

by Aimee Balfe

Last winter, BME introduced a new concentration in medical product development to its master's-level line-up to ensure that students interested in bringing their skills directly to the medical device industry are prepared to hit the ground running.

Led by Professor **Jan Stegemann**, PhD, who heads the Cell-Matrix Interactions and Tissue Engineering laboratory and has prior industry experience himself, the new concentration was developed in direct response to what industry wants and students need.

"Biomedical engineers have always brought to product development a focus on anatomy and physiology, as well as a broad view of how medical devices can solve clinical problems," says Stegemann. "But we also want to be sure they have deep design skills – and an understanding of what it takes to get a medical device to market. This includes the regulatory environment, intellectual property, reimbursement, clinician and public adoption, even the impact of the Affordable Care Act."

The new concentration comes on the heels of a substantial expansion of the undergraduate design sequence and allows master's students to continue on this track, but go broader and deeper. In both cases, students operate in a simulated incubator environment, solving problems for real clients with faculty guidance and professional mentorship.

"Just like in our undergraduate design program, the core course for the concentration is a design-build-test experience," says Stegemann. "But now it's their second time through the process with a completely new product. Students have learned from the mistakes they made the first time around and can go a lot further – beyond just design to development – with a big focus on regulation and quality."

This is because students take the core, year-long graduate innovative design

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CALLING BME ALUMNI

Share Your Industry Insights

To keep this concentration relevant to the changing health care and regulatory landscape, we need industry partners. Support can be as simple as giving tours of your company or a talk to a class in your area of expertise – or as in-depth as sponsoring a project or providing internships or job shadowing opportunities. Whether you are in the local medical device industry or across the globe, we welcome your involvement. Every act of support helps this program shape the next generation of leaders in medical device development. Please email **Jan Stegemann** at jpsteg@umich.edu to learn more.

REQUIREMENTS OF THE MPD CONCENTRATION

In addition to foundational BME graduate courses in life sciences, bioinstrumentation, math, statistics, ethics and enterprise, the medical product development concentration features a year-long design course in a simulated incubator environment, along with at least two technical electives that enrich this design experience in areas like clinical needs identification, quality systems, regulation, and commercialization. The concentration's currently approved courses are listed below; these offerings are being expanded as new courses are developed.

Core Course (two semesters)

- Graduate Innovative Design | Stegemann

Technical Electives (pick two, one semester each)

- Clinical Observation & Needs Finding | Schmedlen
- Global Quality Systems & Regulatory Innovation | Alfano/Greve
- Regulatory Issues in Medical Device Design | Hollister
- Technology, Innovation, Law & Regulation | Alfano/Wang
- Commercialization of Biomedicine | Gordon
- Business of Biology | Canter
- Cellular Biotechnology | Putnam
- Introduction to Innovation Careers | Crumm/Fay

BME News

"CANCER MAGNET" COLLABORATION FEATURED IN MODERN HEALTHCARE

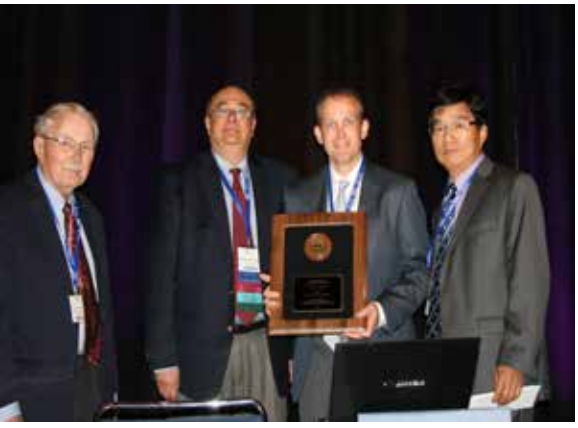
BME's William and Valerie Hall Chair and Professor **Lonnie Shea**, PhD, and his wife, Jacqueline Jeruss, MD, PhD, associate professor of surgical oncology at the U-M Medical School, were featured in an article in Modern Healthcare on collaborations between engineers and doctors. The feature focuses on their development of a "cancer magnet," a device implanted under the skin to determine if cancer cells return following surgery or chemotherapy. U-M's joint Department of Biomedical Engineering was created in 2012 to link the College of Engineering and Medical School to foster just this kind of collaboration.

Read the full article at the *Modern Healthcare* website:

http://tinyurl.com/ofjumns

SHEA WINS 2015 CLEMSON AWARD

Lonnie Shea won the 2015 Clemson Award for Contributions to the Literature presented by the Society For Biomaterials. Shea has published more than 168 papers in peer-reviewed journals and 11 book chapters in the biomaterials and tissue engineering fields.



