

3 Takeaways Podcast Transcript

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Ep 44: Harnessing the Power of Artificial Intelligence and Synthetic Biology To Usher In A New Age of Drug Discovery: James Collins

INTRO male voice: Welcome to the 3 Takeaways podcast, which features short memorable conversations with the world's best thinkers, business leaders, writers, politicians, scientists, and other news makers. Each episode ends with the three key takeaways that person has learned over their lives and their careers. And now your host, and board member of schools at Harvard, Princeton and Columbia, Lynn Thoman.

Lynn Thoman: Hi everyone, it's Lynn Thoman, welcome to another episode. Today, I'm excited to be here with Jim Collins. He's a professor at MIT, a member of the Broad Institute, and a core founding member of the Wyss Institute for Biologically Inspired Engineering at Harvard. He's one of the founders of the new field of synthetic biology. Jim has made numerous breakthrough discoveries, including a completely new type of antibiotic called halicin, which kills two of the three most deadly bacteria in the world. Today, I'm excited to learn how artificial intelligence and synthetic biology are revolutionizing innovation. Welcome Jim, and thanks so much for being here today.

Jim Collins: Thanks for having me on your podcast, Lynn. Very much appreciated.

LT: My pleasure. Jim. Can you start by telling us what is synthetic biology?

JC: Synthetic biology is still a relatively new field that's bringing together engineers with molecular biologists to use engineering principles to model, design and build synthetic gene circuits and other molecular components, and to use these circuits and components to rewire and reprogram living cells in cell-free systems, endowing them with novel functions, enabling a broad set of applications in the real world.

LT: Does that mean reprogramming bacteria and other organisms, much like we program computers today?

JC: In a sense, yes. It very much involves introducing circuit elements. In this case, they're not electronic circuits, but they're wet biological circuits made out of molecular components like genes and promoters, which are on-switches for genes and other basic DNA and RNA, and to use these to endow living cells, including bacteria with, for example, the ability to sense their environment, make a decision about what they sensed, and then act on the environment. And so in many ways it's leading to programmable cells that will serve as a form of living technology for this coming century.

LT: In what ways has synthetic biology impacted the COVID pandemic?

JC: Synthetic biology, it really had a coming of age and a coming out with this pandemic in multiple ways, but the two most prominent are that the synthetic mRNA vaccines, I think are an excellent demonstration of the power of synthetic biology. So for example, in Moderna's case, this

was technology that our lab had a role in co-developing, going back over a decade ago where we teamed up with Derrick Rossi and George Daley, our colleagues at Harvard Medical School, to create synthetic mRNA that was altered in its sequences that could then be delivered to cells directly without triggering viral responses in the cells, that would not be readily degraded, but could lead to high expression of protein. And we initially set this up to deliver proteins that could be used to reprogram a mature cell to make it into a stem-like cell. We published it, and Derrick Rossi actually took the technology and teamed up with a number of our colleagues to launch Moderna, and this synthetic mRNA technology underlies Moderna's vaccine, and a related technology underlies Pfizer's vaccine for COVID-19.

JC: Second big space is around diagnostics. Synthetic biology tools have led to the development of rapid diagnostics for SARS-CoV-2. Notably a number of efforts, including one that came out of our lab and is part of Sherlock Biosciences, uses CRISPR technology integrated with synthetic gene circuits to create a rapid, inexpensive, highly sensitive and highly specific diagnostic for SARS-CoV-2. And in the case of Sherlock Biosciences, COVID testing was approved by the FDA in May of 2020, becoming the first CRISPR product that was approved by the FDA, and since then it's been adopted by three global diagnostics companies who are on pace to use it in three million tests this year, and it's been adopted by the country of Nepal as their national test.

LT: That is terrific. How can synthetic biology take on some of the world's biggest challenges?

JC: Synthetic biology, which is really working hard to transform biology into an engineering discipline, I think is going to become one of the dominant technologies for this century and will be harnessed to help address some of our biggest challenges, starting with food and water. We see efforts now underway where synthetic biology is being used to identify heavy metals and other contaminants in water as well as to filter them. In food being used by companies like Indigo Agri in order to deliver synthetic ecosystems to seeds, endowing them with the eventual plant with new properties. I think synthetic biology is going to be harnessed to address challenges in climate change sustainability leading, for example, to bioplastics being produced by bacterial and plant products, leading to a means to better sequester carbon from the atmosphere. Developing, for example, plants that utilize more efficient means than photosynthesis for sequestering carbon as well as plants and other vegetation that have been programmed to grow faster to cover the planet.

