[MUSIC]

**DAVID BAKER:**

Generally, in engineering and biology, if you want to solve a problem, you go look in nature for a protein that already does something similar, and then you modify it a bit. The relationship between sequence and structure has been really mysterious, but now we can actually design proteins with intent to do new things. So, I think it’s just getting to be very exciting.

**KEVIN SCOTT:** Hi, everyone. Welcome to Behind the Tech. I'm your host, Kevin Scott, Chief Technology Officer for Microsoft.

In this podcast, we're going to get behind the tech. We'll talk with some of the people who have made our modern tech world possible and understand what motivated them to create what they did. So, join me to maybe learn a little bit about the history of computing and get a few behind-the-scenes insights into what's happening today. Stick around.

[MUSIC]

**CHRISTINA WARREN:** Hello, and welcome to Behind the Tech. I’m Christina Warren, senior cloud advocate at Microsoft.

**KEVIN SCOTT:** And I’m Kevin Scott.

**CHRISTINA WARREN:** Our guest on the show today is Dr. David Baker. Dr. Baker is a professor of biochemistry and the director of the Institute for Protein Design at the University of Washington. His research group is focused on the design of macromolecular structures and functions.

**KEVIN SCOTT:** Yeah, I really do think that Dr. Baker is doing some of the most interesting work in the world right now. I for sure – I mean, without question, I would be choosing to study computational biology if I were a graduate student again today. It’s just so fascinating what he’s doing.

**CHRISTINA WARREN:** And I can’t wait to hear him talk about what he’s doing and to hear the two of you interact. So, let’s chat with Dr. Baker.

[MUSIC]

**KEVIN SCOTT:** Our guest today is Dr. David Baker. Dr. Baker is a biochemist and computational biologist who has pioneered methods to predict and design three-dimensional structures of proteins. He is the director of the Institute for Protein Design and professor of biochemistry at the University of Washington. Dr. Baker has received awards from the National Science Foundation, the Beckman Foundation, and the Packard Foundation. He’s published over 500 research papers, been granted over 100 patents, and cofounded 11 companies. Welcome to the show, David.

**DAVID BAKER:** Thank you. Happy to be here.

**KEVIN SCOTT:** So, for listeners who aren’t familiar with your work, can you tell us a bit about the University of Washington’s Institute for Protein Design and the work that you do there?

**DAVID BAKER:** Yeah, sure. So, in nature, proteins carry out essentially all the important functions in our bodies and in all living things. And they’ve come through billions of years – millions of years of evolution. And sort of been optimized to solve the problems that were at hand during the evolution.

And what we’ve worked – figured out at the Institute for Protein Design is how to make brand-new proteins and to design them not to address problems that were relevant during evolution, but to address modern-day, current problems and that’s really what we’re focused on at the Institute.

**KEVIN SCOTT:** It’s such, such cool work. And I’m interested how you got interested in the field. Were you interested in science and math when you were a little kid? Were your parents scientists or engineers? Like, what sparked the interest that has carried you to where you are today?

**DAVID BAKER:** Yeah, it’s interesting. I actually was not terribly interested in science as a kid, perhaps because my parents were scientists. And when I went to college, I actually did not initially major in science. I was initially a social studies major and then wanted to be a philosophy major. And then it was literally my last year as an undergrad that I switched to biology and then I hadn’t really done research before, but I got really excited about what I learned – what I had been learning in biology, which was developmental biology and neurobiology. And so, I decided I would try out graduate school to see what it was like. And I found I liked doing research and I liked, you know, interacting with other people sort of to solve hard problems.

But as time went on as I was a graduate student then – then the next stage in my career, a post-doc, I got more and more interested in sort of more basic questions. And when I had taken my first biochemistry class when I was a senior in college, they had talked about the protein folding problem. And it seemed really interesting, but everyone said it was too hard to work on.

And so – but then when I as a post-doc, and then really when I came to the University of Washington, that I decided to focus on trying to solve that problem.

**KEVIN SCOTT:** Yeah, I remember I think in 1993, I was a research intern at the NCSA at the Beckman Institute working in the computational biology group that Shankar Subramaniam was running there at the time. And he was working on protein folding and I remember how hard it was in 1993. So, it’s – I mean, you picked the challenging problem to get inspired by.

