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Engineering new medicine: an interview with James Collins

At first glance, the commonality among synthetic gene networks, nerve cell response times and the emergence of antibiotic resistance is obscure. Yet, when speaking with James (Jim) Collins, the relationship becomes clear: all are applications-oriented problems, and all inspire unique approaches from this unusual engineer who is empowered by his freedom to fail.

Jim Collins is a pioneer of synthetic biology, the space where biology and engineering collide to facilitate the practice of medicine. This area is suggested to bring the next wave of transforming innovations, with potential likened to that of genetics and molecular biology. Synthetic biology hopes to provide microorganisms that make drugs or kill cancer cells, and inventions that can alleviate patient suffering or improve the efficacy of medications.

Dr Collins's discoveries span an unusual breadth but are tied together by their tractability from his engineering perspective. One overarching goal of synthetic biology is to construct functional genetic circuits in cells to program them for new purposes. Dr Collins's lab produced one of the first: the genetic toggle switch containing promotors and inhibitors that are regulated by transient chemical or thermal induction. They hope that this independent, programmable synthetic gene circuit will facilitate the application of gene therapy. Dr Collins invented vibrating insoles that enhance the sensitivity of the nervous system to weak somatosensory stimuli, and improve the balance of stroke patients. More recent work in his lab sheds light on the emergence of antibiotic-resistant bacteria and suggests how supplements might be created to enhance the efficacy of existing antibiotics.

Dr Collins's unique perspective and willingness to fail allow him to influence change in many areas of biology that directly affect patient lives. This Rhodes Scholar, recipient of the MacArthur Foundation 'Genius Award' and Howard Hughes Medical Institute (HHMI) Investigator is an inventor whose engineering eye can see new inroads to overcome obstacles in human health. To foster the long-term success of synthetic biology, Jim is one of the founders of the Wyss Institute at Harvard, a place where people apply engineering tactics to biological questions. Here, he discusses his unique approach to important scientific questions and why it is so important to fail.

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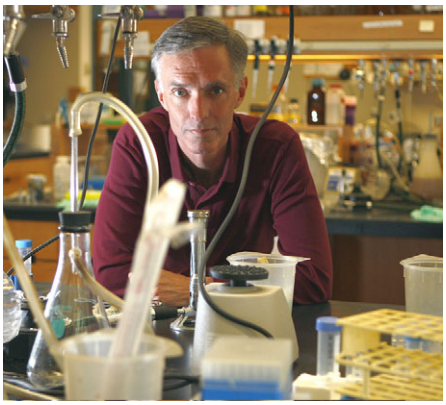
The emergence of antibiotic resistance is scary. Your recent work shows how bacteria quickly change to survive in the presence of bactericidal drugs. How do antibiotics encourage the emergence of resistant pathogen strains?

Stressful environments promote genetic changes in bacteria that help them survive. Bacteria exposed to sublethal levels of antibiotics produce reactive oxygen species (ROS), which increases their genetic mutation rate. Unfortunately, this leads to the emergence of antibiotic-resistant genes and eventually the development of multidrug cross-resistance. Since sublethal levels of antibiotics create a 'stressful' environment but do not kill the bacteria, we actually find that new generations of bacteria arise that are resistant to other antibiotics but are still sensitive to the original antibiotic.

Can knowing how antibiotics influence bacterial changes generate more effective antibiotics?

There are two places where this information could help address the issue of antibiotic resistance. First, it makes it possible to target the bacterial response to antibiotics that promotes their resistance, which is free



radical-induced DNA damage. If you could block the defense mechanisms that are induced by radicals, including DNA repair processes, you could potentially enhance the lethality of the antibiotics. Alternatively, if you could enhance the production of free radicals in bacteria to lethal levels, by amplifying some of the pathways that lead to radical generation in the sublethal drug response, you could make antibiotics more effective. We are exploring both of these approaches within our lab. Our work shows that if you can block the error-prone DNA repair system in the presence of antibiotics, you can thwart substantially the emergence of antibiotic resistance that arises directly from the antibiotic treatment. In the future, it might become possible to do this with a small molecule that could be administered along with an antibiotic. We want the big picture of what happens to cells when antibiotics attack them so that we might exploit their defense mechanisms with adjuvants or potentiating small molecules that could be given as supplements. The supplements could be used in combination therapy to enhance existing antibiotics or resuscitate drugs that are too toxic to be used at effective doses. This systems and network biology approach creates new

treatment strategies that build on currently existing ones.

Your work encompasses an unusual range – from antibiotic-resistant microorganisms, to genetic engineering, to the invention of vibrating insoles to enhance balance in stroke patients. What common elements of a scientific question draw it to your attention?

