# Wendell A. Lim

Wendell Lim didn't even know he was a "synthetic biologist" until he got an invitation to the first international meeting, "SB 1.0." That was four years ago. At the time, synthetic biology could just as easily have been called Grand Theft Cellular, at least as Lim practiced it. In 2003, Lim hot-wired two normally separate mitogen-activated protein kinase (MAPK) signaling pathways in budding yeast. This sent the input from a mating pheromone peeling rubber down the output pathway that set off the high osmolarity response. Lim was studying scaffold proteins, which serve as switchboards for many cell signaling networks. Working with postdoc Sang-Hyun Park, Lim created a "diverter" scaffold protein in yeast mutants that cross-wired the two pathways. It tethered an MAPK protein that normally reported pheromone mating signals to a parallel MAPK pathway that turned on the cell's osmotic response to dangerous solution levels. In effect, Lim's reengineered yeast mutants picked up a mating signal and broke out in a solute sweat.

The experiment was unorthodox but revealing. Lim showed that although scaffold proteins are required for normal signal processing, they can also serve in mutant yeast as alternative tethering frames. The proteins knot together broken pathways into new networks. To Lim, this phenomenon looked much like a natural mechanism that could power evolution at a molecular level. "You don't have to evolve a complicated machinery to link pathways," explains Lim.

Lim is a professor in the Department of Cellular and Molecular Pharmacology at the University of California, San Francisco. He's also one of 56 new HHMI Investigators named by the Howard Hughes Medical Institute last June.

Lim continues, "It's not that hard to rewire [a scaffold protein junction]. You may not get a kick-ass pathway, but you could get a completely new behavior that wouldn't be that hard to create just by changing a scaffold protein. Once a pathway is useful, it's used." Once a new behavior offers an organism some advantage, the behavior increases the organism's chances for survival.

Lim believes that cell systems rely on modules, the biological equivalent of electronic components. One way to understand how "natural" systems work is to take these components apart, rearranging, rewiring, and soldering them into "nonnatural" circuits. It's a way of "letting the organism tell you what's important in order to be able to perform a certain function," Lim says.


George Nikitin/AP, (c)HHMI

Wendell A. Lim with his 12-foot-tall Pipetman.

## Engineering Self-Organizing Systems

Engineering self-organizing systems is the basis of synthetic biology, as Lim has defined it. "Whether synthetic biology represents a truly new field is open to debate, but the boldness of the stated goals—to learn how to precisely and reliably engineer and build self-organizing systems that both recapitulate biological function and show new functions—is unquestionably novel."

Recapitulation of living systems such as cell signaling networks is a powerful use for synthetic biology today. But it's the future of nonnatural biology that draws public attention. Lim talks about assembling microbial biofactories that could turn out drugs, fuels, and biomaterials, or building biobots, synthetically reprogrammed cells that could home in on tumors or deliver drugs on target. Cells could be redesigned to oversee tissue repair or regeneration. The ultimate synthetic biomachine would be a living computer.

Bruce Mayer collaborates with Lim on signal transduction involving the Wiskott–Aldrich syndrome protein. That protein is central to actin polymerization in cell motility. Their work so far has not involved synthetic biology, but Mayer recognizes its "gee whiz" appeal. At the same time he believes that the label misses the point about Lim's science.

Mayer, who is at the University of Connecticut Health Center, explains, "A lot of us have the sense that it's cool to make nature do things that we want it to do. But Wendell takes that coolness and actually answers interesting questions with it," says Mayer. "When you read one of his papers, you don't just say, 'Gee, how great that he can make these bizarre molecules that never existed.' Instead, you say, 'Man, this really shows how systems could evolve.' Wendell has a way of getting profound answers out of these experiments in

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a way that the rest of us would never think of doing."

## Great Expectations

Lim's approach to science was highly original from the start, according to the Massachusetts Institute of Technology's (MIT) Bob Sauer, who was his doctoral advisor. "There are a lot of papers in all fields where people are doing more or less the same experiments using different systems. Wendell's papers have always stood out for taking different approaches and coming at problems from a different angle," he says. "I had incredibly high expectations of Wendell when he left the lab, and he's lived up to all of them," Sauer declares.

**The ultimate synthetic biomachine would be a living computer.**

Lim was born in 1965 in Philadelphia, where his parents, both medical doctors who immigrated to the U.S. from the Philippines, were in graduate and residency programs. "Our families are from southern China, but my grandparents immigrated to the Philippines," Lim explains. The family eventually settled in Chicago, where his parents joined the faculty of the University of Chicago Medical School.

Lim entered nursery school at the famed University of Chicago Laboratory Schools (UCLS). He stayed at UCLS straight through "U-High." Lim then went to Harvard and received his bachelor's degree in chemistry in 1986. He received his doctorate from MIT in biochemistry and biophysics in 1991. He worked under Sauer on protein folding by using classical bacterial genetics approaches.

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For his postdoc, Lim joined the Yale laboratory of Frederic Richards, "one of the early fathers of structural biology," according to Lim. In the Richards lab, Lim's fascination with the complex geometry of cells intensified. However, he found that even a crystallized molecule that had been completely "solved" raised additional questions. "It made me wonder, why is it this way? Why isn't it some other way? I really wanted to take it apart and change it to see how it works and see if it would work another way," Lim recalls.

## Ambitious in a Good Way

In 1996, Lim was hired by University of California, San Francisco (UCSF). He set up a lab to explore how cells process signals and deal with multiple inputs. Faculty member Henry Bourne was not directly involved in Lim's hiring but remembers their first meeting.

