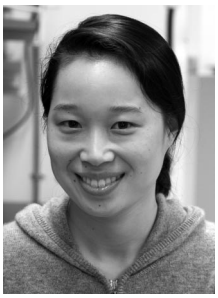
ACS chemical biology

PROFILE

Michelle Chang: Putting the Pieces Together with Synthetic Biology



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Profiles provide insights into the lives, backgrounds, career paths, and futures of scientists who serve as Experts on *ACS Chemical Biology*'s online Ask the Expert feature. Chang will begin answering your questions in mid-January, 2008. Readers are encouraged to submit questions to the Experts at www.acschemicalbiology.org. The editors will post the most interesting exchanges on the web site.

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The very essence of synthetic biology is stringing together an assortment of known pieces and parts that, in the end, work cohesively to create a wholly new function. That is also the essence of many young scientists' careers. By combining their varied interests, these researchers create new fields for themselves, pushing science in novel directions. Michelle Chang, an assistant professor of chemistry at the University of California, Berkeley (UC Berkeley), embodies this enterprising spirit. Working with seemingly disparate interests such as enzymology, chemistry, cell and molecular biology, and synthetic biology, Chang recently set up her laboratory to focus on two objectives: designing new biosynthetic pathways to study *in vivo* cellular production of biofuels and designing fluorinated pharmaceuticals. By melding her interests, she gives her colleagues and students new ways to view chemical biology.

Building a Background. Chang was born in San Diego in 1977. The daughter of two Ph.D. researchers—her parents, both now retired, worked as an engineer and a biologist—she says that she never spent much time speculating on what she would be when she grew up. The choice always seemed clear. "With two scientists as parents, I just assumed that I would go into college as a science major. Science was always my first choice," she says.

When Chang neared the end of high school, her father took a job in Los Angeles and had to live near his new position during the work week. Rather than leaving her mother alone in San Diego, Chang chose to attend the nearby University of California (UCSD) and live at home. She became interested in both chemistry and biology early on, quickly choosing biochemistry as her major.

While she was certain that both fields would be in her future, Chang was not sure whether she wanted to pursue a Ph.D. for a career in research or an M.D. to practice medicine. To help make her decision, she started volunteering at a nearby hospital and searching for laboratories to join at UCSD. She found the perfect fit with Don Helinski, a microbiologist whose laboratory uses genetics and biochemistry to study maintenance of plasmids in bacteria. Chang felt lucky to be welcomed to his laboratory as a freshman, and she remembers feeling valued and respected right away. "You always do grunt work as an undergrad in a lab, but he treated me more like a student than just an extra set of hands," she says.

Chang joined forces with a postdoctoral fellow whose project was focused on studying horizontal gene transfer in bacterial communities. They worked together with environmental isolates from marine sediments, characterizing novel plasmids and their relationship to fitness, such as resistance to antibiotics or heavy metals (*1, 2*).

Her experience in Helinski's laboratory was a turning point for Chang—after just a short time working with her colleagues there, she knew that she wanted to pursue a career in research. At the same time, her course work at UCSD was honing her scientific interests. She became fascinated with enzymology and catalysis.

In her senior year at UCSD, Chang began looking into which graduate schools might be a good fit to encourage these interests. Eventually, she settled on the Massachusetts Institute of Technology (MIT), applied, and was accepted. Originally, she had her

eye on a faculty member in the biology department to be her new mentor. However, once she arrived at MIT, Chang began sitting in on lectures that professors in the chemistry department gave to help new graduate students choose their mentors. "I went to all of them. It was good to learn what people did and see something I didn't know about," Chang says.

One talk, by physical inorganic chemist Daniel Nocera, particularly intrigued her. Nocera's work looked at examining the mechanism of proton-coupled electron transfer (PCET) in chemical model systems. At the time Chang saw his talk, Nocera had no biochemistry projects in his laboratory. Eventually, they struck on an idea that could combine her interests in chemistry with her research background in biology, especially enzymology. Joining the laboratories of both Nocera and MIT enzymologist JoAnne Stubbe, Chang embarked on a project to investigate the detailed mechanisms of long-range PCET in the enzyme ribonucleotide reductase.

A joint student in both groups, Chang spent the first three years of her graduate education in Nocera's laboratory doing synthesis and spectroscopy and the next three years in Stubbe's laboratory working on biochemistry and enzymology. Together, she and her colleagues created amino acid derivatives that could generate a radical in response to light (*3*). By using light-mediated radical generation in a biological system, this method gave a new way to probe the pathway and mechanism for radical transport in ribonucleotide reductase (*4*). They also developed methods to carry out site-specific mutagenesis with unnatural amino acids using intein-based protein semisynthesis in order to explore the relationship between proton and electron transfer (*5, 6*).

