HHMI BULLETIN

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PERSPECTIVES & OPINIONS

WEB ONLY

CELLS BEHAVING BETTER

- JAMES J. COLLINS -

SYNTHETIC BIOLOGY MAY–ONE DAY–CHANGE THE WAY CELLS WORK.

James J. Collins is an engineer at heart. But the system he's chosen to work on is more complex to rebuild than any piece of electronics he's tinkered with. Collins, an HHMI investigator at Boston University, studies living cells. His research gets at the crux of how cells function. The implications are huge but far in the future.

HHMI: WHAT IS SYNTHETIC BIOLOGY?

JJC: Synthetic biology is a new field that's bringing together engineers and biologists to create novel circuits that control cell behavior. Whereas some engineers put together electronic components to build systems such as radios, we are using biologic parts—DNA, RNA, and proteins—to rewire the insides of cells. We'd like to reprogram organisms to address challenges in medicine, energy, and the environment. For example, we could reprogram bacteria to create a fuel that we need or reprogram cells in our bodies to ward off disease.

HHMI: HOW CLOSE ARE THESE IDEAS TO REALITY?

JJC: Many of these practical applications are far off and quite complicated. For now, we are taking smaller steps, creating small genetic networks both to learn how cells normally work and to endow cells with novel decision-making capabilities.

HHMI: DO YOU NEED TO BE TRAINED AS A BIOLOGIST TO RUN A SYNTHETIC BIOLOGY LAB?

JJC: We're mostly doing wet work just like other biologists—cloning bits of DNA into cells, testing how the cells behave, looking at expression profiles. Our work takes a broad spectrum of backgrounds and expertise. In my lab are biologists, chemists, physicists, bioinformaticists, and engineers organized in teams so that people working together have complementary knowledge.

HHMI: AND YOUR BACKGROUND?

JJC: I started out in physics and moved into medical engineering. My dad and uncle were engineers, and my mom was a mathematics teacher, so I was brought up to think like an engineer. In the 70s I saw all these fascinating technologies being developed for the space program and the military and I thought it would be really cool if we could apply these to help restore function to the disabled. I had two grandfathers who were disabled—one lost his vision when I was seven and the other had a series of strokes—and that inspired me to want to make a difference in medicine and biomedical technology.

HHMI: WHAT MISUNDERSTANDINGS EXIST ABOUT YOUR FIELD?

JJC: You have this notion of Franken-microbes, or this idea that engineers are running amok in biology labs trying to create life from scratch. Some scientists within the field propagate these kinds of rumors. I think much of what you read in the popular media about synthetic biology is far beyond what is going on in the labs.

Photo: Leah Fasten

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James J. Collins

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PERSPECTIVES & OPINIONS: Cells Behaving Better

WEB EXTRA

Tinkering With Cells
Listen to HHMI investigator Jim Collins talk about synthetic biology while getting an inside glimpse at his Boston University lab.

MULTIMEDIA

HHMI: TELL US ABOUT A CIRCUIT YOU'VE ACTUALLY CREATED.

JJC: In terms of a cell, a network or circuit means a set of proteins and genes interacting with each other. One circuit we've engineered is the genetic toggle switch. It's made of two genes; each wants to be on and shut the other one off. The circuit can exist in two stable states: in state 1, gene A is on and gene B is off; in state 2, gene B is on and gene A is off. The circuit can be switched between the states when we deliver an inducer—a chemical or environmental stimulus that shuts off the currently "on" gene. It's a relatively simple example of what we do. Toggle switches and related synthetic gene networks can be used to endow cells with the programmable ability to sense and adapt to their environment.

HHMI: YOU WORK IN BOTH SYSTEMS BIOLOGY AND SYNTHETIC BIOLOGY. HOW ARE THEY RELATED?

JJC: In systems biology, researchers are taking computational approaches to studying the natural pathways and circuits inside cells. Whereas in synthetic biology we're trying to put together a new radio, in systems biology we're trying to figure out how an existing radio is wired up. It's like basic electrical engineering classes: students are given circuit boards and told to figure out how they work. They have to go through each component of the board, turn it on or off, measure its effects, and infer the underlying wiring. In systems biology, that's what we're doing inside the cell.

HHMI: WHAT QUESTIONS CAN SYSTEMS BIOLOGY ANSWER?

JJC: I'm excited about using systems biology to reveal how drugs work. Researchers are very good at testing whether a drug hits a target. But they don't know what else it hits inside the cell. We can take a systems biology approach: screen all the genes, proteins, and some metabolites in the cell to identify a drug's target. We've used our approach on antibiotics and shown that they target and activate many more cellular networks in bacteria than we thought. By understanding the inside wiring of the cells, and how circuits respond to a perturbation like an antibiotic, we can come up with better therapies.

We can use this same approach to understand how diseases affect different pathways. We can take someone with prostate cancer or breast cancer, look at the expression of genes in their tumors, and analyze which pathways have been affected. We're just beginning studies like that.

HHMI: WHAT'S MOST CHALLENGING ABOUT WORKING IN THESE NEW FIELDS?

JJC: There are a lot of cool synthetic biology ideas out there. It's pretty easy to come up with a circuit diagram and increasingly straightforward to build the cellular components you'll need. But it's really hard to get the constructed biological circuit to behave the way your schematic or model indicated. We've recently developed an approach that allows us to put together a number of well-characterized parts—genes, promoter, and proteins—and predict with some accuracy how they'll behave together in different circuits. But our synthetic biology toolkit is still relatively small. We're playing around with circuits that consist of two, three, maybe six genes that give cells rudimentary functions. We're expanding our understanding of cellular networks, but the cell is incredibly complicated and it's going to take a long time to figure it out. I'd be surprised if we ever develop a full understanding of every single network in the cell, which is partly why this field is so fascinating to be in. I think we'll be in business for a long time. ■

James J. Collins is a professor of bioengineering at Boston University and codirector of the Boston University Center for BioDynamics.

Interview by Sarah C.P. Williams.

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