LAUNCH PAD

LSI alumni are landing stellar positions in academia and industry

Sumit Bandekar, graduate student in medicinal chemistry

Photo: Lelsa Thompson Photography; Rocket design: KaBlackout / Etsy

No one graduates from the University of Michigan with a diploma that says "Life Sciences Institute," yet students from science departments across campus leave with a lifelong connection to the institute.

"One month into my rotation at the LSI, I knew 'this is it,' " says Alisa Glukhova (Ph.D. '14), who went from the lab of faculty member John Tesmer, Ph.D., to a postdoctoral fellowship at Monash University just outside of Melbourne, Australia.

Earlier this year she was the lead author of a study in *Cell* that used X-ray crystallography to shed light on the binding selectivity of an important adenosine receptor subtype — a G-protein coupled receptor that plays a key role in cardiovascular disease, but which scientists have had a hard time targeting pharmacologically.

Solving the structure opens new avenues for designing subtype-specific drugs.

"We found that it's actually conformational differences, as opposed to any particular amino-acid residues, that are important for drug selectivity between the subtypes," says Glukhova, a graduate of the U-M Program in Chemical Biology, which is directed by LSI faculty member Anna Mapp, Ph.D. "There are four types of adenosine receptors. Others are involved in cancer and immunity. So, we're also interested in continuing to solve more of these structures."

At any given time roughly 100 graduate students and undergrads are working in LSI labs, not to mention some 40 postdoctoral fellows preparing to launch independent careers.

Over the 14 years that the LSI has been around, alumni have gone on to coveted positions in both academia and industry: Baylor, Purdue, Case Western, University of Washington, University of Michigan, MIT, Peking University, the Mayo Clinic, Genentech, AbbVie — to name just a handful.

"Our goal is to train not just the next generation of scientists, but the next generation of scientific leaders," says LSI Director Roger D. Cone, Ph.D.

BOLDLY GOING

Omer Yilmaz (M.D., Ph.D. '08), a pathologist and cancer researcher in Boston who did his doctoral research under former LSI faculty member Sean Morrison, Ph.D., says he misses the institute's open-lab architecture and fondly recalls its collegial, collaborative spirit.

"My time at the LSI really launched my career," says Yilmaz, now an assistant professor of biology at the Koch Institute for Integrative Cancer Research at the Massachusetts Institute of Technology, an associate member of the Broad Institute and a clinician at Massachusetts General Hospital. "My scientific success is directly related to the very rigorous training that I received at the LSI and at Michigan. It's a world-class institution."

As a high school student, Yilmaz frequently accompanied his father, an internist, on hospital rounds in Battle Creek, Michigan, before morning classes started. This passion for science and medicine propelled him to U-M, where he completed his undergraduate, medical and doctoral degrees. Three of those years were spent in Morrison's lab at the LSI studying the stem cells that renew the blood system and the stem-like cells that give rise to blood cancers.

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After Michigan, Yilmaz pursued a pathology residency at Mass General, followed by postdoctoral research with David Sabatini, M.D., Ph.D., at the MIT-affiliated Whitehead Institute.

"In the Sabatini lab I became really fascinated with this question about how diet and organismal physiology impact adult stem cell function and cancer development, particularly in the intestine," Yilmaz says.

And this is precisely what his research at MIT now focuses on. A recent animal-model study, published in *Nature*, found that a high-fat diet can spur a population boom

among intestinal stem cells as well as stem-like cells that can reproduce themselves indefinitely, giving rise to intestinal tumors.

Yilmaz's research employs organoids — balls of miniature, stem cell-derived tissue — that more closely resemble their real-world counterparts than traditional two-dimensional cell cultures.

"So not only do we put preclinical mouse models on different diets, we can also interrogate how different nutrients alter the biology of these intestinal organoid assays," says Yilmaz.

Last year, Yilmaz was named a Pew-Stewart Scholar for Cancer Research — one of 37 "scientists who could change the world," according to the news release announcing the 2016 class.

"I was lucky to have such great mentors," says Yilmaz. "With Dr. Morrison, I really learned how to think like a scientist, how to set up really careful experiments and never to take for granted any piece of data."

Mentorship was also a highlight for Amélie Bernard, Ph.D., who now leads a research group within the Laboratoire de Biogenèse Membranaire at the University of Bordeaux in France. Bernard came to the United States in 2012 to be a postdoc in the lab of LSI faculty member Daniel Klionsky, Ph.D., drawn by his international stature in the field of autophagy — a vital recycling process within cells.

"Dr. Klionsky was a fantastic mentor," says Bernard, who last year landed a rare plant biologist opening with France's Centre National de la Recherche Scientifique, the country's largest governmental research organization. "He brought me into a number of collaborative projects and made it clear he'd do whatever he could to help me accomplish my career goals."

While the autophagy research at the LSI is conducted in yeast and focuses on human health and disease, Bernard studies autophagy in plants.

"Plants can't move, so they really need to have tightly regulated adaptation mechanisms to survive," she says. "Autophagy is critical for plants undergoing multiple stresses, like nutrient starvation and water deprivation. It's especially important in the context of global warming, which is causing increased drought and shortages of cultivatable land."

Former LSI postoc Omer Yilmaz, Ph.D., right, now leads a lab at the Koch Institute for Integrative Cancer Research at MIT.