Lonnie Shea accepts the 2015 Clemson Award.

THREE BME FACULTY INDUCTED INTO AIMBE

BME Professors **Cheri Deng**, **David Sept**, and **Shuichi Takayama** were inducted into the College of Fellows of the American Institute for Medical and Biological Engineering (AIMBE). Fellows are peer-nominated and represent the top two percent of the medical and biological engineering community. They were recognized for outstanding contributions in the following areas: Deng – ultrasound imaging and therapy development; Sept – biomolecular computational simulation; and Takayama – micro- and nanofluidic technology.

FAN JOINS LAB ON A CHIP EDITORIAL BOARD

BME Professor **Xudong "Sherman" Fan** was elected to the editorial board of the Royal Society of Chemistry's journal, Lab on a Chip. A paper from his lab titled Optofluidic Lasers With a Single Molecular Layer of Gain was featured on the cover of the publication in 2014. "The paper titled, Optofluidic lasers with a single molecular layer of gain, was authored by Qiushu Chen, Michael Ritt, Sivaraj Sivaramakrishnan, Yuze Sun, and Xudong Fan."

HUGGINS CO-EDITS JOURNAL SUPPLEMENT ON BCI

Jane Huggins, a BME research scientist, co-edited the March 2015 supplement of the Archives of Physical Medicine and Rehabilitation. The issue documents clinical and translational developments in brain-computer interface (BCI) research from the fifth international BCI meeting.

BME STUDENT STARTUP "PUFFBARRY" WINS FUNDING

BME BSE graduates **Allison Powell** and **Kyle Bettinger** co-founded a startup called "PuffBarry" to develop an alternative communication device for people with ALS, multiple sclerosis, and muscular dystrophy who have lost the ability to speak. Born out of their BME 458 team project, the PuffBarry device uses puffs of air as code that a computer can interpret and translate into speech. Powell and Bettinger took their idea to the U-M Center for Entrepreneurship competition "The StartUp" and came away with $3,000 in seed funding plus the grand prize of $15,000. They also won the $1,000 TedXUofM prize.

Allison Powell and Kyle Bettinger accept their TEDxUofM prize.

M-HEAL GUATEMALA 2015 SANA TRIP

Michigan Health Engineered for All Lives (M-HEAL) is the U-M student organization that brings biomedical engineering to global health work. The organization launched its first spring break trip to Antigua, Guatemala, through its Service Abroad and Needs Assessment (SANA) Program. Student teams conducted health outreach in schools and community centers, performing health awareness skits and distributing antiparasitic medication, vitamins, and dental supplies. They also shadowed and interviewed a local doctor and medical specialist who were working in these settings to document the health-care challenges in local communities. The key issues they identified were upper

M-HEAL Guatemala team.

respiratory infections, anemia, hygiene education, and a lack of diagnostic equipment.

A new Guatemala Project Team has formed from this trip, composed of six undergraduates and two graduate students. They've developed needs statements, which they're now prioritizing and researching so that they can develop design concepts in the fall. M-HEAL plans to make the SANA spring break trip an annual volunteer and learning opportunity.

STUDENT SUPPORTS SAFER HELMETS

BME master's student **Scott Haber** is working with two physicians who are developing helmets that aim to reduce the incidence of traumatic brain injuries in contact sports and military applications. As a project manager and research coordinator with FIRST Contact, Haber is helping to raise funds and develop additional research/product testing connections at U-M for Steven Kalkanis, MD, chair of the Department of Neurosurgery at Henry Ford Hospital, and physiatrist Stephen Hyman, MD. Hyman has developed a patented carbon-fiber helmet insert that is custom-fit to wearers' heads to dissipate the forces of impact and protect the brain. The group is currently testing and further refining this design.

LAI WINS DISSERTATION AWARD

David Lai, a recent PhD graduate of **Shuichi Takayama**'s lab, received a ProQuest Distinguished Dissertation Award from the Rackham Graduate School for exceptional scholarly work by U-M students completing their dissertations in 2014.

DAY & NOVAK WIN NSF FELLOWSHIPS

James Day, a BME PhD student in **Ariella Shikanov**'s lab, and Caymen Novak, a BME master's student in Geeta Mehta's lab, won 2014 NSF Fellowships as part of the Graduate Research Fellowship Program.

MUCKLEY WINS RACKHAM PREDOCTORAL FELLOWSHIP

Matthew Muckley, a PhD candidate co-advised by **Jeffrey Fessler** and **Douglas Noll** in the Functional MRI Lab, won a Rackham Predoctoral Fellowship. Muckley is using his expertise in signal processing to develop sparse models that would remove physiological noise from functional MRI scans, making them powerful tools for diagnosing neurological disorders.

