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<MT>IB Interview

<CT>A Conversation with Jay Keasling, Ph.D.

<CA> Jay Keasling

Professor, Department of Chemical & Biomolecular Engineering and Department of Bioengineering, and The Hubbard Howe Jr. Distinguished Professor of Biochemical Engineering at University of California, Berkeley; Director, Physical Biosciences Division, Lawrence Berkeley Laboratories and Synthetic Biology Engineering Research Center; and CEO Joint BioEnergy Institute (JBEI)

INDUSTRIAL BIOTECHNOLOGY: *Dr. Keasling, congratulations on receiving the George Carver Award for innovation in industrial biotechnology from BIO. This award was conceived to honor an individual who has worked successfully toward the goal of using biotech innovation to develop sustainable biobased value chains. Please tell us what receiving this award means to you.*

JAY KEASLING: Thank you, and thank you to the BIO for the award. I really appreciate it, and it means First, I am an academic, I am not in the industrial side. I try to do science and basic research that will apply to the industrial side, because I'm really interested in getting products to people. One of the first things we worked on was artemisinin, and the goal was to get a product to some of the poorest people in the world. It could save the lives of more than a million children a year. So as an academic, this award from an industrial organization and this recognition from industry has special meaning. It means I am doing something that industry notices and uses and that might benefit people. Generally these types of awards go to industry folks, so it is especially an honor to receive it.

IB: *Throughout your career you have, and currently do wear many different hats. This has undoubtedly given you a broad perspective—from academia, industry, and government—how does this shape your vision of industrial biotechnology?*

JAY KEASLING: I do wear many hats. Most of those hats involve managing or doing science in some way. I am very interested in doing science that will benefit the public, and I am very interested in biology; when you put those two together you get industrial biotechnology. I think we can do so much with biology. It is still very hard to engineer biology to solve problems, but there are so many problems that need to be solved. Industrial biotechnology will be a real growth area for the world. It is a way we can begin to save the planet, to produce renewable products in environmentally ways, we can begin to pull some of the carbon out of the atmosphere and put it into our products and limit the amount of carbon we put into the atmosphere, and create fuels that will burn cleanly in our automobiles. There is so much promise and I am really excited about the future of this industry.

(Does that answer this question at all?!)

I have been very fortunate in that I have been able to experience industrial biotechnology from basic science all the way through application. The basic science in my laboratory through teams

of scientists working together in a national laboratory, in JBEI, where it's focused on teams working on the problem of turning cellulose into biofuels, and then through founding companies in which we are taking the basic science and turning it into a process. So I have had the opportunity to experience all of those aspects of the field.

I think it does shape how I feel about the field and the types of projects I take on, and I think it influences how I educate others. Many graduate students and postdocs come to my lab now because we do biology with some application in mind--use-inspired biology. So we are not only creating these companies that are producing products, but we are also contributing to the next generation of scientists and engineers who will found more of those companies and enable this area to grow even more.

IB: *the people working their individual "silos" whether they be in academia, industry, or government laboratories, do you have a message for them based on this broader perspective.*

How can private industry work more collaboratively with academia to stimulate and accelerate commercialization of new biotechnology advances?

JAY KEASLING: The first thing I would say is not to look at the silos, but instead to try to break down the silos wherever possible. That's really hard, because we are talking about academic and government labs and the corporate world. How do we break down those silos so the researchers can talk and interact more, because that is the real key. We need to get the basic science funded and out of the laboratory as quickly as possible and into companies so they can test it. We want basic scientists to work on the questions that are really hard and may be game-changers, but that companies--even a large company--might not have the fortitude to stay with for a decade. Those are the types of problems we should be pursuing, especially in government laboratories.

So the first message is to break down the silos and figure out how to work together. I think there is a lot that government could be doing to stimulate this interaction. More grants that would bring together industry and academics that would bring together scientists and stimulate them to work together. I think industry could be doing more to communicate the problems to academics. As academics, we can think up all kinds of scientific problems and ask all kinds of scientific questions, but we do not necessarily know the best questions to ask when it comes to how to commercialize a product or what are the most important products to work on. We need more dialogue from industry to academics expressing the key areas to pursue that could be game-changers for industry.

IB; *What are the next innovations that will further enable advances and new applications of systems biology? For example, what will be the impact of the ability to back-translate from an amino acid sequence to a fully functioning, high-level expressed gene?*

JAY KEASLING: This is just my perspective. We are now able to sequence DNA really well, and we have a set of rules and a parts list. We don't really know what the rules mean, though, because we do not yet fully understand how to translate that language when we sequence a genome. What we would like to be able to do is to put genes together and get them to function so we can produce a product, an organ, the next biofuel, or the next chemical. We are getting better and better at writing DNA, although it is still not as cheap as it needs to be.

What we still lack is how to put all of the parts together--the genes and the control systems--to make a functioning whole. I think a large unmet need is computer-aided design for biology. If you were to write a whole genome, what would you write? What story would you tell in that genome? We have a story to tell, but we do not yet know how to tell it because the genome is complicated and we haven't captured all of the complication in accurate models. This makes it very hard to design biology. We need the tools that will enable us to design biology better.

I mentioned the story of artemisinin and how long it took us to build a microbe to produce artemisinin [*Editor's Note: see excerpts of Dr. Keasling's acceptance remarks following the interview*]. It is one of the most complicated metabolic pathways industrially or academically engineered, and yet the timescale relative to other accomplishments really weren't that long. This reflects just how "bad" we are in building biology. Computer design tools could help us immensely and I think we should be moving in that direction. There are countless other innovations I could think of, but this one is at the top of my list. It would make the science we are doing so much easier. If all of the students in my lab and all of the scientists in companies could design and build microbes in silico rather than at the bench, send out the instructions, and have the microbes synthesized and sent back, that would be fantastic.