Season Ji, Courtesy of Bostonese.com

IT'S NOT THE DARK SIDE

A number of LSI alums have also struck out beyond the walls of academia. Kristoff Homan, Ph.D., a postdoc at the LSI from 2010 to 2014, now works as a senior scientist in the Global Protein Sciences division of Global Biologics at AbbVie.

Matthew Smith (Ph.D. '12), is vice president of operations and strategy for Pear Therapeutics, a Boston-based company that recently received clearance from the Food and Drug Administration to market the first ever mobile medical application to treat substance use disorders.

"In making the leap from academia to industry, there are transferable skills that, while valuable, can be difficult to quantify," Smith says. "But your doctoral work provides extensive training on how to think through complex problems and develop a strategy to solve them."

Meanwhile, Leah Makley (Ph.D. '14) co-founded a biother-

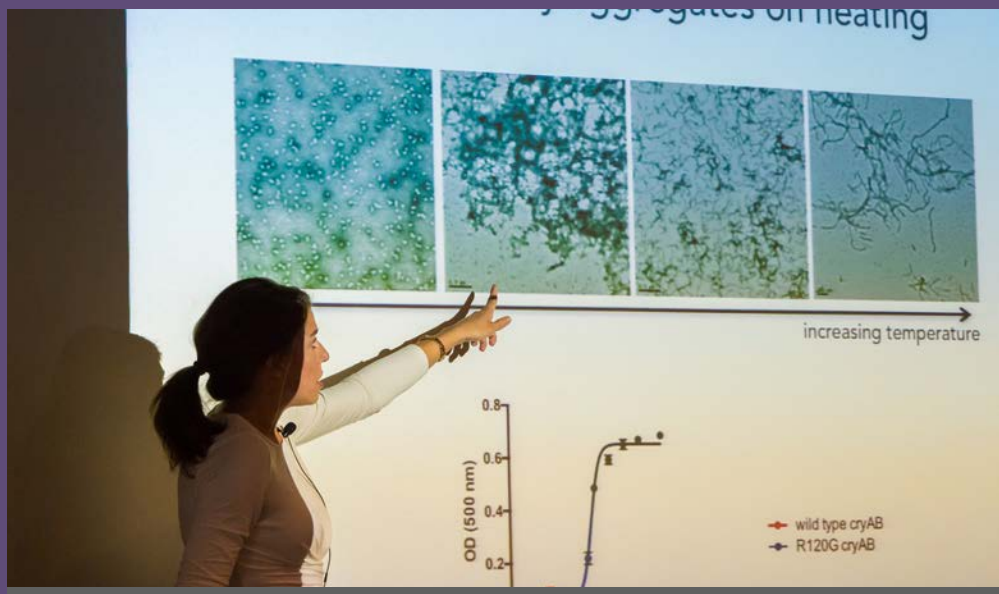
apeutics startup in San Francisco with former LSI faculty member Jason Gestwicki, Ph.D., to develop and commercialize a treatment for cataracts based on discoveries they made at U-M. The goal is eventually to market eye drops to treat human patients and potentially pets. It's hoped clinical trials might start within 18 months, she says.

Makley met Gestwicki during her initial campus interview for the College of Pharmacy's medicinal chemistry graduate program and was intrigued by the research underway in his lab at the LSI. It helped convince her that Michigan was where she needed to be.

"In many ways, the company we founded, ViewPoint Therapeutics, is a product of the cross-disciplinary synergy built into the LSI model," she says.

A high-throughput screen at the LSI's Center for Chemical Genomics on the third floor identified several anti-cataract "hits" of interest. The Gestwicki lab was among the chemistry labs clustered on the fourth floor. And Makley learned how to use electron microscopy through collaboration with faculty member Daniel Southworth's lab on the sixth floor in order to characterize the activity of the compounds identified in the screen.

"The lens of the eye is a very finely tuned system that requires the proteins to stay stable, properly folded and well organized over decades," Makley notes. "We developed a screening strategy to identify compounds that could prevent the protein aggregation that causes cataracts. We began by studying genetic mutations that are associated with cataract phenotypes, and looking for molecules that corrected their stability so they looked like a normal, healthy, properly folded protein."



Leah Makley, Ph.D., presents the Leroy B. Townsend Lecture at the U-M College of Pharmacy in 2016.

Unexpectedly, the group found they could not only prevent aggregation, but also reverse clumping that had already occurred.

"I remember Dr. Gestwicki suggested an experiment in which we would first allow the protein to aggregate in a test tube and then add in the compound to see what happened," Makley recalls. "And I remember thinking that was a really dumb idea, because I wasn't expecting the aggregation to be reversible — but to our surprise it worked. And we repeated it and it kept working."

The research team and their collaborators went on to further refine and test these cholesterol-like molecules *in vitro*, in animal models, and on lenses from human patients who had undergone cataract surgery.

Last summer, Makley was invited back to U-M to give the annual Leroy B. Townsend Lecture, sharing her experiences founding the company.

"Now that I'm at a small startup where resources are a lot more scarce, I appreciate everything that was available at the LSI even more," Makley adds.

David Thal (Ph.D. '11), who is also doing high-impact postdoctoral research at Monash, says he too has many fond memories of the LSI. "You don't really realize it when you're there," he says, "but the setup at the LSI is pretty special and not something that's that common elsewhere."

Daryl Marshke, Michigan Photography