An Idea Sticks

A Lillie Award team gains traction on how cells move

"It was a naïve idea that became very refined in the MBL Physiology course, because of the different 'brains' in there!" says Clare Waterman of the National Institutes of Health.

Waterman was co-directing the course in 2012 when the right constellation of students and faculty aligned to freshly approach a critical question: How do cells migrate in the body in a specific direction?

Answering this is important to many branches of medicine and drug discovery, from cancer and immunology to tissue repair.

Waterman and a few intrigued collaborators tested her idea of visualizing the mechanics of cell migration using fluorescence polarization microscopy, but it didn't quite work. "We didn't have a lot of experience in thinking about polarization, and we didn't set the experiment up correctly," she says.

They learned a lot about how to do it right, though, and she kept the idea in mind. When the University of Chicago and the MBL announced the Frank R. Lillie Research Innovation Awards to support novel, collaborative investigations at the MBL, Waterman knew she had a great opportunity.

"There is no better place to do this research than here. It's perfect," says Waterman. Selected for an inaugural Lillie Award, she and her collaborators tackled the problem anew at the MBL last summer. They already have exciting results, and will be back next summer to complete the work.

Getting a grip

Waterman, who has been studying how cells migrate for many years, is a distinguished investigator at the National Heart, Lung, and Blood Institute. It's an area known as "adhesion biology," because cells must adhere to a surface in order to gain traction, exert force, and then move.

One of the students in Waterman's 2012 Physiology course was Pontus Nordenfelt from Timothy Springer's lab at Harvard Medical School. Springer is an immunologist known for his co-discovery of the integrins—a family of very dynamic cell adhesion proteins—and for describing their crystal structure. ("If this guy doesn't win a Nobel Prize, there is something wrong with the world," Waterman says.)

The integrins are transmembrane proteins—part of them lies inside the cell, and part lies outside. Springer had partially figured out how the integrins are activated to attach the cell to its external environment.

"Springer showed that the integrins change shape when they are activated," Waterman says. "At first they're curled up, like an arm. When activated, they unfurl. It's like the arm stretches out so the hand, at the tip, can grab onto the extracellular matrix and adhere."

But what prompts the integrins to unfurl? Springer and Waterman thought it might be the pull of dynamic filaments inside the cell (the actin cytoskeleton), which bind to the integrins.

"A sea anchor is an analogy," says Springer, who spent his first summer at the MBL this year as part of Waterman's Lillie Award team. "When a boat is attached to an anchor at its bow, and the wind is blowing on it, the force of the wind will align the boat so the bow is facing toward the anchor and the stern is facing away. It is exactly the same way, we think, with the integrins. The integrins (the boats) get aligned by the forces (the actin cytoskeleton) acting on them."

"Clare had the idea that we could get at this question using fluorescence polarization microscopy. I was quite excited by that," says Springer.

Polarization microscopy, a specialty at the MBL (see sidebar), allows one to see how the molecules are aligned in a cellular structure, for instance in a cluster of integrins.

Waterman brought MBL microscopists Tomomi Tani and Rudolf Oldenbourg into her Lillie Award collaboration, as well as Satyajit Mayor, director of the National Center for Biological Sciences, Bangalore, who was part of her Physiology course faculty team.

Their results are very encouraging. "We've found that, no doubt, the integrins are aligned," says Springer. "We can tell that by the fluorescence. It's really quite remarkable. I think this is the first time that anybody has shown that a molecule on the cell surface (the integrin) gets oriented by something inside the cell, or anything else."

"I think this is going to be an important contribution to adhesion cell biology," Waterman says.

Integrin drugs in the clinic

There could be medical benefit, as well. Springer is active in drug discovery based on integrin biology; he has co-founded three drug companies and is in the process of starting a fourth. Two drugs currently in clinical use to treat patients—one for multiple sclerosis and one for ulcerative colitis—were developed from Springer's basic research.

It's too early to tell whether the Lillie Award research results will have an application in drug discovery, Springer says. "But the integrins are certainly very important drug targets, and the more we know about them, the more insight it gives us to develop new drugs and use existing drugs more effectively."

Springer looks forward to returning to Woods Hole next summer. "It was awesome being at MBL," he says. "I love going there for the ability to meet people I don't normally meet at Harvard. And there are a lot of very good physicists and microscopists at MBL that I enjoy hanging out with. It is really a gem of an institution." • —DK

The MBL is the perfect place to conduct this research, says Clare Waterman (right) with (from left) Tomomi Tani, Shinya Inoué, and Rudolf Oldenbourg of the MBL's Cellular Dynamics Program.

REVEALING THE CELL WITH POLARIZED LIGHT

"The only microscope in the world that can answer our question well is at the MBL," Clare Waterman says. She is referring to the TIRF PolScope built by Associate Scientist Tomomi Tani, which is part of a lineage of groundbreaking, polarized light microscopes invented at the MBL.

"TIRF is a fluorescence technology that allows you to see molecules right on the surface of cells, which is where the integrins are," Waterman says. "By adding polarization, Tomomi's microscope also tells you whether those surface molecules are aligned or not."

Other highlights of invention and discovery with polarized light at the MBL include:

1951 In Lillie Auditorium, Shinya Inoué shows spectacular, polarized-light movies of dividing cells that reveal parallel fibers ("the spindle") pulling on the chromosomes as the cells split. Previously, the reality of those fibers and their role in cell division had been seriously doubted. Using his hand-built microscopes, Inoué continued to push the power of polarized light to reveal the inner workings of cells over the next six decades as an MBL Distinguished Scientist.

Mid-1990s Senior Scientist Rudolf Oldenbourg and colleagues invent the LC-PolScope, now widely used in clinical and research settings around the world. In fertility clinics, it is used to assess the health of human eggs by observing their spindles.