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A PROGRAM SPARKS RESEARCH ON WOMEN'S
HEALTH | BY ALLA KATSNELSON

FELLOWS

The first time Steven Abramowitch met with Pamela Moalli in her office at Magee-Womens Research Institute, he was a little embarrassed by all the talk of vaginas. It just wasn't a topic he was used to discussing in a professional setting.

Then a graduate student in biomechanical engineering, Abramowitch was less than a year away from defending his PhD thesis about another body part—the knee and the injuries it sustains in elite sports. His work was moving along well, and he had a bit of time to spare, so he had volunteered to also work with Moalli, an MD/PhD associate professor of obstetrics, gynecology, and reproductive sciences at the University of Pittsburgh, who had recently sought out a collaboration with his supervisor, Savio Woo, founder and director of Pitt's Musculoskeletal Research Center and a PhD, DSc, DEng Distinguished University Professor of Bioengineering. Moalli studies pelvic organ prolapse, a disorder in which the muscles charged with keeping the bladder, uterus, vagina, and other organs in place begin to droop, which can lead to a protruding vaginal wall.



Melissa McNeil

Junior faculty at Pitt come together to probe the sorely understudied field of women's health. A National Institutes of Health program supports their efforts.

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She wanted Abramowitch to do some preliminary cell and animal studies on how hormone levels affect these pelvic floor muscles; this would help them understand the structural mechanics of the problem. But the more Abramowitch asked about the underlying biology of the condition—which affects perhaps 35 percent of women older than 40, often in connection with childbirth, hysterectomy, or menopause—the more it stunned him that the answer to most of his questions was, “Nobody knows, exactly.”

The same basic parameters of functional anatomy were so well understood in the knee, he realized, that he took the existence of such information for granted. It wasn't until a month or two later, however, that the importance of Moalli's work really struck him. While shadowing her in the clinic one day, he watched her examine a woman in her 40s. As soon as Moalli asked the patient to apply some pressure to her abdomen, Abramowitch could see the insides slouch out of her vagina as a sharp stream of urine shot out, almost hitting Moalli in the face. A moment later, the woman's despair came tumbling out, as well.

Her condition made her feel terribly disconnected from her family, she reported, sobbing: She couldn't be intimate with her husband. She couldn't pick up her three young children to give them hugs or play with them



Pamela Moalli (left) and Steven Abramowitch

he ran across a call for applicants for the BIRCWH fellowship program.

BIRCWH, which stands for Building Interdisciplinary Research Careers in Women's Health, was designed by the National Institutes of Health to attract young investigators from diverse disciplines and encourage them to bring their talents to any topic at all related to women's health.

Pitt received its first institutional BIRCWH

forefront of priorities in biomedical research, says Melissa McNeil (MD '80, Res '83, MPH '93), a professor of medicine who is program director for Pitt's BIRCWH program and also heads Pitt's Comprehensive Women's Health Program and its women's health fellowship.

“Where there's funding, people will go,” she says. “I firmly believe that the program has expanded the profile of investigators seeking to answer questions in the area of women's health,

“So many research questions were only being addressed in the 70-kilogram man.”

the way they wanted to play. Her children would ask why she was pushing them away, but she was too embarrassed to explain, and she felt they were too young to understand.

“That was 2004,” says Abramowitch. “I still get emotional thinking about that woman more than a decade later.” The scene sent a lightning bolt through Abramowitch's career plans. Here was a biomechanical problem that was prevalent and could have devastating effects on those who experienced it, yet it was understudied.

When Moalli was awarded the grant that he had helped her submit, Abramowitch convinced his department to take him on as a research assistant professor; he planned to jointly pursue his old and his new interests. But he felt constantly short on time, money, and lab support for his urogynecological research; and after a couple of years, the prospect of steering his work in that direction began to seem tenuous. Luckily, that's when

grant in 2002 and has awarded fellowships to 18 junior scholars so far. The program, underwritten by a training grant called a K12, funds 75 percent of fellows' total work time, allowing them the freedom to pursue their chosen research projects; just as importantly, fellows receive intense and coordinated mentorship on every possible challenge an early career investigator might face, from designing experiments to achieving work-life balance.

Says Abramowitch, the award “came at a perfect time for me, and I definitely credit it with the ability to transition my research successfully.” Today, he is an associate professor of bioengineering, as well as of obstetrics, gynecology, and reproductive sciences; his lab still collaborates closely with Moalli's, and he now serves as a mentor in the BIRCWH program himself.