**DAVID BAKER:** Yeah, well, I always tell my students, people in our group, you’ve got to pick – you have to pick hard problems that aren’t solved. That’s the only – those are the only ones really worth trying to work on.

**KEVIN SCOTT:** And so, at that moment when you were a – you were thinking about being a philosophy major and you decided to switch to biology, was, you know, was that a magazine article you read, like, an inspiring teacher, a movie you watched, a book, like, or just plain curiosity?

**DAVID BAKER:** It was – well, I think it was a little bit sort of getting fed up. I mean, I – it – you know, I started realizing that more and more of the questions were sort of, you know, issues about language and language games and that there wasn’t really – started seeming to me that there wasn’t really a way to make consistent forward progress like discovery. I’ve always liked trying to discover things. Then when I took the biology class, in contrast, there were just all these new discoveries right and left. People were just working out how, you know, the principles of developmental biology and it just seemed like this huge, unexplored territory that was much more ripe for exploration than philosophy would have been.

**KEVIN SCOTT:** So, you made the switch, and you went to graduate school at Berkeley and UC San Francisco. And were – how important was the computational part of biology when you were in grad school? Like, did you have to learn not just biology, but, like, a little bit about computer science or you know while you were a student, or did you have to learn that stuff later?

**DAVID BAKER:** Oh, yeah, well, so, I was a graduate student in the lab of Randy Schekman, who worked on sort of cell biology, how proteins get moved – sorted around in cells.

At that time, well, I was famous and outspoken for ridiculing anyone who sat at a computer, because, you know, what people used computers for was pretty rudimentary. It was word processing, and you know, you could waste time on computers the same way you can waste time on them now. I did not do any computer programming and really my major – my major interactions with computers, like I said, was to ridicule anyone who touched one.

**KEVIN SCOTT:** You know, in a little while, I really do want to get into what’s changed between then and now because you know, I think we’ll talk about soon, you know, how much of the work that you’re doing happens by influence of some sort of digital technology. It’s still, I mean, like, still, the biology is what’s driving, but computers play a big role, right?

**DAVID BAKER:** Yeah, absolutely, I mean, yeah, we’re probably one of the biggest users of computers in all of academia. So –

**KEVIN SCOTT:** Yeah, which is so cool. But, so, what did things look like after you graduated? Like, what did – what were you working on and, like, what did that stage of your career look like?

**DAVID BAKER:** Well, let’s see. At the end of my PhD, I sort of discovered how to re-create in a test tube a very complicated biological processes, the ones that were involved in sorting these proteins to where they need to go in cells. And it seemed to me it was going to be a very long, complicated process to sort of purify all the proteins out and figure out their mechanisms.

And I had been getting interested in sort of more basic questions about the structures of proteins, which I really didn’t know much about. And so, then when I – for my post-doc, I went to David Agard’s lab at UCSF, and he studied structural biology and protein folding. And the first day when I went in, there was this computer terminal on my desk. And I asked, “What was that for?” And he said, “It’s for computing.” So, then I had to kind of learn what that was, so, that was one of the things I did.

But I do have another sort of funny story about that time which was that whole area of the building was really devoted to crystal structure determination – determining the atomic coordinates of proteins. So, one of the first days I was there, I went into the room where everyone was sitting at their workstations trying to trace a protein chain through an electron density map. And so, I said, “Oh, can I try?” So, they said, “Sure.” So, I sat down at one of the screens and tried to trace the chain through.

And I remembered then that I have horrible 3D visualization capabilities. I was totally incapable of doing it. So, everyone in the room turned to me and said, “David, shouldn’t you have checked out whether you’re any good at this stuff before you went into structural biology?” (Laughter.)

**KEVIN SCOTT:** That’s – that is funny. So, I mean, maybe you could explain to the listeners a little bit about, like, what exactly that looks like. So, like, you get a protein, you try to crystallize it. Like, at the time you were shining a bunch of x-rays through it and sort of looking at the – the diffraction patterns of – I mean, like, I’m probably describing it wrong –

**DAVID BAKER:** That’s right. No, you’re absolutely right.

**KEVIN SCOTT:** But, so, like, that’s just an incredible amount of work just to figure out what a protein looks like when it folds itself up, right?