In our lab we are drawn to projects that are application oriented. We try to identify projects that could result in a potential product to address either a clinical or biotech application. The project around vibrating insoles very much fits that bill. We had the notion that you could input noise into the human body to enhance the sensitivity and function of sensory neurons and therefore improve a patient's motor control.

The way we approach projects that are creative and high risk is to fail fast. What we find is that if we are going after a project where we need to develop a new technique, we assume that we need ten good ideas to find one that will work. The odds are stacked against us even more when we delve into the basic science realm. Out of 100 new ideas, only one will probably be correct. We try to very quickly triage out the bad ideas. My feeling is that our willingness to fail, and to fail quickly, will get us to that one idea that will work. One proposed definition that I've heard is that a scientist or engineer is someone who can go from failure to failure with undiminished enthusiasm. We do not want to avoid failure, but rather to use the experience to steer us toward success.

That's a lot of pressure to fail. How does your value on accepting failures influence your perspective on teaching?

I think an unwillingness to teach kids to learn from mistakes is a big problem. Increasingly, educators cater to kids rather than teaching them how to learn. Students get A or B grades for regurgitating spoon-fed information. This environment may be fine for a few really smart kids who will challenge things on their own. Many of the kids I see are really smart and many are willing to work hard. Still, when they move into research or any real-world area that includes intelligent peers and competition, the environment they face becomes largely unforgiving. The reality of their future is that their own close colleagues may expose their bad ideas or reject their manuscripts. It is important to know how to handle this criticism. I think we are doing a great disservice to our young people because they are not prepared to fail and to use the experience to learn.

I like to give young students two messages. First, I hope they fail. This idea usually makes their mouths open agape. I explain that what I mean is that, although they may be protected from failure in their studies, I hope that they venture beyond this and challenge themselves. Second, I hope that they become comfortable with doing nothing for at least some period of each day. By this, I mean that they should allow themselves to be unconnected from their phone, text or computer and actually spend time thinking about their ideas. This could include discussing ideas or introspectively ruminating about them. This activity is too largely ignored. To move the world forward requires thinking about new ideas and then trying a few, even though some will not work.

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It is like my dad says, 'If you are not failing, you are not really trying.'

You have to be comfortable with failing. You don't have to accept failure but you have to be willing to fail and you have to have the coping mechanisms to handle it. Many of my scientific colleagues focus on the most obvious question that they can identify, a question that will guarantee them enough results to secure their next paper or grant. This 'safe' science is often important, but real advances require innovation and risk. Failure is hard on the ego and can definitely diminish your spirits. It is sometimes hard to keep going if you are constantly thwarted, but this is the reality of moving forward into innovative space. Kids need to be encouraged to develop the skills to withstand it.

In the face of inevitable failure, how might young people push into creative space?

They can ask questions without being intimidated by the notion that multiple geniuses may have already thought of everything. I like to present historical cases where a seemingly innocuous and simple question was asked that changed the way that people thought about significant issues. Most people would have assumed that the answer to the question would be known by the time the question was ever asked. In many cases, I think that young people have very good questions that they automatically assume have been asked and either answered or dismissed altogether. I encourage them not to put the simple questions aside so quickly.

One example is the issue of muscle contraction. Up until the late 1600s people thought that muscles changed their volume when they were activated, that they became bigger when they contracted, but no one had tested the theory. Jan Swammerdam, a Dutch scientist (1637-1680), actually asked the question 'Do muscles in fact expand when they contract?' He did a very simple experiment to show that the prevailing idea was wrong. Muscles don't change their volume when they activate. His findings overthrew centuries of thought about what drives the activation and specifically contracts the muscle. So, students need to become comfortable with their ideas, and willing to ask questions and test them.

Students also need to read. At their fingertips, students have the world library, which often makes them quite lazy and unwilling to search and keep up with a field. The notion that information is always right there and available has the unusual effect of preventing people from staying up to date with what is happening. There is as much to be gathered from reading a very traditional textbook as from reading the most current research. When I have new students coming into the lab, I encourage them to read textbooks on microbiology and cell biology with their engineering perspective in mind so that they might think about features of the system that could be exploited in a synthetic biology approach. I ask them to do this before they get into the literature so that they can bring their untarnished eye to some basic biological principles and concepts. Then I encourage them to bring their ideas into context with the current research literature and see, from the flow of papers coming out, what interesting problems people want to attack.

In the classroom I try to tell stories to the students. Not stories about what happened to me when I went to the supermarket, but

stories that teach the fundamental principles of engineering and physics. The stories show them how these principles apply to real-world problems, whether the issue is how to drug the liver system, how to implement a surgical control system, or how to design an artificial respirator. In each case, I try to build the fundamental principles that address how they, as bioengineers, can exploit these principles and make a difference by putting them into play. I feel their angst when they don't understand why they are studying a topic and how it might be used in their career. I try to show them the application. Students are eager to have an impact, eager to make a difference. I saw one survey where the number one aim of students today was to become famous, which I thought was quite shallow. I don't find my students to be so self-centered. The bioengineering students we get at Boston University (BU) are incredibly motivated. I think students are interested in making the world a better place.

