

# Michael Laub: The systems savant

When Michael Laub arrived at Stanford University in 1997, genomics was in its infancy, with many DNA technologies just being developed. So when he wanted to study cell cycle gene expression in *Caulobacter crescentus*, he decided to build his own DNA microarray. But the equipment he needed to make primers for the array was booked for months, so Laub began working at the lab during the only hours it was free, from 11 p.m. to 4 a.m. After four months he finished the device. "Now you can just buy them," laughs Laub. "This was a lot more effort."

The California native did his undergraduate work at the University of California, San Diego. His first experience in a lab was working with slime mold, a "super cool organism," says Laub. "I really fell in love with experimental work at that time."

Laub traded slime mold for *Caulobacter* as a graduate student in Lucy Shapiro's lab at Stanford. At the time, Craig Venter had just sequenced the *caulobacter* genome, and no one except Laub was questioning whether there was a hardwired program of genes that turn on and off during the cell cycle, says Shapiro. With his custom microarray, Laub was able to analyze RNA isolated from *caulobacter* cells at various stages during the cell cycle. "I saw all these amazing patterns," Laub recalls, of genes turning on and off exactly when needed. Nicknamed "just in time" transcription after the business concept of "just in time" manufacturing (a system of producing goods exactly when needed without excess inventory), Laub's thesis work made it into *Science* in 2000.<sup>1</sup> "He published the first hardwired program of a bacterial cell cycle as a young grad student," says Shapiro. "He's among the best."

After finishing his PhD, Laub was recruited to be a Bauer Fellow in the Center for Genomics Research at Harvard University (now the FAS Center for Systems Biology) where he broadened his interest from studying gene expression to examining the larger systems that influence it. He chose to map *Caulobacter*'s two-component signal transduction system, a network of histidine kinases and response regulators that control gene expression in the bacteria. To determine their binding preferences, Laub purified all 64 kinases and 42 substrates made by the bacteria, matched them up in vitro, and then mapped their pathways.<sup>2</sup> Richard Losick, Harvard biologist and one of Laub's fellowship mentors, recalls listening to Laub describe the work: "He doesn't hit you over the head, he's very matter-of-fact, but once you think about [what he's said], it's breathtaking. I mean, he made every histidine kinase in the genome!"

Both advisors agree Laub's hallmark is his interdisciplinary approach. "He combines exquisite technical skills with excellent bioinformatics and computation knowledge," says Shapiro. And in the field of systems biology, that's exactly what's required, says Losick. "He has all the skills you need these days to succeed."

In 2006, Laub took up a teaching appointment at MIT. Now that he knows which kinases bind what substrates, Laub is studying their binding specificity on the level of amino acids. Recently, he used a computational approach to identify the amino acids involved and showed that by mutating them, it's possible to rewire kinase specificity.<sup>3</sup> Losick isn't surprised by Laub's efforts: "He's been unstoppable," he says, "always on the cutting edge of systems biology." —Megan Scudellari

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Representative publications:

1. M.T. Laub et al., "Global analysis of the genetic network controlling a bacterial cell cycle," *Science*, 290:2144–8, 2000. (Cited in 197 papers)
2. J.M. Skerker et al., "Two-component signal transduction pathways regulating growth and cell cycle progression in a bacterium: a system-level analysis," *PLoS Biology*, 3:1770–88, 2005. (Cited in 38 papers)
3. J.M. Skerker et al., "Rewiring the specificity of two-component signal transduction systems," *Cell*, 133:1043–54, 2008.