**DAVID BAKER:** Yeah, yeah, it’s a lot of work and it’s very difficult, too, because you have to coax the proteins to crystallize and I don’t really – I don’t think – this is probably – would be – it’s probably not exactly how it was, but at some point around there, I decided I really wanted to learn how to predict protein structure from sequence so that you wouldn’t have to do all this crystallography and chain tracing and all this stuff. But –

**KEVIN SCOTT:** Yeah, and so –

**DAVID BAKER:** Yeah.

**KEVIN SCOTT:** So, like, talk about that a little bit. Like, it’s sort of a big leap, I guess, from this idea that you’re using a bunch of scientific tools in the physical world to try to spy into the world of biology, much of which we can’t see at all. You know, at this molecular level that you’re, you know, that you’re working at to trying to go from this sequence of amino acids and say, like, if I understand the sequence of acids, like, what is this thing going to look like? And what a protein looks like dictates a lot of what its function is in an organism, correct?

**DAVID BAKER:** Yeah, you’re absolutely right. There couldn’t be anything more different than the two processes which have the same end goal, which is each protein – each gene in our genome encodes a unique protein that carries out a unique function. And it does so because the DNA sequence in the gene encodes a (inaudible) sequence of amino acids, which then folds up into a unique three-dimensional structure.

So, it’s been known since the ‘60s that the amino acid sequence of a protein determines its precise three-dimensional structure.

But like you said, the way that people actually have been figuring out what the three-dimensional structures are is not reasoning from the amino acid sequence, but instead, building hundreds of million dollar equipment and x-ray beams and all this complicated stuff to try and work out what the coordinates of the atom – where the atoms are.

But all the information we know is in the amino acid sequence. So then, when I moved to the University of Washington, that was really the problem that I decided to focus on, like, to really look at the simplest possible cases of protein folding and understand how they work and do that both with experiments to try and understand what the steps – what the process – the key aspects of the process were and what the determinants of protein folding were. And then on the computer to try and develop methods for actually going straight from the sequence to the structure.

**KEVIN SCOTT:** And so, why is it important to be able to predict the structure of proteins using a computer or any other mechanism?

**DAVID BAKER:** Yeah, well, the same reason it’s important to be able to determine the structure of proteins. It’s because, like I said earlier, proteins carry out the – essentially all of the important functions in our bodies and in everything in life. So, if you want to understand how biological processes work or how disease comes about, you have to understand the interactions between proteins, and those are kind of – a lot of them are kind of like lock and key, where things are fitting together very precisely. So, you have to understand the geometry, how these structures fit together and if you want to understand how they work, like, how they generate – they capture solar energy and convert it into the formation of chemical bonds. All those things, you really have to understand the structures.

And the same way that if you want to know how a machine that does any arbitrary thing works, you really have to know what it looks like.

**KEVIN SCOTT:** Yeah, so, we may be at a really unusual point in time where people probably know a little bit more about, like, protein structure and what its implications are than they ever have before because of the COVID-19 pandemic, correct?

**DAVID BAKER:** Yeah.

**KEVIN SCOTT:** So, you know, maybe in terms of SARS coronavirus-2, like, can you describe–

**DAVID BAKER:** Yeah, that’s a great idea. Really good suggestion. In fact, now, when I give talks, I explain protein design in the context of coronavirus.

So, let me just spend a couple minutes describing what we’ve been doing at the Institute with regard to coronavirus. So, the genome sequence was determined and made available at the beginning of last year. So, we took that amino acid sequence and used the methods we’ve been developing to predict the three-dimensional structure of the protein on the surface – the spike protein.

Of course, you’re right, there’s higher literacy about this now than there ever was. And we knew that the spike protein bound the ACE-2 receptor on the target cells.

So, starting initially with that model, and then shifting over to the x-ray crystal structure when it was determined of the spike ACE-2 complex, the first thing that we did was to design small proteins that we predicted would fold up in such a way that they have a shape and chemical complementarity to the part of the spike protein called the receptor binding domain that binds ACE-2.

So, these are like – I talked about sort of lock/key interactions. So, we – if you imagine the ACE-2 is the key and the RBD is the lock, so it’s sort of – or the spike protein goes and binds to the ACE-2. We basically made things that would compete away that interaction, that is, bind more tightly to the virus than ACE-2.

And we were able to make compounds that bind to the virus about 1,000 times more tightly than ACE-2.

