In the Business of Synthetic Life

Synthetic biology might someday lead to artificial organisms. To James J. Collins, it already offers pharmaceutical promise, like turning a person's cells into custom drug factories   By SAM JAFFE

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JAMES J. COLLINS: MAKING LIFE

- **Practices synthetic biology, in which researchers tinker with genetic networks, rather than single genes of conventional genetic engineering.**
- **Found in previous work that a vibrating insole can improve the elderly's sense of balance, sparking interest from athletic shoe companies.**
- **On why engineering is easier than science: "All you have to do to succeed at engineering is to build something bigger, cheaper or faster. Science is creating new knowledge. That takes a lot more sweat and pain."**

At first glance, the bacterial colonies that dot a petri dish in the Boston University laboratory of James J. Collins do not seem all that special. Each *Escherichia coli* bacterium has been genetically altered to manufacture a specific protein once the population density of the colony around it reaches a predefined level.

A skeptic might yawn. After all, genetic engineering isn't new. But these cells haven't just had a foreign gene spliced into them. Collins inserted a whole genetic network—he put in many genes that interact together as well as with the natural genetic machinery of the cell. In this case, he dropped in a quorum-sensing network from a *Vibrio fischerii* bacterium. If conventional genetic engineering is like changing the blade on a screwdriver, then Collins's approach is akin to altering the contents of the entire toolbox at once.

The 39-year-old Collins is a member of an emerging field called synthetic biology. Practitioners create novel ingredients for the recipe of life, including nucleic acids, amino acids and peptides. Some of them even hope to manufacture an artificial organism [see "Synthetic Life," by W. Wayt Gibbs; Scientific American, May 2004]. It is still considered a seed-stage discipline, where brilliant young scientists wow one another with proof-of-concept experiments and publish papers filled with pages of mathematical formulas. Collins, on the other hand, is the first to generate commercial technologies that are in the advanced stages of development. More than any other, he is proving that synthetic biology is ready for the marketplace, much more quickly than others expected it could be.

The most promising of those technologies is an RNA ribo-regulator, which Collins first described in 2004. It consists of a sequence of DNA that, with the help of a genetically engineered virus, integrates into a host bacterium's genome. The DNA then creates a loop of messenger RNA that binds to a site on the ribosome (the cell's protein factory), thereby blocking the production of a specified protein. The regulator can do the opposite, too: it can unblock the ribosome on command in order to start making that protein. Essentially the ribo-regulator enables scientists to dictate protein production, with close to 100 percent accuracy and efficiency.

Others quickly improved on the ribo-regulator. Richard Mulligan of Harvard Medical School designed one that can be activated when a specific molecule is added to mouse cells. If these technologies prove successful inside humans, a person's cells could be turned into pharmaceutical plants. Pills would be popped only to turn the micro factories on or off. Such a future is still years away, but the progress thus far amazes Collins. "I never would have dreamed that within a year this technology would already be working in mammals," he says. A company founded by Collins, called Cellicon Biotechnologies, is now negotiating with several firms for use in drug discovery.

The ribo-regulator is not the only technology with such tremendous commercial promise coming from Cellicon. The company has encoded the principles behind synthetic biology into software to help screen drug candidates for their effect on the whole cell, rather than just on one protein target. "Drug companies are great at creating an assay that proves a compound hits a specific target," Collins states. "Thus far they haven't been very good at predicting what it will do to all the other genes and proteins in a cell."

By forward-engineering the cell, science could reveal its secrets more readily, Collins says.

Collins's success in technology development lies in the fact that he straddles the line between engineering and science so effortlessly. "I'm not sure if the conventional definitions are very helpful anymore," he says. "In the end, I'm far more interested in seeing the fruit of my work help a human being. If I do some good science along the way, that's great, too." Others agree. "Collins's scientific work is all the more impressive because he's done it while doing real engineering," remarks George Church, a biologist at Harvard Medical School.

Collins wanted to be an electrical engineer. But while attending the University of Oxford as a Rhodes scholar, Collins found himself studying nonlinear dynamics—popularly known as chaos theory—with Ian Stewart, the famed University of Warwick mathematician and former columnist for *Scientific American*'s Mathematical Recreations. "I haven't met anybody more emblematic of the concept of multidisciplinary research than Jim," Stewart says of his former protégé. "Some people just can't function without clear boundaries that define their discipline. Jim excels in such an environment."

After his work in the U.K., Collins became a faculty member of Boston University's department of bioengineering. He became intrigued with the relation between the human sense of balance and stochastic (or random) sensory inputs—better known as noise. "Normally you think of noise as hindering the clarity of a signal," Collins explains. "But in some cases, noise can enhance a signal." Collins hypothesized that senior citizens were losing their balance with age in part because they become less sensitive to stochastic stimuli, such as pressure on the soles of the feet. He designed a battery-powered shoe insole that produces just enough random vibrations to improve an average 75-year-old's sense of balance to that of a 25-year-old.

In the midst of working on the insole, he received an unusual request from Charles R. Cantor, his department chair. Cantor wanted Collins to use his expertise in nonlinear dynamics to make a presentation about genetic networks to a visiting grant-dispensing committee. Genes usually don't work alone. Instead they function within a system of interdependent genetic networks whose individual genes are constantly modifying the behavior of the other genes within the network. Collins, who at that point had no specialized education in molecular biology, spent the next four days preparing the presentation. The department didn't get the grant, but Collins realized from his crash course that biology was far closer to becoming an engineering discipline than most people realized. "Everybody was trying to reverse-engineer the cell, but that's the hardest way to understand it," Collins declares. "By forward-engineering it, science could reveal its secrets more readily."

Collins soon led a team that in 1999 created a genetic toggle switch. It consists of two foreign genes, each of which produces a protein that inhibits the other gene. Depending on the chemical added to the bacterial broth, the proteins of one gene would effectively be deactivated, disabling that gene. "The toggle switch is significant because no further modulation is necessary," Cantor says. Conventional genetic engineering needs continual insertion of a stimulant to keep the new gene running. The toggle switch stays on, or off, for as long as the organism remains alive.

Collins continues to optimize his toggle switch, which, like the ribo-regulator, has drawn interest from pharmaceutical companies. To some extent, the greatest promise of Collins's synthetic networks is that they help to verify the ever more complex software models that try to mimic the human cell. Yet Collins is adamant that such in silico modeling has its limits. "My holy grail isn't a virtual cell," he says, emphasizing a point that he believes the entire field of synthetic biology has to agree on to make further progress: "No matter how good we get at modeling, the model will never replace the actual experiment." SA

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