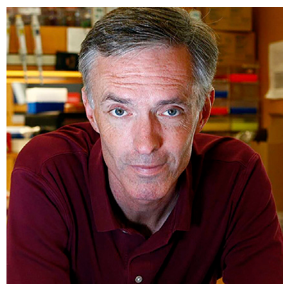
The Future Is Synthetic Biology

Increasingly, synthetic biological systems and molecules are being used to drive biological applications and discovery. At the 2018 Fall Meeting of the American Chemical Society, *Cell*'s Andrew Rennekamp met up with John Glass, Jim Collins, and Floyd Romesberg to discuss synthetic biology as a discipline and to get their take on where it's headed. Annotated excerpts from this conversation are presented below, and the full conversation is available with the article online.

John Glass
J. Craig Venter Institute



James (Jim) Collins
Massachusetts Institute of Technology

Floyd Romesburg
Scripps Research

Andrew Rennekamp: I've been hearing a lot of great talks from you and others on the topic of synthetic biology. One thing that struck me—that one of the presenters said—was that "biology will drive manufacturing in the 21st century." I thought that was a really cool thing to think about: how we're going through a revolution in synthetic biology. What are some things that you're most excited about?

John Glass: I'm dazzled by the things that I see labs like Jim [Collins]'s here doing in terms of building circuits, things that we couldn't imagine doing 5, 10 years ago. In terms of producing chemicals that were unobtainable except through really difficult synthetic organic chemistry and perhaps not even then. During my career at Eli Lilly and the pharmaceutical industry, we would identify, from mixes of natural products, things that we thought might have some antimicrobial activity. And the chemists would just look at it and say, "Nope, can't make that, move on." And now it is feasible to think about getting some things like this made at a reasonable cost. . . . Things are attainable that we couldn't imagine before. . . . I [also] think that there will be technologies that enable us to genetically modify people for therapeutic purposes to improve our lives. And I'm excited about these things.

Jim Collins: I'm excited to see the field [of synthetic biology] moving from an emerging discipline to a developing discipline. At MIT, young students coming in with interest in the life sciences now appear to have three dominate interests: neuroscience, cancer, and synthetic biology. And our field is still relatively young, but the talent infusion is remarkable and encouraging. And within the field, I'm struck by two areas that appear to be developing quite rapidly. One is clinical applications. A large number of groups, academic and growing industrial interests, [are] harnessing synthetic biology to get after novel therapeutics and diagnostics, using viral or what we call living bacterial and mammalian systems. But also, I think an underappreciated and under-addressed aspect of the field is the second area. And that is, I like that a number of groups are turning to synthetic biology as a tool to probe basic questions in biology. I think synthetic biology is well positioned now to become the patch clamp for molecular biology, by using the tools of synthetic biology to get after questions of control via transcription to translation aspects of regulation at systems level that really were unattainable a decade or two ago.

Floyd Romesberg: The sort of synthetic biology that we do in my lab I think is a little bit different. We tend to focus on building synthetic molecules that are then used in biological systems. I think that's [also] kind of similar in that [we are] taking the core disciplines and approach that has developed in synthetic biology and applying it in an area that brings in a little

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bit more chemistry. And I think that also speaks to the sort of draw that synthetic biology has for people in traditionally different disciplines to come in and work and apply their discipline in a more biological system. And then drawing on something you [both] said, I think that protein therapeutics is a particularly interesting and powerful thing. And I think that synthetic biology is going to play a big role. Not only simply in the production of valuable proteins that people want to get in large quantity and scale, but also in their modification and exploring a sort of medicinal chemistry on proteins to produce different sorts of therapeutics with desirable properties.

AR: So what is your dream experiment? If you could do one thing in the realm of synthetic biology, what would you?

FR: We have an unnatural base pair that we can now use in bacteria that now can be stored and replicated and translated into protein. . . . And we're beginning to toy with the idea of starting to create semi-synthetic organisms—try to create new forms and new properties at the organism level—and the reason that's so exciting is the sort of selections that you could do to try to harness new functions. That's pretty pie-in-the-sky, and that's something that we think about.

JG: Certainly something that we think about at the JCVI, where we have built our synthetic organism, is going down the street to Floyd's lab and seeing if we can convince him to start working with us to have us synthesize genomes that utilize his chemistry and seeing what we could do in terms of really designing an organism around such things.

FR: Okay. [everyone laughs]

JG: I mentioned more applied things in the first question, but the thing that's driven me and our group at the Venter Institute for the last 15 years is this idea of really understanding how life works. How the cells work. What does every atom in the cell do? What's its role? Every gene, every protein, everything. So that you could understand cells at a level that just wasn't practical before. And in our study of this minimal organism we made, we were astonished to see that for a third of the genes in this organism, we don't know what they do. And most of those genes are conserved across all domains of life. . . . After 100 years of serious biology, we still don't know so much about these absolutely simple systems that are still at the kernel of life. That's what keeps me going as a synthetic biologist.

