Scientists

Forward engineering

James J. Collins
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Jim Collins' work on programmable cells and his contributions to synthetic biology caught our attention. Curious to know more, *BioTechniques* contacted him to find out about the ambition, character, and motivation that led to his success.

How did you first become interested in bioengineering and synthetic biology?
I became interested in bioengineering at a young age when both of my grandfathers became disabled: one lost his vision and the other had a series of strokes and became hemiplegic. My father did engineering work for NASA and the military, so I often heard about marvelous technologies developed to shoot things into the sky, but I saw very little being developed to help my grandfathers regain function. This motivated me to harness engineering and science insights to enhance the lives of those affected by disease or injury.

When I joined the faculty at Boston University, my lab focused on whole body dynamics and biomechanics including how humans walk, run, and balance. In that context, we developed a number of interesting devices to enhance sensory and motor function. However, over the last several years, I have made a pretty dramatic shift into systems biology and synthetic biology, which started when my colleagues Charles Cantor and Charles DeLisi encouraged me to think about reverse engineering gene networks using data from the Human Genome Project. We set about applying engineering control theory techniques and non-linear dynamics principles at the molecular level, but quickly recognized there was insufficient expression data at that time to reverse-engineer natural networks. Molecular biology was primed for forward engineering approaches though.

Up to this point, what has been your most significant contribution to your field?
We helped to launch the field of synthetic biology by creating a bistable genetic toggle switch in *Escherichia coli*, one of the first synthetic gene networks. We used engineering principles to create a circuit schematic, identified the appropriate components including promoters, proteins, and bits of DNA, and assembled them with techniques developed for recombinant DNA and genetic engineering applications. We designed the switch as a mutually inhibitory network that included two repressor genes driven by constitutive promoters; the protein product from gene 1 shuts down the promoter for gene 2, while the protein product from gene 2 binds the promoter for gene 1, shutting it down. So in principle, this system may exist in two states: gene 1 is on and gene 2 is off or vice versa. We can switch between states by delivering an inducer for the currently active gene, using this control circuit to regulate, in a bistable fashion, the expression of up to a relatively large number of proteins.

What is the application for these synthetic circuits?
Basically, they are a means to endow programmable cells with a simple form of memory. For example, we have used toggle switches to create whole cell biosensors that detect heavy metals, chemicals, or even pathogens in their environments, designed genetic switchboards for metabolic engineering applications, and we have plans to use them in the context of cell and gene therapy. The advantage of toggle switches in these situations is that switching between the on and off states requires only transient delivery of a chemical stimulus rather than continuous application.

What are you working on now?
We are very excited now about designing programmable cell sentinels that can be used to sense and respond to viral or bacterial pathogens. We are exploring the possibility of modifying the human microbiome with engineered cells capable of detecting and responding to cholera infections. In the absence of an infection, the bacteria simply live and divide in the host; but when small molecules produced during a cholera infection are detected by the circuit, it switches on and releases an antimicrobial peptide to counter the invading cholera.

We are also looking into platforms for treating tuberculosis (TB) by delivering synthetic circuitry into macrophage or granuloma cells. Rather than engineering bacteria for this application, we are planning to create synthetic vesicles, engineered liposomes for example, that can be administered to a patient by nebulizer following identification of a TB infection.

Do you have any additional projects outside the main focus of your lab?
By combining our engineering approaches with George Daley's group's outstanding expertise in stem cells, we are trying to gain additional insight into reprogramming and differentiation of embryonic stem (ES) cells or induced pluripotent stem (iPS) cells for biomedical applications. We use systems and synthetic biology methods to study the regulatory networks underlying reprogramming to identify the components needed to produce specific cell and tissue types of interest from ES or iPS cells for regenerative medicine.

What is the biggest challenge in synthetic biology today?
The biggest challenge for the field right now is developing the ability to predictably design integrated circuits, components, and pathways that function as we desire. That challenge will require an expanded understanding of the underlying biology of these components and how they function, the development of better models for interactions that are currently unknown or unaccounted for in our modeling, and the development of expanded libraries of well characterized parts that can be harnessed for such design purposes.

Interviewed by Kristie Nybo, Ph.D. Image by Robert E. Klein/AP, ©HHMI.

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