And this was really cool. They were just completely made-up proteins, completely unrelated to anything that had been seen before. And with our collaborators, we were able to actually determine experimentally how these small proteins bind to the spike, and they bound basically exactly like in our computer model.

So, we could then go – that means we could go from – essentially from the sequence of a virus to these very, very tight, high-affinity binding proteins. The next thing we showed was that those proteins blocked the virus from getting into cells. And then we showed with collaborators that they protect animals from infection by the virus.

And I think this was – this was kind of a real ah-hah moment for me, because we’d been developing these methods for designing proteins over the years, and here in the midst of a pandemic, we were actually able to apply them to make therapeutic candidates. And those are now headed for clinical trials. It’s been slow, because this is a completely new modality, this whole idea of computational designed proteins. So, there’s been a little bit of a pushback because these are completely new things, no one knows exactly how they’ll behave. But for the next pandemic, we’re going to be ready, so we have all the methods worked out and I think we’ve gotten over a lot of the sociological issues to actually using these as drugs.

And there’s nothing really that can be as fast. If you can go from amino acid sequence to actually computing a protein which fits perfectly against the virus. So, that’s the first thing we did.

The second thing we did was to design, again, completely from scratch little molecular devices that emit light – luminesce – when they encounter the virus. And those are pretty neat. We’re developing those now for – not only for detecting the virus, but also for monitoring responses to vaccination, like, how good are my antibodies against the virus? And so rather than that being just like a fixed key that fits into a lock, that’s actually a device that can undergo changes in its state when it encounters the virus.

And the third area, my colleague Neil King at the Institute has been developing sort of a next generation of coronavirus vaccines using designed protein nanomaterials that we’ve created at the institute, which self-assemble into big things that look like Death Stars, and we can put the parts of the coronavirus spike on the surface. And when Neil does that, it binds, it gets very, very strong immune responses – stronger than with the current vaccines. So, those these designed nanoparticle vaccines are now in clinical trials.

So, that sort of illustrates some of the key areas in protein design now, being able to design, you know, very precise shapes that can block – can bind very tightly to targets, being able to design molecular devices that can undergo – that can basically do logic calculations and being able to design nanomaterials like these protein death stars.

**KEVIN SCOTT:** Yeah, to me, this is some of the most incredible stuff that I’ve ever seen in my life. Like, it’s just amazing to me that you can go from a published sequence for this virus, simulate a – like a compound that has this incredible binding affinity to the RBD, like, in this computational domain. And then you know, just be able to go from there to a, like, diagnostics, vaccines, you know, like, potentially therapies. Like, I’m guessing even that you can use these same techniques to try to assess how effective a human antibody response might be to the variants of the virus, so–

**DAVID BAKER:** Yeah, in fact, yeah, that’s – we’re actually doing that now. Yeah. That’s, yeah, you know, it sounds kind of “science-fictiony” to me, to you it also still sounds that way to me, which is why – I mean, this field has been moving so fast we’ve been able to make so much progress. There are things we can do now that still are a lot of work, but I don’t think I would have thought would be possible just even, you know, several years ago. And that’s what’s been exciting. I mean, people always ask me to predict the future of the field. And I always say, “Well, my biggest hope is that it will move so fast in such new directions I can’t predict it.” And that’s actually what’s been happening pretty continuously, so–

**KEVIN SCOTT:** Yeah. And so, what are the big things that are moving progress forward right now? Like, what is – I mean, and like, you can sort of take a long view, right?

**DAVID BAKER:** Yeah.

**KEVIN SCOTT:** Like, I think the landscape was very, very different when you started than it is now, like, what’s been the big thing–

**DAVID BAKER:** It’s totally different.

**KEVIN SCOTT:** What are the big things that have–

**DAVID BAKER:** There are just – there are so many things that are coming together. And I think when you have technological revolutions, that’s generally what’s happened. There have just been a lot of things that come together and, you know, I think we just happened to be at the right place at the right time.

So, what are they? Well, our understanding of the basic principles of protein folding have been improving over the years. And we’ve been developing this computer program called Rosetta to model these for, you know, for 20 years now. So, there’s been – we’ve been doing a lot of work at sort of trying to get more and more of the details right.