Fighting Malaria. After looking for a postdoctoral laboratory that would allow her to combine her interests in chemistry and biology, Chang secured a position with Jay Keasling, a professor of chemical engineering whose work had a unique biological twist.

Few researchers at the time were calling themselves "synthetic biologists", but Keasling's work embodied that term—and still does today. When Chang joined his laboratory, Keasling and his colleagues had just received funding from the Gates Foundation, which is dedicated to treating diseases of the world's poor. The project focused on a natural compound called artemisinin, a sesquiterpene lactone isolated from sweet wormwood. Long used as a folk remedy in Chinese medicine, artemisinin is also a powerful treatment for malaria.

The compound is significantly more effective than traditional malaria treatments such as chloroquine, which have become ineffective over time as the protozoa that causes malaria developed resistance. However, artemisinin can be as much as 20× more expensive than traditional malaria treatments, a cost that puts this drug out of reach for the people most likely to need it.

Artemisinin's expense stems from the fact that it must be isolated from plants, says Chang. "There's a limited supply, and scaling up is a huge part of the cost," she explains. However, Keasling's project focused on bumping up artemisinin production using microbial fermentation, a method that has been able to revolutionize cheap, large-scale production of many natural products.

Keasling's group was using synthetic biology techniques to string together the complex group of genes that assemble a precursor to the artemisinin molecule and prompt *Escherichia coli*, which do not normally make the compound, to produce it in high quantities (*7*). When Chang arrived at the laboratory, she worked to develop methods that use plant P450s to tailor that precursor *in vivo* and produce a semisynthetic intermediate that could be isolated from fermentation and chemically converted to artemisinin (*8*).

By the time she wrapped up her work in Keasling's laboratory three years later, she had accepted a faculty position at UC Berkeley in their chemistry department. She started her new position in July 2007.

Supporting Society. Chang's work in the Keasling laboratory on antimalarial therapeutics gave her a new appreciation and excitement for basic research that could have positive and broad impacts on society. While thinking over ideas for her own independent research, Chang chose to take a problem-driven approach to explore and interrogate interesting questions in fundamental science with an eye toward future applications.

Since setting up her laboratory this fall, she has developed two main research foci. Both areas involve studying the detailed molecular mechanisms of enzymes that catalyze unique reactions, then using this knowledge to build new functionality into living cells and organisms.

Her first project is exploring new ways to create biofuels—inexpensive and renewable fuel sources—using microbial fermentation. She and her colleagues are exploring the specialized chemistry that microbes have evolved to break down and consume biopolymers in plants. Several research groups are exploring similar lines of work on cellulose, hoping to exploit use of this chemically simple molecule to make fuel. However, Chang's group hopes instead to apply their research to lignin, a component of plants that often goes unused in biofuel production. Once they have a grasp on the pathway that some microbes use to break down this more complex molecule, they plan to take advantage of the pathway's most useful elements to ferment lignin for biofuel.

A second project that her laboratory is working on involves investigating how carbon–fluorine bonds can be made enzymatically, with the hopes of using this knowledge to create new fluorinated drugs. Chang explains that many popular drugs, including Cipro, Lipitor, and Advair, contain fluo-

rine. Fluorine atoms are electron-withdrawing but small, so they can change a molecule's electronic properties without drastically changing its shape. As such, chemists have used fluorine to "tune" an atom, Chang says, to bring a hit on a molecular screen into fruition as a drug.

However, as useful as fluorinated molecules are, creating them has been difficult using traditional synthetic chemistry. Chang's laboratory is exploring how to create fluorinated molecules in a biological way, using enzymes to catalyze carbon–fluorine bond formation.

Chang has three graduate students working with her on these two objectives, as well as one undergraduate student and a research associate. She notes that each of these colleagues has entered her laboratory with a liberal idea of how chemistry can be done. "Chemistry is a relatively traditional field, and it's clear that the stuff I do wouldn't fit in many chemistry departments," she says. "The faculty here at UC Berkeley are open-minded with their definition of chemistry, and the students are, too."

She is helping to broaden this flexible idea of chemistry by teaching a new class at the school for undergraduate and graduate students. "We basically talk about all the stuff I like," she says. With a focus on synthetic biology, the class explores enzymology, using it as a basis for talking about natural product synthesis and expanding into ideas for biological approaches for engineering production of natural products in their native host or in a heterologous host.

She explains that stirring up others' interest in these ideas in turn fuels her own, helping her identify new strategies for tackling her laboratory's long-term goals. She also stays inspired by considering the benefits that new biofuels and pharmaceuticals could eventually bring.

—Christen Brownlee, Science Writer

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