JC: I think we'll see a resurgence back toward bioenergy, which had been a very big focus for synthetic biology going back about 15 years ago. But the efforts found that the efficiencies were too low to compete with fossil fuels, but in looking out ahead several decades, we're going to need to have significant alternatives to fossil fuels as we use up our [inaudible]. And I think as synthetic biology advances on efficiencies, we'll squeeze down those price points to make it more competitive and as a reasonable alternative. And then finally, the space that we're very active in, I think synthetic biology is well-positioned to revolutionize the way we come up with diagnostics, the way we come up with vaccines, the way we come up with therapeutics, and will lead to new classes in each of those. Basically enabling us to rapidly program new diagnostics, rapidly program new vaccines, rapidly program new therapeutics to address a range of emerging pathogens as well as more complex diseases like cancer.

LT: Can you tell us a bit about why there's an antibiotic crisis and how you are harnessing synthetic biology to address it?

JC: In the midst of the COVID-19 pandemic, which truly is a major global crisis, we have another infectious disease global crisis underway, and that's around antibiotic resistance. We've had antibiotics for of par a century. They really are medical miracles that have saved millions of lives. We generally think of antibiotics as curing bacterial infections, which is actually true, but they do much more. Antibiotics have really ushered in the modern medical age, enabling safe surgeries, enabling cardiac implants, enabling joint implants, enabling activities of daily living like getting a blister to be safe and not life-threatening. Unfortunately, the age of antibiotics is coming to a close due to two competing challenges. One is that the number of resistant strains is growing. This is due to the overuse of antibiotics through prescriptions to human patients, but also overuse in the agricultural business as a prophylactic for livestock.

JC: These resistant strains in the past were limited to a hospital. Worst place to be when you're sick is a hospital. Get out as soon as you can because of these superbugs, but unfortunately these resistant strains are now out in our communities. They're in our childcare centers, they're on our athletic fields, they're in our university settings, they're in our campus settings. That situation is coupled with problematics on the economics, which is the economic market is broken for antibiotics. Over the past few years, with each year, another major biotech or pharma has gotten out of the antibiotic business, and they're doing so because it costs more or less just as much to develop an antibiotic as it does to develop a cancer drug or a blood pressure pill. And whereas with an antibiotic, you might take a single dose or use it for a few days, a blood pressure pill you could take for the rest of your life. And so from an economic standpoint, the business model is much better to go after these chronic conditions versus the acute.

JC: And so we face a big challenge. Right now it's roughly about 1.5 million deaths per year around the world from antibiotic-resistant infections. It's been projected if we don't address this crisis, that number could grow to 10 million per year, outpacing deaths due to cancer by 2050. And so we have a huge challenge in front of us. We think that emerging technologies like artificial intelligence can be harnessed to address this crisis, and we, to do so have actually launched very recently the Antibiotics AI Project at MIT, with support from The Audacious Project that's run through TED to really go after this with the audacious goal of developing a completely novel class of antibiotics over the next several years against some of the world's nastiest pathogens using AI.

LT: How did you discover halicin? Could you have discovered it without artificial intelligence, without computers?

JC: It's possible that it could have been done. Halicin was a molecule that we found in a drug repurposing library, and it had been initially under development as a diabetes drug. So I think with smart screening and directive screening, somebody could have uncovered it as a very powerful antibiotic as we did. Nobody was looking for it where it was, and it wasn't obvious because it looks very different than any known antibiotic. But it sets up nicely to just share how we found it, and I can speak to then the value of it. So we teamed up with Regina Barzilay and Tommi Jaakkola, two of my faculty colleagues at MIT, both of whom are experts in AI and set up a very simple unfunded project to start to see if we could use AI to discover new antibiotics.

JC: And what we did was we brought together 2,500 compounds, 17 FDA-approved drugs, and 800 compounds found from nature. We applied these to e-coli, a bacterial pathogen that's also used in molecular biology labs around the world, and asked which of those molecules exhibited antibacterial activity. We took those data, along with the structure of each compound, and then

trained an AI model, a deep neural net in a computer, to associate the structural properties of each compound with whether or not it exhibited antibacterial activity or not. We then took the trained model and initially applied it to this drug repurposing library that included 6,100 molecules, and then we asked the model to do two things. One was identify compounds and molecules that are predicted to be good antibiotics, and, two, to identify amongst those, molecules and compounds that don't look like any existing antibiotics.