What characteristics contribute to effective mentoring?

An effective mentor is someone who is really candid. If they think that you're not working as hard or working in the right way, they tell you. A mentor is someone who is going to challenge you to take the risk but is going to be on your side when it seems like the outside world is attacking you. If you get tough reviews or grant rejections, you want a mentor who's going to be there to tell you that it's going to be okay. You want a mentor who can really help you identify your interests and know your strengths. A mentor should help you find your path to success. Many students today seem almost paralyzed by the number of choices that they have. They become so fearful that they are going to move in a direction that is irreversible. I think a good mentor will tell them to look at life like a Woody Allen film; when you come to a fork in the road take it. You have to make decisions that affect your career, but almost none of them are irreversible.

How does the inevitable threat of failure influence your approach to new ideas? For example, with the vibrating insoles, did you sit down and try to generate a number of ideas to approach it at the outset, knowing that some of them will fail, or is the progression more linear?

The approach is dictated by the nature of the project. With the vibrating insoles, we started with computer models that allowed us to test many ideas almost simultaneously. Once I had the idea that we could introduce noise to enhance sensory neuronal function, I very quickly began to program model neurons so that we could predict how they might respond. In this case, I was able to easily test the idea in a linear fashion and explore a number of different possibilities very, very quickly. We then moved on to animal studies to show that what we had found in our computer model could work in real neurons. After this, we performed neuropsychological studies in humans. We then carried out perceptual studies in humans and eventually we did a motor study on young and elderly subjects, and finally on patients, to see if we could alleviate their balance problems. In this project, the study design was linear because we were able to quickly cycle through a number of possibilities. Most of our work is not approached in such a linear way.

In a field like microbiology, you can have a boatload of cool ideas that each take months of experiments to generate the feedback that is necessary to know whether the idea is correct or not. I saw that you did some work with Roger Tsien's group, so I'm sure you know what I mean. I found that many of my colleagues in these fields were taking linear approaches and that the time lag did not let them fail fast. My first student in synthetic biology and microbiology, Tim Gardner, was an engineer who brought an engineering approach to his biological questions. He considered multiple possible answers to a scientific question in parallel. Instead of just considering how one construct might interact with a gene, he would consider ten or 20 and was then able to pick out the ones that were the most significant. Using this approach, he was able to design one of the first synthetic gene networks in a relatively short period of time.

How do you make the progressive leaps that carry an idea from concept to a mathematical model, to an animal model system, and then to human trials?

Executing ideas relies heavily on building great teams. You can have some good ideas and be a generally interesting person, but to make a contribution you must be able to execute your ideas. The leaps first happen conceptually, as you imagine how the project might evolve and who might help you. The students and post docs in the lab work together and then reach out to collaborators that are experts in the spaces where we are moving. To a large degree, we jump between fields by collaborating with outstanding people who are already established members of their field. They bring established skill sets and protocols into the collaboration with them. I am often impressed at our colleagues' willingness and enthusiasm to take on risky projects that might be very different from their mainstream work.

So, find the right people to help you along the way.

That is the key. The number one thing you can do to be a great lab director is to recruit outstanding people. If you do that, you'll look like a genius.

And who wouldn't want to look like a genius?

What type of reception do you get from scientists as you move into their fields with such a different approach to the science they work on?

It really depends upon the area. In the case of the work with the vibrating insoles it involved physicists, neurobiologists and clinicians. The physicists and mathematicians were delighted to see their ideas influence medicine. They were absolutely thrilled and greeted the idea with cheers. The neuroscientists were not as open. They were highly skeptical and it was difficult to convince them of our results. Eventually, they came around and became interested. The clinicians were much more open and are actively looking for translational work that might make a difference for their patients. So, each group responded uniquely.

Our first experience in synthetic biology was very different because there was not really a field for it at the time. We introduced a genetic toggle switch in bacteria that allowed us to manipulate gene expression with transient chemical or thermal induction [Gardner et al. (2000) *Nature* **403**, 339-342]. Initially, it did not make a big splash. *Nature* published it, but did not do a News and Views piece to highlight it. The week after it was published, *Nature* presented an editorial that referred back to our paper and one by Michael Elowitz and Stanislas Leibler [Elowitz and Leibler (2000)

Nature **403**, 335-338] that was published back to back with ours. The traditional microbiologists and cell biologists were not engaged by it initially. Most of the interest came from engineers, physicists and chemists who were keen to get involved in microbiology. But the work continually gains interest. *Nature* has just highlighted that work in a tenth anniversary editorial (*Nature* **463**, 269-270). As a result of this and Michael Elowitz's work, a vibrant field of synthetic biology has developed as a gateway to bring new technical and engineering concepts to molecular and cellular biology.