Second is computing power. These things are – despite my ridiculing people when I was a graduate student, these calculations now are – these systems are really complicated, and the basic principle is that proteins fold to their lowest energy states. So, if you want to design a sequence that folds to a new structure, then you have to do – you have to search through this huge landscape and it’s very time consuming. So, the fact that computers have just gotten more and more powerful continuously has really opened up. And we could not have done what we did for coronavirus in that amount of time with computing even like 10 or 15 years ago.

And the third that’s really completely independent is the – because of the Genome Project, there’s been this huge advance in gene synthesis technology. So, we design – on the computer, we can compute, you know, millions of different possible proteins that are, you know, all, you know, possible creations, but to actually bring them into the lab, we need to encode them in synthetic pieces of DNA – synthetic genes. And after we do that, we can put them into microorganisms, who will then produce them.

But synthesizing DNA is still expensive, but it used to be hundreds of times more expensive. And so now we can routinely design 100,000 brand new proteins for all kinds of different applications. I mean, the range of things we’re doing now in the group – trying to degrade plastic, trying to capture solar energy, trying to do exotic chemical reactions, all sorts of things. This just would not have been possible, again, with the technology of 15 years ago.

So, being able to manufacture DNA very rapidly and cheaply is really enabling us to move forward quickly and these things all go together. Because since we can compute – since we understand the principles, we can compute very large numbers of designs. Because we can manufacture so many genes, we can then bring them all to life. And then we can do measurements to see which ones work and which ones don’t. And then we can fold that back in to improve the methods. And that brings up the fourth thing that’s coming in, which is deep learning. And, you know, deep learning has just advanced by, you know, in the last 10 years has just been incredibly – has advanced as fast as the other areas, if not faster.

So now we’re complementing the Rosetta picture folding, which is sort of this physical model where you have this protein chain folding up with more of a deep learning approach, which is basically looking for recurring patterns and related sequences to structures using those. That’s turning out to be very, very powerful. We can also use machine learning to try and interpret – to basically relate all this data that we’re collecting to improving the computational models.

And the fifth thing that’s happening is that for the first time, these de-novo designed proteins are being developed as drugs. So, there are probably four or five different proteins that we’ve designed which will be in clinical trials this year. So, we’re kind of at this inflection point in all these different areas. So, you know, we don’t really know how they’ll turn out, but if one or two of them actually work pretty well, then you can imagine that we’ll have de-risked this whole kind of platform and I think the things – the way engineering and biology has worked up until now is not intentional in this way. If you want to make a drug that binds to something, you either screen a huge random library of compounds or you try and coax an animal to make an antibody against it.

Generally, in engineering and biology, if you want to solve a problem, you go look in nature for a protein that already does something similar, and then you modify it a bit. The relationship between sequence and structure has been really mysterious, but now we can actually design proteins with intent to do new things. So, I think it’s just getting to be very exciting.

**KEVIN SCOTT:** There’s so much that you just said that I find fascinating, and I want to follow up on. But, like, one of the things that as a computer scientist that wasn’t super obvious to me as I started diving deeper into biosciences is the extent to which – we’re now at this point where you can actually use biological machinery to go do work. So, what you just described a minute ago is you want to synthesize a protein, but you don’t synthesize the protein by, like, having some 3D printer that just lays out a bunch of amino acids. Like, you program a little piece of genetic material to use the cellular mechanisms that turn DNA into the protein that you want.

And, like, that’s sort of – like, that’s just fascinating to me that, like, we understand enough about some of the basic biological machinery that you can leverage that to do some of the work for you.

**DAVID BAKER:** Yeah, and you know, I left out, there was a sixth thing I should have added to my list, which is exactly what you’re saying, the whole recombinant DNA protein expression thing. Our advance is understanding basic biology, which we play a lot – we use biology right and left when we’re making these proteins, and then we’re screening them for activity. So, you’re absolutely right, that’s another thing. It’s like all of these different technologies have come together.

**KEVIN SCOTT:** Yeah, and so I’m – one of the things that you, you know, that you’ve described is the end state of this is de-novo drugs like being able to design therapies for diseases like COVID-19 and like in the limit, like, what you would be able to do – what you’d like to be able to do for cancer therapies, for instance, is you would like to be able to look at, like, the very specific cancer mutation that you have, like, making someone ill and be able to custom tailor a therapy to, like, the very particular illness that you have.