The influx of talent BIRCWH fellows have brought to the table has been a huge boon to a field that has not traditionally been at the

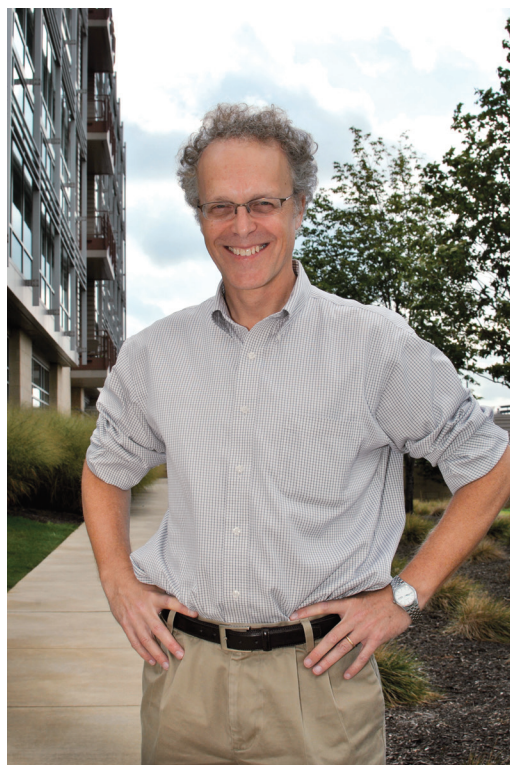
not only by attracting people with a long-standing interest in the topic, but also by encouraging investigators from other fields to think about how their research could be adapted to it.”

The last two decades of the 20th century were a time of awakening for women's health on a national scale. After an eternity of systematic exclusion of women from clinical trials and an approach to health research that ignored biological differences between women and men, health officials began to admit that this outlook was leading to health disparities in women.

“So many research questions were only being addressed in the 70-kilogram man,” says McNeil.

NIH guidelines adopted in 1986 urged the inclusion of women in clinical research; yet for years, little seemed to change in practice. On the plus side, this prompted the establishment of the Office of Research on Women's Health (ORWH) in 1990, but even a 1993 congressional mandate to include women in NIH-funded

Yoel Sadovsky (below), Bryan Brown, and Heather McCauley



clinical studies did little to nudge the status quo. Multiple government reviews repeatedly deemed that clinical studies still weren't analyzing the role of sex differences on the efficacy of therapies. In an effort to build up research on women's health that was poised for translation into clinical practice, ORWH started the BIRCWH program in 1999. Meanwhile, Magee-Womens Hospital established the Magee-Womens Research Institute in 1990. By the mid-1990s, MWRI had expanded to 25 basic scientists and 15 clinical, behavioral, and epidemiological researchers, who collectively held more than \$18 million of NIH funding. The MWRI's first director, James Roberts, an MD, brought in the BIRCWH grant in 2002. When the grant came up for renewal three years ago, Yoel Sadovsky, Roberts' successor as director, took the reins. (Sadovsky is also the Elsie Hilliard Hillman Professor of Women's and Infants' Health Research and a professor of obstetrics, gynecology, and reproductive sciences, as well as of microbiology and molecular genetics.)

Pitt's current crop of four fellows hails from bioengineering, public health, pharmaceutical, and ob/gyn backgrounds. Boosting the program's diversity by recruiting applicants from basic research and translational fields has taken considerable effort, says Sadovsky, and it is one of the program's major strengths.

"I think it provides a level of education and training that far exceeds what they would individually acquire," he says. One component of that is simply having the much-needed protected time—and money—to develop research projects. At its core, the program serves as a kind of bridge funding until fellows can amass enough data to secure a major funding source for their work. But beyond financial support, BIRCWH's value lies in an extensive web of mentoring. Each fellow selects up to four mentors. Every couple of months, Sadovsky corrals all the fellows and mentors at a venue where two of the fellows present their work and receive feedback from the whole crew.

Overall, the level of involvement and support from senior faculty that BIRCWH provides is almost unheard of for young researchers today, says Harvey Borovetz, a PhD professor of bioengineering and a BIRCWH mentor.

"I just can't say enough about it and the opportunities it offers for young people to grow professionally," he says.

Borovetz's mentee Bryan Brown, a research assistant professor in the same department, agrees. "[Borovetz] serves on tenure committees, he's been the department chair, so he knows how things work," Brown says.

Moalli piqued Brown's interest in applying his research to women's health much like she had Abramowitch's—by reaching out to suggest a collaboration. That was back in 2011, when Brown—who had done his PhD at Pitt on immune responses to surgically implanted biomaterials—returned to Pittsburgh to start his own lab after a postdoc at Cornell.

Moalli's team was studying why a widely

used treatment for pelvic organ prolapse—inserting plastic mesh into women's vaginas—turned out to be so fraught with serious side effects. (To date, some 70,000 women have filed lawsuits against mesh manufacturers.) She wanted Brown to examine the basic biological properties of the host response to the material, and he was happy to comply.

"It gave me an opportunity to expand into a direction in which few researchers are working presently, and it helped bring some funding and independence to my research program," Brown says. Shortly thereafter, Abramowitch pointed him toward the BIRCWH application; and when Brown received the award the following year, Moalli and Abramowitch joined Brown's mentorship crew.