JC: Only one molecule fit both of those criteria and that molecule turned out to be halicin, which as you shared in the introduction, is this new, highly powerful antibiotic that works against multi-drug resistant, extensively drug-resistant and pan-resistant bacterial pathogens, as well as some of the nastiest ones on the World Health Organization's list. We then went the next step and took that trained model and applied it to the ZINC database that included 1.5 billion molecules, which would be impossible for any group, including a large pharma, to screen empirically in a lab. We looked at a significant portion of the library, and in just three days could screen that significant portion in a computer. Again asking which of the molecules are predicted to be good antibiotics but don't look like existing antibiotics? Now, in this case, several hundred fit those criteria. We looked at about two dozen of them, eight of which exhibited strong antibacterial activity, two of which had very broad spectrum against again a wide range of nasty pathogens, and we're now pursuing one of those two that we've called Salicyn as a potentially new antibiotic.

LT: You mentioned cancer, can you tell us a little about new approaches to fighting cancer?

JC: There are a couple. One, I'll start from where I've just ended, the AI approaches are opening up possibilities now to find new molecules that could work against cancer, using AI screening, just as we did to find halicin. So there was nothing specific about our AI approach in the model creation for antibiotics. What was specific about antibiotics was the screen we did, which was look to see which compounds worked against e-coli. We have efforts underway now to see can we set up screens against cancer cells that would allow us to look at a much wider chemical space to identify new and potent anti-cancer drugs. In the synthetic biology world, there's two efforts underway. One is engineering bacteria to go after solid tumors. So one of the companies that was spun out of our lab, Synlogic, actually has human clinical trials underway where they've engineered bacteria that can be injected into tumors to stimulate immune responses to fight the tumor. And in another company that was spun out of our lab, Senti Biosciences, that I co-founded with Tim Lu, which Tim is leading, Tim is engineering human cells, so human CAR T-cells with synthetic gene circuits that enable next-generation CAR T therapies to sense multi-antigens on tumors, that can then be used to go after a broad range of different cancers and Tim's company soon will be launching clinical trials testing this new technology.

LT: You are also working on new classes of medical devices like face masks that can detect COVID, as well as vibrating insoles. Can you tell us about the new classes of medical devices that you're working on and that you see on the horizon?

JC: I'll speak to the face mask, because that's the one that we're currently engaged in. And our efforts around the face mask diagnostic grew out of our interest in trying to have an impact on COVID-19 pandemic. And this effort grew out of a special space, which we helped pioneer was around freeze-dried, cell-free synthetic biology. What does that mean? We initially started getting after cell-free systems, so it's possible to open up a living cell and take the machinery out of living cell out of the cell, and play with it in a petri dish or test tube. In this case, the machinery would be

DNA, RNA, ribosomes and other molecular machines and molecules, like ATP and nucleotides. This has been done for over six decades in molecular biology. In our lab, we showed that you could take those cell-free extracts, along with synthetic biology constructs, they could be biosensors or synthetic gene circuits, spot them on paper, freeze-dry them and sometime later rehydrate them, and what you had freeze-dried, would then function as if it was inside a living cell. And we use this as the basis to create paper-based diagnostics, that we initially did for antibiotic resistance.

JC: We then did it for the Ebola crisis, we did it for the Zika crisis, then we developed paper-based diagnostics also for the COVID-19 pandemic. But what we also uncovered was that this freeze-drying capability was not limited to paper, it could be extended to other porous substrates, including clothing. And so prior to the pandemic, we were advancing efforts to create wearable synthetic biology elements where you could freeze-dry cell-free extracts, along with synthetic biology biosensors to create wearable diagnostics for first responders, to healthcare personnel for the military. In response to the pandemic, we looked to see if we could repurpose this technology to create a wearable face mask. And what we did was really straightforward, was the idea, could we create an insert using freeze-dried, cell-free synthetic biology that could be added to any face mask with the assumption you would then wear it, and the normal act of breathing, talking, coughing, sneezing will give off water vapor, water droplets.

JC: If you're infected that water vapor or those water droplets will contain viral particles, that could be captured, detected, and give a readout. And we showed that we could develop these wearable schemes using and developing foldable paper-based microfluidic castings that could be just added. We could collect the vapor, process it, and then detect, with high sensitivity and high specificity, so we could differentiate COVID-19, SARS-CoV-2, from other circulating Coronaviruses. And we've now expanded this face mask diagnostic, so that it could be multiplexed, and not only report out do you have SARS-CoV-2, but do you have, for example, the seasonal flu. And so we're excited about where these wearables could open up possibilities, really for more surveillance testing than a rigorous diagnostic but it's something that you or I could wear as we go for a walk or before we go to our jobs or to school, and give us an indication, oh, you might be infected with something, you probably shouldn't be interacting with others.