And in order to, like, there’s sort of two axes that I think are interesting, like, one is you know upper respiratory viruses are probably a little bit better understood than cancers, but like, the trick with them is, like, you need to go very fast, so you need to go from new virus to you know therapeutic for it to drug that you can start delivering and, like, the amount of time that that takes dictates, like, how bad, you know, a public health crisis you’re going to have.

For custom tailoring a therapy to an individual, like, what you’re trying to drive down is cost. So, like, we have some of these therapies right now, but it may legitimately cost $1 million to synthesize the treatment just because it’s very complicated and, you know, you have five people who have the sickness a year.

So, like, do you see both of those things getting better? So, like, time to you know deliver a therapy or, like, the cost of delivering a therapy, are those both getting better?

**DAVID BAKER:** Yeah. I think there’s also the precision of the therapy. So, you brought up a number of really good points, but one of the issues with current protein drugs, which is why they’re so expensive, is they’re antibodies – they’re very complicated proteins. Antibodies are what we make to defend ourselves against disease. So, naturally, in the sort of spirit of sort of emulating what’s in nature, when pharmaceutical companies want to solve a problem now, they try and make a new antibody and then that’s the drug.

The problem with that is antibodies are very expensive to manufacture. That contributes to the high cost of them. These proteins that we design, in contrast, can be manufactured for a hundredfold lower cost. They can be made in bacteria, not in complicated mammalian cells, which are much more sensitive and much more difficult to grow.

As far as precision goes, antibodies, the way they work is they’re kind of blunt instruments. They home in on a target. They’re basically – they’re like the coronavirus binder I described. They just bind.

We can, with designed protein, we can actually design logic systems that actually can go into the body and pick out cells that have combinations of proteins on their surfaces that are indicative of disease, because in some cancers, there isn’t really a single distinguishing mark. There’s a number of things. There are some things that are higher and some things that are lower in abundance than they would be in normal cells, and you need to be able to resolve those differences. So, you need more sophisticated types of – a more sophisticated drug, one that, like I said, can sort of do logic calculations in the body to really approach that.

And in terms of time, you know, we’re not there yet, but since everything’s going on in the computer, then in principle, the reaction time should be much faster, say, to a new pandemic than it is if you have – so with the antibodies, the antibody therapies for COVID-19, they weren’t designed on the computer or designed by anybody, instead, there was a lot of searching after – in the bodies of people who had been infected with the virus or animals for antibodies that happen to bind to the virus and really be effective at blocking it. And it’s pretty rare that you find those antibodies. So, if you can design things by intent – I mean, it’s kind of like the way that biological drug discovery and engineering has worked is sort of like you’re trying to build a building, you keep throwing a pile – bricks into a pile and you hope it assembles into a building. Well, it’s much better if you understand the principles of construction and can just build it. So, I think the future will be very bright.

**KEVIN SCOTT:** Yeah, and I’m just always reminded how complicated these biological systems are, like, things are very rarely as neat, you know, as you as like a computer scientist or mechanical engineer have. Like, you think, you know, like I will say for myself as a computer scientist, like, I often think that I’m dealing with complicated systems, but compared to biology, like, our artificially engineered digital systems that we’re building are, like, nowhere even remotely as complicated as a biological system.

**DAVID BAKER:** Yeah.

**KEVIN SCOTT:** One of the things is, you know, I think we’ve all looked at these vaccines as you have two types of vaccines now that are prevalent. You have sort of the MRNA vaccines that we are very excited about and you have things that are – look more like classical vaccines. So, they use something like an adenovirus to carry the, you know, the spike protein into the body to try to produce an immune response. But, like, one of the funky things about adenoviruses, right, is like if you already have antibodies for the adenovirus, itself, like, the antibodies may swarm in and kill the vaccine before it can produce, like, the new immune response.

So, I mean, I’m just sort of wondering, you know, one of the things that you said that’s really fascinating to me is, like, I think we very quickly you know especially by classical vaccine development standards went from the genetic sequence of this virus to, like, vaccines or therapeutics. Like, you – how long did it take you to design this 1,000X binding thing once you had a sequence? Like a month, two months?

**DAVID BAKER:** It was probably – it was a few months, but that was because we hadn’t done it before, and we had to sort of learn by doing. And I think now we’re working on methods for really doing that. What we’d like to do is be able to do that within two weeks, so the sequence for a new pandemic threat comes out and then two weeks later we have a really high-affinity antidote. That’s aspirational, but I think it’s possible.