JC: What I see is three critical capabilities that I think we need to build upon, and then I'll mention the ideal experiment. First, I think John's point is spot on, I don't think we know enough biology to engineer biology efficiently. I don't think biology's close to being an engineering discipline yet. And thus, we need to better expand our understanding of biology and couple it to design principles and design platforms to enable us to either build molecules or circuits or whole genomes that function as desired. It's still incredibly hard to do so. And I think it goes to the point that we don't understand how the different components actually fit together in a biological context. The second is that I think we're still playing with very few parts. I'm glad to hear of Floyd's work. We need to expand our toolkit of available parts and components. I think we have to enhance our ability to harvest from nature what's out there. For the most part, we're still using a few dozen parts in a reusable fashion in synthetic biology. And we need to expand that to hundreds of thousands and millions of great diverse parts. And then third, in this scenario that the JCVI has been pioneering, is that I think we need to significantly enhance our ability to synthesize DNA in a rapid, inexpensive, error-free way. We're not there yet, where somebody like me at a circuit level would use synthesis to make my circuits. I'm still using old cloning methods. So, I'll give you my ideal experiment right now. Could I create highly conjugative bacteria that would enable me to distribute synthetic circuits, say for example, in a microbiome? That will allow me to re-functionalize a microbiome to either address illness (say a bacterium, go after a bacterial infection) or to re-functionalize it to endow a human with novel properties. Be it to break down lactose or break down gluten so as to address a clinical need.

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AR: You mentioned some hurdles: we need more knowledge, we need more tools, we're not taking advantage of the diversity of what's out there. Are there other hurdles that you've encountered that are keeping you from realizing these dream experiments?

JG: I think DNA synthesis has gotten so cheap and so easy, and it's going to keep getting cheaper and easier, but installing what you build, as what you build gets larger, I think is going to become the limiting factor. We develop this genome transplantation technique, but we can only make this work in a small group of bacteria. Whereas the conjugated methods that Jim talked about are the best we can do, but if I can build a genome in yeast and then install it in any cell I want in a way that it works, that would be truly brilliant and would enable so many things. The notion of making really synthetic organisms—that is ramping up in the US, China, Germany, and the Netherlands—I think that there's real potential to use all the tools of say, yeast genetics. A Chinese group was able to make a single

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chromosome that's 12 mega-bases. So if you can build a 12-megabase synthetic genome and then install it or parts of it in anything you want, that would be incredibly enabling for our field. So it's not the synthesis that's the hard part; it's the booting it up.

JC: To pick up on that, I do think that delivery remains a major challenge for us. Particularly in mammalian synthetic biology. If I think back to the very early days of synthetic gene circuits, when we introduced the bacterial genetic toggle switch in 2000, in my talks I would indicate that I think the field could play a big role in gene and cell therapy from a control standpoint. And my comment then was: once the fields of gene and cell therapy work out safe and effective delivery means, [synthetic biology is] going to come in to provide control and safety. But I don't think the fields have worked out, in a suitable way, safe and effective delivery means for the larger circuits of the type we do let alone genomic elements of the type that John and company do. So there's a big challenge yet figuring out how do we get into the cells what we want to get in.

FR: Synthetic biology, I think, has really developed into a spot where you can ask fascinating questions. They're challenges, but it's also a means to generate really interesting answers. Answers that you would not have been able to think about or questions you wouldn't have even asked before. But building out the sort of associated biology around the sorts of things that synthetic biologists build and deploy in living cells is both an opportunity to learn, sort of in a unique way, and also just a really exciting idea.

JG: And this is why our teams will have non-biologists on them—engineers and computational people—this is where you get ideas for solutions that you wouldn't get in a traditional biology lab. No matter how smart your team is, it takes these different ways of looking at things, and this is how I see so many groups doing so many remarkable things with these diverse approaches.

AR: So, if you were going to advise a student in how to become a synthetic biologist for the future, what kinds of things would you have them pursue? What different areas could they strengthen to develop as their toolkit to become a synthetic biologist?

JC: Maybe I'll pick up here, and I'll pick up on John's point. I think we certainly are an enthused, current field. It's a young field. I would not encourage a young person to major in synthetic biology; I think that would be a mistake. I think the beauty of our field is that engineers, physicists, chemists, biologists, and computational sciencists can all come together. And I would encourage a student to find his or her passion in a traditional area, go deep in that traditional area and then team up with a synthetic biology lab, leveraging their strength in that space to get after the biology or the biotechnology.

FR: Yeah, I agree with that completely. But the only thing I would add to it is that you also have to sort of passionately pay attention to what's going on around you too. Science has been traditionally very walled off, and I think that you do have to become an expert in something, be it a synthetic chemistry or biology or computational or systems biology or whatever. But at the same time, constantly be trying to learn about the sort of surrounding areas and the opportunities to apply your interests.

JG: As a chair of a synthetic biology department, I'm being asked to hire synthetic biologists. And I say, "I don't want synthetic biologists." I want someone who's passionate about some area of biology that would fit in with the JCVI, but I want them to be wanting to use the synthetic biology approaches to deal with that area of biology. But I want real, great knowledge in some area of biology, because I think that's a harder thing to find—someone who can assemble genomes efficiently or assemble pathways efficiently.

AR: I have one last question for you guys. Is the world ready for synthetic biology?

JG: Like it or not, there's no putting this cat back in the bag. I believe that in my lifetime, we will see someone with nefarious intent use synthetic biology in a bad way to cause mayhem, terrorism, you name it. But I also believe that this same technology is going to save the world. I have faith in what we do and its potential. Every technology is a double-edged sword: with language you get Shakespeare and slander, and with synthetic biology you're going to get really great things and maybe a few bad ones.

JC: I think synthetic biology will become one of the defining technologies of this century. And to pick up on John's point, I think it will contribute to solving some of the world's big problems, including those in health, those in food, those in the environment, and those in energy. Any technology has dual-use potential, and I think in this case we squarely do, and I think there'll be a need to continually educate the public about the benefits and potential risks. And I think the field has done a good job of getting out in front. But I think it's a very exciting time for the field and, for now, the impact that I think we're beginning to see on the broader world. There's never been a better time to be a biologist.