And now you are bringing people with very interesting backgrounds together in the interest of synthetic biology as a founder of the Wyss Institute for Biologically Inspired Engineering at Harvard. As your own laboratory grows, what types of people do you hire to make it successful?

We started with physicists, engineers and mathematicians because these groups were immediately enthusiastic. Increasingly we are recruiting bona fide molecular biologists and cell biologists who want to apply systems approaches to organisms. In the past, I'd say starting in the mid-1990s, I had great success recruiting what I call 'the misfit toys of science'. This might be the physicist who was drawn to biology but could not get collaborative interest from biologists because they did not have a biological background. Physicists were equally resistant to train them because of their biological leanings. I was able to bring them into my lab since they had backgrounds that jived with my background and interests. They tended to be really smart amateurs who, by both their intelligence and their freedom from conventional thinking, were able to make very innovative contributions. Their work has had a pretty big impact.

Although it is initially different, work from people who think between fields is more rapidly understood and accepted than it used to be. When we moved into the antibiotic space, a little over two years ago, with our discovery that all bactericidal antibiotics induce a common death mechanism in bacteria that involves damage from oxidative stress [Kohanski et al. (2007) *Cell* **130**, 797-810], many in the field were highly skeptical. Several of the initial skeptics have now reluctantly come to believe the findings as an increasing number of groups build on them, extending them rapidly. Soon, I think our idea will become an accepted notion. This is an amazing time scale since, in the recent past, it was generally thought that in order to get a truly innovative scientific idea accepted, you had to literally wait for the established members of the field to die. We are moving on a much faster time scale in modern science. There are so many studies coming out that you don't have to wait for the old guards to die, you can just overwhelm them.

Most of your work has been done at Boston University. Are there things about BU that enable creativity?

I think BU made a strategic decision to go after interdisciplinary science in the mid-1980s. University leaders looked around and recognized their presence in the very big shadow of Massachusetts Institute of Technology (MIT) and Harvard. They knew it would be very difficult to compete with them in many traditional areas, particularly those in science and engineering. I think they recognized that there were emerging possibilities at the interfaces of disciplines like biology and physics, or biology and engineering, which would not immediately excite more traditional and conservative institutions. In the early days, BU was leading the charge in this area, which made it very comfortable for someone like me to fit in immediately. BU brought in many innovators like Eugene Stanley, Nancy Kopell, Charles DeLisi and Charles Cantor. Although interdisciplinary science is now becoming the norm, BU cultivated this space before it was popular.

Another interesting feature about BU is the freedom that it gains by not being number one. The university is willing to take risks and to try things without concern for maintaining our position. Here, we look straight ahead with an eagerness to try new things. What I see at more traditional places, whether it be the Ivy League schools or established tech institutes, is an almost institutional reluctance, either in the department at chair level or dean level, to take on risks. At these places, if you take a risk and fail there is a serious fear of losing rank or status. I never felt that fear at BU. Instead my risky ideas were greeted largely with 'that sounds great' or 'go for it'.

That answer makes you the second person to tell me that they wanted to work somewhere that would let them work on the edge and take risks. The other person who said that was Mario Capecchi, who did all of his Nobel Prize winning work at The University of Utah. I hadn't thought about it much before, but of course to be innovative requires the freedom to be unconventional and move away from what is safe.

Is there a particularly vexing scientific question that you would love to know the answer to, perhaps short of the meaning of life?

The big question is how the earliest life forms developed and began to evolve. It's an incredible puzzle that is increasingly the topic of discussion for synthetic biologists. Jack Szostak recently won a Nobel Prize for his work on telomeres along with Elizabeth Blackburn and Carol Greider. He is brilliant and, in the last three or four years, his focus is on approaching life forms from a synthetic biology standpoint. Clearly we won't get an absolute answer, but to get some 'wet' existence proofs would be really exciting. I suspect that Jack will find something quite interesting in the coming few years.

Another vexing scientific question is how to apply engineering techniques to effectively reprogram stem cells into functional new tissues or cell types that can be used to treat patients. Our group is beginning to move into this area in collaboration with George Daley at Harvard Medical School. We are very motivated to bioengineer techniques to bridge injured spinal chord nerves. I think we will see some significant advances in this area over the next decade as molecular cell techniques integrate with tissue engineering and synthetic biology approaches.

DMM greatly appreciates Jim Collins's willingness to share his unique experiences and thoughts with us. His contributions to medicine are rapidly growing and influence many diverse areas. We are grateful to present him as A Model for Life.

Jim Collins was interviewed by Kristin H. Kain, Associate Reviews Editor for DMM. This piece has been edited and condensed with approval from the interviewee.