Brian Syverud and Ryan Thomas. Photo: Brandon Baier

STUDENTS WIN PHI KAPPA PHI GRANT

BME graduate student **Brian Syverud** and BME undergraduate **Ryan Thomas** each won a Phi Kappa Phi project grant to extend learning beyond the classroom. Each will receive $5000 to pursue their passions. Phi Kappa Phi is the nation's oldest, largest and most selective all-discipline honor society.

COE LEADERS & HONORS AWARD RECIPIENTS

BME had nine outstanding students receive awards as part of the 2015 College of Engineering Leaders & Honors Awards. **Natalie Setterberg**, **Paras Patel**, **Ana Rioja**, and **Karen Schroeder** received Distinguished Leadership Awards. **Marika Grabowski** won the Distinguished Achievement Award; **Ryan Thomas**, the A.D. Moore Award; and **Hannah Cheriyan**, the Mildred and Steele Bailey Prize. Richard F. and Eleanor A. Towner Prizes went to **Sahar Rahmani** for distinguished academic achievement and to **Eli Vlaisavljevich** for outstanding PhD research.

Monica Rondeau. Photo: Joseph Xu.

NEW STAFF

Monica Rondeau joined BME as a purchasing clerk. She is providing administrative support for purchasing and reimbursements for several BME faculty and staff. Before coming to BME, Monica worked for the Michigan Molecular Genetics Laboratory at UMHS as an administrative coordinator/project coordinator.

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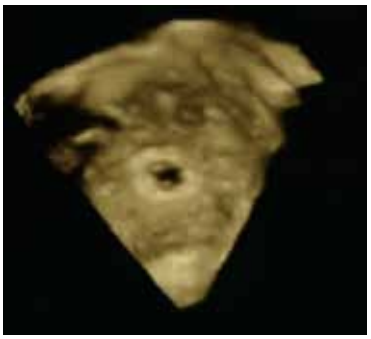
sounds implausible, Xu's group has already done it in fetal sheep, which she says are even more difficult to work on than humans. "Sheep develop early, and they have hooves and multiple fetuses," she says. "Even so, we've had nice results."

Their hope is that as they prove the technology in human newborns, they will be well-positioned to expand it to fetuses, which could be a game-changer for this devastating disease.

BATTLING BLOOD CLOTS

Xu's lab is collaborating with cardiologist Hitinder Gurm, MBBS, to advance another histotripsy application for which they are now seeking industry partners. With support from an NIH R01 grant and the Focused Ultrasound Foundation, they've shown that histotripsy can be used for thrombolysis, the destruction of blood clots. Their bench work showed that by scanning along the clot, they could destroy one as large as 2 cm in length and 4 mm in diameter within 5 minutes. And their work on pig models of deep-vein thrombosis (DVT) suggests that histotripsy is currently more effective and orders of magnitude faster than other clot-busting treatments, without the side effects.



3D ultrasound image of a perforation generated through the ventricular septum of the piglet heart 2 days using histotripsy after the treatment.

Reducing side effects would be a real win. Systemic drugs take hours or even days to work, and they break up clots indiscriminately, creating the potential for bleeding. Catheter-based procedures are invasive and carry risks like infection.

Xu hopes ultimately to make the procedure even more effective by using her recent R01 renewal to advance two innovations – microtripsy and bubble-induced color Doppler feedback.

Microtripsy, as its name implies, generates very small cavitation. As such, it can be confined within the lumen of a blood vessel, preventing collateral damage to the vessel walls.

Bubble-induced color Doppler feedback would allow doctors to see their clot-busting progress in real time. "Cavitation bubbles induce different motions in a clot that is intact vs. one that is partially fractionated vs. one that is completely destroyed," says Xu. "We can see that motion with color Doppler ultrasound and are using it as an indicator of treatment progress."

They are working on a clinical system that incorporates these features so that they can test it in their pig models of DVT. However, Xu is quick to point out that the treatment would be appropriate for a range of thrombolysis applications, from heart attack to stroke.

A 'SMART' TREATMENT FOR LIVER CANCER

To say current treatments for liver cancer are not ideal is an understatement. Liver transplants are curative but hard to come by. Surgery is available only to patients with a very small number of very small lesions that have not metastasized. Thermal techniques like radiofrequency ablation, which uses an electrode to destroy lesions by heating them, are also only appropriate for a small percentage of patients. Plus, the liver is a highly vascular organ and blood flow carries heat away from the locus of treatment, so temperature-based techniques are not uniformly effective.

To offer liver-cancer patients another option, Xu is collaborating with liver surgeon Theodore Welling, MD. With support from the American Cancer society, they're exploring whether histotripsy can treat this disease more effectively in more patients.