**KEVIN SCOTT:** Yeah, and, like, you know, everything that I’ve seen – seems like you know far better than I do, but like, it sounds like a reasonable aspiration to me. Like, the thing that I don’t understand as well is then the hard part starts, which is trying to assess the safety of the thing that you just synthesized. And, like, that’s – you know, even with the MRNA vaccines that we made, like, you had a pretty good idea that they were going to work. Like, we just didn’t know whether or not they were going to be safe.

**DAVID BAKER:** Yeah. Yeah.

**KEVIN SCOTT:** And so how do – I mean, like, can we use the techniques that you are describing to, like, do some of that safety assessment to drive the, you know, the time to–

**DAVID BAKER:** What we can do – yeah, it’s a really good question. And that is probably one of the biggest question marks currently. So, what we can do is on the computer, design in properties that we think will correlate with safety. But humans are very, very complicated, so it’s hard to predict exactly what will happen. And so, I think that evaluating safety is the thing that is slow, and that actually is what has been taking all this time, much longer than the design. So, it’s a good question. And there, we’ll just have to learn from experience, I think.

**KEVIN SCOTT:** So, what are you – what are you most excited about over the next handful of years? And, like, what do you think we as, you know, like, citizens, like, folks who are very encouraged by what you’re doing, who want to, like, help things go faster. Like, what can we do to, like, get some of this goodness that you’re building, like, moving faster?

**DAVID BAKER:** Well, let’s see. So, we have – we’re – I’ve been very interested in involving the general public and scientists at large in what we’re doing. So, we have an online game called Foldit, where we post a lot of the current problems we’re working on. For example, now, we’re in the Fold It puzzles is that we’ve designed small proteins which bind to different parts of the coronavirus and now Fold It players are being challenged to connect them in just the period of time way. So, you get sort of the much stronger binding.

So, Fold It is one way. And then we have a project called Rosetta@home, where you – which is how we do a lot of our computing. If we send out jobs to people’s computers and they compute new design proteins and send them back and then we select from those which ones to make. So, those are two of the ways in which people can get involved in what we’re doing.

**KEVIN SCOTT:** Yeah, like, in my opinion, like, that’s a much more beneficial thing for, like, our collective human wellbeing than, like, using your spare GPUs to do cryptocurrency mining, for instance.

**DAVID BAKER:** Yeah, that’s right. (Laughter.)

**KEVIN SCOTT:** So, you know, just in terms of, like, your work, like, what are you really excited about over the next handful of years? Like, what do you – you know, how do you prioritize your energy among, like, all of the many, many, many things you could go explore?

**DAVID BAKER:** Well, one – there’s a magic ingredient to all of this, which I haven’t really talked about yet, but that’s part of the answer, which is that the most brilliant people in the world, graduate students and post-doctoral fellows are now coming to the Institute for Protein Design to sort of – to push the next wave of discoveries and make their fortune and start out exciting new, independent careers in this area.

So, what I actually do every day is I talk to these absolutely brilliant people in my group about, you know, new people come in and, you know, we sort of brainstorm different ideas, they go and talk to everybody. I have sort of a theory of scientific creativity, this idea of a communal brain, where everyone’s talking to everybody all the time. And like connected neurons, you can get these really emergent things.

So, in terms of the new areas that we’re going into, really, it’s very wide and it’s driven in part by the interests of people who come in, but some of the really exciting areas are, well, really sort of pushing ahead on this very rapid therapeutic design, making better vaccines, biological designed machines, nanomachines that can do work. For example, we’re making rotary motors now, trying to couple them to energy sources. We’re really excited about making new types of materials. So, in nature, we have examples like bone and tooth and seashells, where it’s proteins interacting with inorganic compounds to create all sorts of hybrid structures. I think that’s a really rich area.

What if those things that you were interacting with were semiconductors rather than calcium carbonate? Sky is the limit there. Catalysts, you know, trying to catalyze chemical reactions which don’t exist.

We have a big effort now in exploring molecules that really nature couldn’t explore because they’re made out of more exotic stuff than just the 20 naturally occurring amino acids. So, new classes of compounds. We can take the same computational methods we’ve been developing and apply them well beyond – outside proteins. And we’re making systems that can sense the environment, respond. You know, I could go on and on. I’m excited about it all. (Laughter.)