That research thread has remained a major focus of Brown's work. His lab now examines whether the host response to an implanted material like mesh is different in young individuals compared to older ones; and indeed, Brown's animal studies suggest a strong distinction. "If you think about the types of surgical implants that are out there—for hernias, pelvic organ prolapse, hip implants—those are used in aging populations," he says. And yet nobody had explored the question in older animals. Although his research on biomaterials has always had clinical applications, aligning his work so closely with Moalli's feedback has helped him home in on design problems he would not have previously considered, Brown says. For example, his lab is



Francesca Facco and Haitao Yang



also working on an immunomodulatory collagen coating that could smother the body's damaging inflammatory response against vaginal mesh; after discussions with Moalli, he is considering what might encourage or discourage physicians from embracing such a product. No matter how well it works in new iterations that Brown's lab might develop, coating mesh with collagen will probably yield hesitation, because in the past that approach didn't work, Moalli advised him. "The first thing clinicians are going to think is that collagen mesh from five years ago made things worse," he says.

Another fellow, Heather McCauley, an ScD assistant professor of pediatrics and a social epidemiologist, focuses on the interpersonal dimensions of women's health. Her BIRCWH-funded project, which she began last year, explores support systems for young women in foster care—particularly mentorship by adult role models who aren't their parents. The hope, McCauley says, is to identify ways that "this relationship could be strengthened and bolstered to impact pregnancy risk among this particularly vulnerable group of women."

At a group presentation of her work a few months ago, in which McCauley described the experiences of some of the women she recruited into her study, McNeil asked McCauley about the young women *without* mentors—that is, the ones likely to be the most vulnerable. After mulling it over, McCauley applied for an internal grant to expand her research to include their experiences. "It helped me to identify the holes in the project and expand its intellectual scope," she says.

Along with the guidance she receives here

at Pitt, McCauley says she appreciates the access she and her fellow scholars receive to a kind of national networking superhighway of BIRCWH scholars. Even before she became a fellow, her mentor Elizabeth Miller began introducing her to researchers associated with the program. (Miller is an MD/PhD professor of pediatrics and chief of the Division of Adolescent Medicine at the University and at Children's Hospital of Pittsburgh of UPMC; she's also a former BIRCWH fellow.)

Each month, McNeil brings all Pitt BIRCWH fellows together at a little Middle Eastern lunch spot near campus, where they've gotten to know the owners. At a recent gathering over hummus and gyros, McNeil kicked off the conversation by checking in with one fellow who has a new baby and another whose spouse lives in another state. That's always how it starts, says McCauley—with the personal.

Then the conversation moves on to topics of recent BIRCWH group presentations, with McNeil providing feedback and guiding each fellow in strategizing what to do next. "Dr. McNeil finds a way to connect each one of us to one another—using the struggles or successes of one BIRCWH scholar as an example to help another BIRCWH scholar," says McCauley.

"What's been the most wonderful to see," says McNeil, "is, despite the field of origin, despite the gender of our scholars, despite differences in research interests, the program seems to generate a camaraderie and a peer

support system that is really unique. That's been true of each and every iteration of scholars."

And Pitt's BIRCWH fellows are starting to see their hard work pay off.

Francesca Facco, an assistant professor of obstetrics, gynecology, and reproductive sciences recently stepped down from the program when she was awarded an R01, the holy grail of NIH project grants for a young investigator. Facco came to Pitt in 2013 with a plan to build research into her clinical career; she examines how sleep disorders might affect maternal and fetal health.

Facco turned to her mentors for help primarily with questions of study design, ethics protocols, budgets, and other elements of assembling a grant. With her new grant, she recently began a study examining whether treating mild forms of sleep apnea in pregnant women improves the outcomes of their pregnancies.

Catherine Chappell, an assistant professor of obstetrics, gynecology, and reproductive sciences, was just made a BIRCWH fellow. Chappell will investigate hepatitis C virus treatment during pregnancy. Chappell is (like Facco was) the only one of the four BIRCWH fellows with an MD.

Brown isn't quite at the BIRCWH finish line yet, but he's coming close.

"Now I feel like we're approaching the point where I can submit grants as a principal investigator, or submit coinvestigator grants with Dr. Moalli," he says.

"I came into the fellowship as a research assistant professor, and now I'm moving into a tenure-track position, which is a great step for me."

Haitao Yang is a PhD assistant professor of pharmaceutical sciences in the School of Pharmacy whose BIRCWH project involves using nanoparticle technology to develop drug delivery systems for HIV prevention. He says, "Speaking with the other fellows, I learn a lot of things I would never think about."

Yang and Brown have lit upon a prospect for a joint project using Yang's drug delivery techniques to target macrophages, inflammatory cells that Brown studies. Yang says it's just one of the ways that the program has opened up his research horizons:

"These things that other fellows are studying—like sleeping problems in pregnant women—I never really thought about them as health problems before." ■