"My impression was that Wendell was enormously energetic, very smart, and ferociously ambitious—but in a good way. He wasn't ruthless. He just really wanted to do something important and worthwhile."

Bourne served on a three-member advisory committee to help the new faculty member write his first grant application. Lim's first draft bowled them over, Bourne recalls. "Wendell's [outline] was tremendously ambitious, with lots of questions that he was going to ask and answer. The outline was quite clear. It just had vastly too much in it." The advisors suggested that the National Institutes of Health would be more likely to fund something a little less sweeping. But Lim was perplexed. There was nothing here that he couldn't solve in a year or two years at most, he told them. Bourne and colleagues talked him down.

"We won in the sense that he made it appear a little less ambitious, but he actually didn't do a thing about his real goals." Bourne laughs at the memory. "In fact, Wendell did exactly what he'd told us he was going to do."

He has done much since. Lim climbed the tenure track to full professor at UCSF in seven years. Besides the new HHMI award, he is codirector of the UCSF Center for Systems Biology, deputy director of the National Science Foundation-funded Synthetic Biology Engineering Research Center, and director of an NIH "Roadmap" Nanomedicine Development Center (known as the "Cell Propulsion Laboratory" in homage to the Jet Propulsion Laboratory of space-age fame).

## Coach Lim Takes Over

Last year, Lim took over as coach of UCSF's team in the International Genetically Engineered Machine (iGEM) undergraduate competition. Because UCSF has no undergraduate students, Lim built his iGEM team around five seniors from San Francisco's public Abraham Lincoln High School. Using UCSF grad students and postdocs as trainers, Lim presented the students with the basics of synthetic biology. Then he stepped back as they brainstormed their way toward a project—an artificial organelle in yeast.

The only high school students in the 19-country competition, the 2007 UCSF team finished in the top six of 54 teams. Heading into the 2008 iGEM Jamboree this November, "Coach" Lim had high hopes for his new team;

his high schoolers were engineering epigenetic control of gene expression.

Today Lim lives with his wife, Karen Earle, and their daughters, Emilia, 7, and Nadia, 4, in San Francisco's Sunset District. Their home is near the original UCSF Mt. Parnassus campus. Lim now commutes across town, however, to the new UCSF research facility at Mission Bay. Earle is the chief of endocrinology at California Pacific Medical Center and the current president of the American Diabetes Association San Francisco advisory board. Emilia, says her father, is a deeply thoughtful child, in love with art, science, and math. Nadia is a force of nature, he says, with a smile for everybody.

If Lim has an interest outside science, it is art, except that he makes art around his science. With small children and a big lab, Lim says that his drawing and painting have suffered in recent years. Visitors to Mission Bay are still greeted by his 12-foot-tall, handmade, papier-mâché and fiberglass Pipetman. This creation is Lim's whimsical tribute to an instrument that he believes "hasn't received its due in the history of molecular biology."

## Vision

This visual side is integral to Lim's scientific imagination, according to colleagues. Bourne believes that Lim's journal figures are clearer and more to the point than almost anyone else's.

"I think that's a really important gift," Bourne says. "When you're thinking about 3-D structures, you try to imagine how they move in space. That requires a kind of 3-D imagination. You have to color the different pieces and imagine watching the colors moving around. Wendell does that instinctively."

Mayer says that Lim's visual knack is integral to his "big picture" thinking. "There are people who know everything and know all the details," Mayer explains. "They've been to every meeting and heard every talk. Their knowledge is encyclopedic. But Wendell has this big-picture view that can cut through to the center of a problem. In biology, he has a unique way of thinking about things that's different from the rest of us." ■

—*John Fleischman*

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# San Francisco Safety Alerts for Annual Meeting Attendees

### The Tuesday Noon Siren

Every Tuesday at 12:00 Noon, San Francisco tests the Outdoor Warning System. During the test, the siren emits a 15-second alert tone. In an actual emergency, the siren tone will cycle repeatedly for five minutes. If you hear the sirens at any time other than Tuesday at 12:00 Noon, go indoors and immediately tune to a news source such as KCBS 740 AM, or other local media stations. Any emergency messages will also be broadcast on the outdoor siren system. Learn more about the siren system at www.72hours.org.

### AlertSF Notification System

AlertSF will send watches and warnings for tsunamis, flooding, and tornados as well as post-disaster information to your registered wireless device and email account. To register, please visit www.alertsf.com.

For information on what to do in case of an earthquake, power outage, fire, or other emergency, visit www.72hours.org. ■

# Wikipedia Workshop at Annual Meeting

### Tuesday, December 16, 2008
### 12:30 pm–2:30 pm, Room 220

Presenters: *Tim Vickers*, Washington University in St. Louis
*William Wedemeyer*, Michigan State University

Join forces at the ASCB Annual Meeting to improve the Wikipedia cell biology entries! This hands-on session will provide a general introduction to writing cell biology articles on Wikipedia. Every participant will either improve an existing article or create a new article on a topic that is in the scientific literature, but not yet covered in Wikipedia. In both cases, the articles will be illustrated and referenced to the scientific literature. In addition to the two workshop presenters, Wikipedia volunteers will be at the workshop and also online to assist participants.

Participants should bring laptops, scientific references, and three or four images/diagrams to illustrate the cell biology topic of their choice. Images on Wikipedia are covered by a free-content license (the GNU Free Documentation License). Therefore, the images supplied should either be uncopyrighted, or the copyright should belong to participants. Submitters will retain the copyright, but the images, as long as they are credited, will be freely available. ■