NICK HIGGINS

Q&A James Collins
Circuit capacity

A Boston University biomedical engineer, Collins reprograms organisms to endow them with novel or improved functions. Nature Outlook *asks him how things are evolving.*

Which potential applications look the most promising, and which don't?

Many of the initial applications were for bioenergy — tools from synthetic biology can be used to re-engineer organisms so they can convert biomass or sunlight into fuels of interest. But so far these have not scaled up well. It has been difficult to go from a table-top experiment to an industrial-scale bioreactor. It can cost US$4 to make $1-worth of fuel.

On the positive side, there is excitement about medical applications and moving from synthetic biology of microorganisms into mammalian systems, which will open up many possibilities. Another application being pursued is synthetic ecosystems — engineering the microbiome that resides in the digestive system for therapeutics. For example, researchers have modified a strain of *Escherichia coli* bacteria that, in a mouse model, was able to keep cholera bacteria from colonizing the intestine.

What are some applications in biomedicine for which synthetic biology methods are uniquely suited?

Synthetic circuits containing molecular components such as DNA, RNA and proteins can be designed for a range of applications, including biosensing, bioremediation and bioproduction. One of the bioproduction success stories comes from Jay Keasling and colleagues at the University of California, Berkeley. They inserted an engineered bacterial metabolic pathway containing several genes into yeast to make the precursor of artemisinin, a major malaria drug. This worked out to be less costly than synthesizing the drug chemically. And our group has engineered bacteriophage viruses to break up bacterial biofilms that are highly resistant to antibiotics. Such films form on the surfaces of artificial hip implants and can be very difficult to treat. We have engineered a phage to express an enzyme that breaks up the biofilm that forms on catheters. We also have used synthetic biology tools to turn on or off gene networks that block microbes' defence against antibiotics.

Engineered circuits inserted in bacterial cells are being studied as biological sensors and sentinels, to detect environmental toxins, infections and even cancer. Early work in the field laid the groundwork for constructing basic circuits that could sense and process signals, perform logic operations, and trigger biological responses. Wiring these modules together to bring about reliable functionality is one of synthetic biology's next goals.

In a 2011 publication in *Science,* a group led by Ron Weiss, a biological engineer at the Massachusetts Institute of Technology, and Yaakov Benenson, a synthetic biologist at the Swiss Federal Institute of Technology in Zurich, described an engineered gene circuit designed to detect cancer cells and target them for destruction by the immune system. When they inserted the gene network into cervical cancer and normal cells, only the cancer cells were destroyed. Although the strategy is still far from human application, the work is a first step toward cancer diagnosis at a single-cell level.

Critics have said synthetic biology is nothing new — it's just a buzzword for sophisticated genetic engineering.

That perspective comes from the academic community, and I understand it. Academics are trained to be critical and sceptical. They don't like new terms. But I say that synthetic biology is genetic engineering on steroids. We're using tools and methods developed for genetic engineering to redesign the fundamental molecular interactions and pathways of living cells. Instead of focusing on single gene modifications, we're putting together a number of molecular components to build circuits with control elements.

What hurdles does the synthetic biology field face?

Because the field is so young, we're still at the artisan stage. People in a few dozen labs make their own parts — gene promoters, reporter proteins, repressor proteins, ribosome binding sites, and so forth. But there are still many molecular parts that are not sufficiently characterized to be used as tools in synthetic biology. As industry interest in synthetic biology increases, companies will begin to create libraries of components.

Another challenge is that the work is labour intensive and slow. It takes many weeks to build circuits of interest. There is growing interest in harnessing evolution in the test tube to create protein or RNA molecules with novel properties. A protein is mutated, producing a library of variant forms from which those of interest are selected in successive rounds of 'directed evolution'. The biology remains very messy, though — we can't yet reliably predict how the parts will behave and work together.

Is there sufficient commercial interest to support the progress of synthetic biology?

After the initial investment in bioenergy applications, venture capitalists are looking around, trying to figure out where the commercial opportunities are going to be. One source of investment is the US Defense Advanced Research Projects Agency (DARPA). In June 2011, DARPA announced a $30-million, three-year programme called Living Foundries. It will support academic and corporate researchers to apply an engineering framework to biology for biomanufacturing, with the goal of speeding the process and lowering the cost of making a variety of products. It's too early to predict the commercial importance of such a young field — whether it will turn out to be the next semiconductor industry is hard to say. ■

Interview by **Richard Saltus**, *a science writer based near Boston, Massachusetts.*

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