That is how the microelectronics industry works. You design it on the computer, send it out to be fabricated, they send it back, and you test it. We're not there yet; we're a lot way away

IB: What are the next big societal challenges in which systems biology can be utilized, such as addressing issues related to air quality or water supply and quality?

JAY KEASLING: Oh gosh, there are so many challenges. Let's take one that was promised at the dawn of genetic engineering and still hasn't been realized: engineering plants to make their own nitrogen fertilizers. We expend huge amounts of energy and put a lot of carbon in the atmosphere producing ammonia fertilizers. I think it's about a third of the energy in agriculture in the US and 1% of the world's energy goes to producing nitrogen-based fertilizers that are basically used to fertilize corn in the US. Imagine if that corn could fix its own nitrogen. It's a huge problem. If corn could self-fertilize, we would save a lot of energy and produce less carbon, and even people in the developing world could grow it without having to apply fertilizer.

Having crops that are drought-tolerant. If we look at how the planet and climate is going to change with the carbon we have added to the atmosphere, drought is one of the big problems. If you look at a map of the US, the projection for many decades into the future is that it will get much drier, and yet the population of the planet is going to grow. We are going to get

up to 9 billion people. How will we still provide the necessary food and all the biobased chemicals we want to have.

IB: In the industrial biotechnology arena overall, what do you envision as the top technology breakthroughs that will emerge over the next 5 years?

JAY KEASLING: Bringing back the woolly mammoth!

Is that on your "bucket list?"

No, but it's on some peoples' bucket list.

I'll tell you what I would like to have. I would like to have designer microbes that are built for the chemicals we would like to produce. I would like to be able to rebuild a bacterial or yeast set of chromosomes and the "bag" it sits in so it is designed to produce the products we want to synthesize. I would like to have processes in which we would not have to sterilize the process before we produce the chemical we want, in which the microbe could fend off its competitors and still produce our product. I would like to figure out how to grow crops not in monoculture, so we could have built-in crop rotation and plant multiple crops together in a field that could produce food and fuel, for example. I would like to have crops that could be modified in a way so they would not just produce starch, but after you collected the starch you could then collect the rest of the plant for something else. So the plant would be modified in multiple ways and not just selected for one property.

These are "small" projects--they'll only take a couple of decades.

Oh, the next 5 years. I would like to see us be able to produce any chemical we now get from petroleum, but from a renewable feedstock. I think that is a big challenge, but I think we're up to it. Innovations in how you design enzymes and translate that into producing replacements in petroleum-based products is something we could achieve in the next 5 years.

IB: *How do you see the federal funding landscape for industrial biotechnology research and development evolving over the next 5 years?*

JAY KEASLING: I'm really worried about the federal government and its plan for industrial biotechnology and even biology. I think there is a lot of opportunity, and the US has been the leader in biomanufacturing for the last four decades. There is a risk that we could lose that leadership, and I think the government has the opportunity to make sure we do not lose that edge we now have. If you look at many other countries, they have solid plans about where they want to take synthetic biology. I don't think the US yet has such a plan. It's not too late, but the government needs to have a plan. We have shown over and over again that if we have a plan, like we had for nanotechnology, the US can continue to be in the lead.

There is no doubt we are the innovation capital of the world. But maintaining that status requires a plan, especially when you have potential spending cuts. You need to have a good plan for what you are going to do with that limited funding. We have plenty of people to help with

those plans, and BIO is a great way to work with industry on such a plan. We need more dialogue on what industry might need. That is not to say that industry's needs should drive all of the funding or policy decisions, or all of the academic research, but we should be aware of that. Industry has to communicate that information in a way that academia can pick up on it and the government can start to create programs around it to maintain our leadership.

IB: *If we had a time machine and could jump ahead 10 years, to the 20th anniversary of the BIO World Congress on Industrial Biotechnology, what do you think the biofuels and renewable chemicals industry will look like in the U.S.?*

JAY KEASLING: The optimist in me says that the biochemicals and biofuels industries will be vibrant by that time, and especially the biochemicals industry. We will be producing renewable plastics, renewable fibers for our carpets, and a whole host of products we currently produce from petroleum will come from sugars and other feedstocks. I think we will have a lot of fermentation facilities in the US, and we will continue to build those outside the country to gain access to cheaper resources. So the optimist in me thinks we have a very bright future.

The pessimist in me worries about government policy and making sure the government has stable policies in place. Those policies do not have to favor the biochemicals and industrial biotechnology industry, they just have to be stable over time and to level the playing field. The worst thing is to have policies that fluctuate over time.

A venture capital speaking about the healthcare industry once said to me that what government policy was did not matter as much as having stable policies. They would deal with whatever the policies were and find a way to optimize around them over time, but the most difficult scenario is when the government changes the policies all the time.

The biofuels industry, for example, does not need a hand-out from the government, it just needs stable, level policies. The government would not have to give a dime to help the biofuels industry if it would just put some regulation in place, some value on carbon. If it were a long-term value on carbon, there would be no question the investments would be there. You could take it to the bank!

The optimist in me sees the rapid change taking place in biology. It is growing faster than any other technical field. If you plot any aspect of biotechnology against Moore's Law, biotechnology is growing at a faster rate, and that is a great thing. The optimist says it is going to be a vibrant industry.

That was painless!