LT: Your lab is also working on vibrating insoles that provide sensory enhancement to the feet of users. Can you tell us about those?

JC: This technology goes back to efforts we did a couple of decades ago, and there we showed that it was possible to introduce small amounts of noise, and by noise, I don't mean a loud sound, but by noise I mean static. So it would be a random signal. It might be electrical in nature, or mechanical in nature. So from the mechanical, it might be a vibration you would feel if you're riding a subway or a train. We showed that if you deliver sub-sensory levels of this noise to a sensory neuron, that might be on your fingertip, or on the soles of your feet, you can enhance its ability to detect very weak signals. So we got excited about how this could be used in the context of older people, or individuals with stroke or Parkinson's disease, where their thresholds for detection have become elevated as a result of aging, disease, or injury. And then introduce devices that could enhance their sensory function, thereby enhance their motor function, the ability to move. And we showed that you could create vibrating insoles, that could deliver a very low dose amount of vibration to the soles of your feet. Enhancing the ability of the sensory nerves at the bottom of your feet to sense where you are in space, how much load you're doing, and thereby improve your balance. And most stunningly, we showed that with the vibrating insoles, you could enable a 75-year-old to balance as

well as a 25-year-old.

LT: Just amazing. How do you think that the COVID pandemic will impact synthetic biology?

JC: I think the COVID pandemic, as I mentioned, enabled synthetic biology like a coming out party, to show how our approaching biology as an engineering discipline could have very rapid and meaningful impacts. I think in looking at a larger level, one of the positives one could think of is, coming out of this pandemic as a positive, is I think it will serve to encourage more young people to consider synthetic biology and broadly infectious disease as an area worthy of their study. For the young folks at MIT who entered interested in life sciences, they're two dominant areas of interest, neuroscience, and cancer. Both areas of tremendous input, both areas with exciting tractable problems. I think that the pandemic will encourage young people to expand their interests to include infectious diseases and to include synthetic biology. And for sure, we need as much talent as we can to come into these fields, because these challenges are going to continue to come at us, and I remember saying years ago that the next pandemic is coming, we don't know from where, we don't know when, and unfortunately, the next pandemic is coming, we don't know from where, we don't know from when. And I'm hopeful that engaging our young people will put us in a much better prepared position to handle the next pandemic.

LT: I certainly hope so. Jim, is there anything else that you'd like to mention that you haven't already touched upon?

JC: I've been really encouraged at how many folks have stepped up and responded to the challenges faced by the COVID-19 pandemic, and I think it speaks to the value of motivating folks to have an impact. And I think it's helped to reground us that profit shouldn't be the prime driver in much of what we do. It's really about having an impact, and so from that, and again, I see a secondary positive outcome of this pandemic.

LT: What are the three key takeaways you'd like to leave the audience with today?

JC: To give three key takeaways around innovation, particularly for young people, that if you're thinking about doing innovative work in whatever your space is, I can speak more from the research, but in scientific research and beyond that. One is that I think to be innovative, it's critically important to become an expert, and I think that's undervalued by our young people. And, it's making a commitment to learn as much as you can about a particular area of discipline, to become as good as you can in the fundamental properties of that discipline. Be it scientific researcher or it might be painting or some other art form, but being an expert is putting in that time and truly embracing it. I'm an anti-authoritarian, I don't like authority. Authority is given to someone by an institution. Expertise is earned by putting in the work, and expertise is not a matter of having a large number of followers or a number of likes. It's putting in that work.

JC: Second is, that if you're going to be innovative in today's crazy world, you really need to carve out time in your day where you do nothing and allow yourself the time to daydream. Allow yourself the time to uncouple and to live in your head. Where if you're going to put in that time to be an expert, the machines can only do so much for you. Your best device to find those innovative leaps is your brain, and if you've put in that time, to put in the content, to put in the experiences in your head, you then need to give yourself time to make those connections and be comfortable with doing nothing. And it can seem like it's unproductive for a day, or week, many months, and it may be

unproductive in the short term, and by appearance. But it's those quiet moments that I think can really lead to innovative leaps and insights.

JC: And then third, from an innovation standpoint I think in so many areas, and I mentioned it at the end of what I found very positive about the pandemic is that we increasingly need teams, collaborative teams to go after these challenges in innovative ways. And if you aspire to be a team leader, I think your number one job is to figure out how to recruit and foster talent. If you can recruit and foster great talent, you will be a great team leader, and so it's putting in that time and learning how to do it.

LT: Jim, this has been great, thank you so much.

JC: Thank you, Lynn.

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