A major challenge until recently has been that the access window to the liver is impeded by significant overlying tissue, including ribs, which absorb ultrasound energy. However, thanks to recent improvements to the therapy device, Xu was able to demonstrate in pig models that they could treat the liver very precisely without overheating the intervening tissue.

She also found that they could treat a large volume of liver containing blood vessels of various sizes and that larger vessels remained intact. "This makes histotripsy a smart, self-limiting, vessel-sparing ablation technique," says Xu. It can destroy lesions, tumors' weak and leaky vasculature, as well as smaller vessels, while protecting the normal, larger ones that are essential to liver function and whose destruction could cause excessive bleeding.

While delightful, the findings were not a complete surprise because Xu's lab has done extensive work on how histotripsy affects tissues of varying mechanical properties.

Her lab's next steps are to analyze imaging data from liver-cancer patients to identify the acoustic path and optimal transducer design. They'll then 3D print not only a human model but also a prototype transducer to continue their testing.

"We are excited about this progress," says Xu. "We feel confident that we're right on track to translate this technology."

Xu received the 2015 Frederic Lizzi Early-Career Award from the International Society of Therapeutic Ultrasound. It is given annually to an early-stage researcher who's made a significant contribution to this field.

CONTINUED FROM MPD MASTERS PAGE 7

class, which Stegemann teaches, in conjunction with semester-long technical electives (see sidebar, right) that expand and enrich what's being covered in the design class. For example, students in Rachael Schmedlen's Clinical Observation and Needs Finding class identify clinical needs and issues that can be addressed through a design project. Likewise, those in Professor Scott Hollister's Regulatory Issues in Medical Device Design class are able to drill down into the regulations relevant to the very project they're working on in Stegemann's class. This allows course content to dovetail seamlessly and come to life through direct application in the design project.

To ensure students have the richest, most relevant medical product development experience possible, design faculty are reaching out to alumni and industry partners to share their insights (see box below). The BME design program has been supported by gifts from local medical device companies, including Terumo Cardiovascular Systems and MC3 Cardiopulmonary, Inc.

In addition, they've just received NIH funding to support activities like prototyping and fabrication; project-continuation grants; a medical technology roadtrip/site tour; and specialized training in design controls, regulatory affairs, communication and teamwork.

They will also develop a clinical needs identification pipeline, where a group of students from Schmedlen's class will continue with a summer project packaging key needs and observations into a resource that student design teams can use to define future projects.

The end result, says Stegemann, is students with industry-ready skills, who can step into a variety of product-development positions, start contributing immediately, and advance readily up the career ladder. "Students with the kind of experience this concentration offers are golden," he says. "Quality is key to medical device manufacturers, and these students will understand how to engineer quality."

WHERE ARE THEY HEADED?

Jake Heller (BSE) graduates with a biochemical concentration along with a minor in community action and social change as well as the international minor for engineers. He has accepted a job with the Engineering Leadership Program at National Instruments in Austin, Texas, where he plans to pursue technical marketing or sales.

Elizabeth Hyde (master's/SGUS*) will attend medical school this fall at either Stanford University, University of Michigan, or Dartmouth, where she plans to focus on health care in low-resource areas.

Andrew Lynch (master's/SGUS*) is working this summer with M-STEM Academies, a program of the Colleges of Engineering and Literature, Science & the Arts that provides support and coaching for U-M freshman and sophomores entering science, technology, engineering and math fields. In August Andrew will join the Jesuit Volunteer Corps in Syracuse, NY, as a health coordinator/community advocate for AIDS Community Resources, Inc.

Anjali Saripalli (master's/SGUS*) will pursue a medical degree at U-M Medical School this fall.

Samantha Spierling (master's/SGUS*) graduates with a biotechnology concentration. She will begin a PhD program this fall in chemical and biological sciences at The Scripps Research Institute in La Jolla, California.

Samantha Stephenson (master's/SGUS*) starts a job this fall with Accenture Consulting. Samantha has worked in Professor Joseph Bull's Biotransport Lab for the last two and a half years. She was also on the U-M Equestrian Team and qualified for nationals.

Brandon Bruhn (PhD) leaves Professor **Michael Mayer**'s Biomembrane Lab to pursue a career in industry with a biotechnology start-up called Berkeley Lights. He will be working as a single cell genomics field applications engineer at Mt. Sinai Hospital in New York City.

Rahul Singh (PhD) was advised by BME Professor **Andrew Putnam**. For his thesis, he developed an approach to measuring forces generated by developing capillaries. Rahul is joining Baxter Healthcare in its medical products R&D division.

*Sequential Graduate/Undergraduate Study (SGUS) is a five-year program that combines undergraduate study in an engineering field with a master's degree in biomedical engineering.

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