**KEVIN SCOTT:** Well, and it is sort of super exciting. And, like, going back to, you know, the – our intro, like, your bio, like, you’ve started – you cofounded 11 companies. And so, you know, I think beyond the – you know, the fact that this is all scientifically some of the most interesting stuff in the world right now and it has this huge potential for, you know, impact in the same way that great scientific discovery usually does, like, you also are – like at the epicenter of this new entrepreneurial engine. So, like, you’re – in a lot of the ways, like, Silicon Valley, like, you go to a Silicon Valley school and, you know, like, a bunch of the professors there are starting companies and, like, it’s this vibrant ecosystem. Like, I’m really excited to see this happening with what you’re doing.

**DAVID BAKER:** Yeah, that’s a really important part, because I told you with all these – many brilliant people in their 20s are coming here to do great things, many of them – it used to be they all wanted to go on and be professors. Now, many of them come with the idea of starting companies and many of them are doing that. I mean, I think we’ll probably be spinning out three more companies this year. And it’s just – it’s sort of accelerating.

There’s so many different things that proteins can do. And that’s great because it is creating this whole new ecosystem. It’s people – you know, the people who don’t want to start companies or take faculty positions, instead, are taking jobs at these companies. The companies can then really go much deeper into the various application areas. We’re kind of like a discovery engine – the Institute for Protein Design, but then actually bringing things out in the real world is a whole ‘nother, you know, effort and so that’s what our spinout companies are doing.

Yeah, and then I also really have to thank, you know, the reason – you didn’t really touch on this, but the – what’s really also fueling this is philanthropy because, you know, what we’re doing is so new. It’s almost impossible to get grants to do this. And so, a lot of – a large fraction of our work is supported by private philanthropy, people sort of see this as, you know, that this really is the – you know, a technological revolution and that pushing it forward rapidly will you know lead to all kinds of great new things for society and we’re really completely indebted to the people who are supporting our work.

**KEVIN SCOTT:** Yeah, which I’ve – I wish we could channel more funding. Like, if I had a magic policy want to wave, like, I would, you know, 10X, 100X the level of collective investment from philanthropy to government funding to corporate funding that was happening with this stuff. Like, the return on those investments both financially and in terms of, you know, goodness for society, like, you know, better healthcare for us all for instance, like, I think is just tremendous.

**DAVID BAKER:** Yeah.

**KEVIN SCOTT:** So, what’s – what would be your advice to students who are thinking about this as a career path? Like, what should they study? What should they learn? It seems very interdisciplinary to me that, you know–

**DAVID BAKER:** I would say don’t–

**KEVIN SCOTT:** You know it’s chemistry, biology, computer science, entrepreneurship, like, it’s just a bunch of things.

**DAVID BAKER:** I would say be a generalist is – I mean, that’s – you can sort of see from my trajectory. There’s not, you know, the tech – this field is changing so fast that even if you are an expert in protein design today, you know, five years from now, you would probably have to relearn everything. So, yeah, so, I think any – it’s exactly what you said. There’s biology, there’s physics, there’s computer science. There’s some sociology. We live in the world. And so, I think it’s – it’s important to – yeah, to get a broad education.

And, you know, and actually, when I look back at my own education, for a long time I thought that – what the hell did social studies or philosophy have anything to do what I do now? But, actually, it’s turned out to be very, very useful in a lot of ways. And so, anyway, I think that’s in terms of a broad education. And then, you know, to actually – if you actually want to start doing this kind of work, being – and joining a research group in some capacity where this – where such work is going on is, really, there’s no substitute for that.

**KEVIN SCOTT:** Yeah, well, so, we’re almost out of time here. The last question I like to ask everyone, and it’s a weird question because everyone I chat with has such interesting work that they’re doing in their professional lives, but I’m always curious what you do for fun or what you find interesting outside of your professional life.

**DAVID BAKER:** Oh, yeah, well, that’s – I love the mountains and – or just going out, getting away from things. You know, whether it’s on the water in a kayak or climbing or skiing or hiking. It’s really what I love to do. During the week, there’s a lot going on and a lot coming in and I need – and having time just out in open space to process every once in a while is really great. So, it’s –

**KEVIN SCOTT:** Yeah, and you live in the Pacific Northwest, like, one of the most beautiful places in the world to be outside hiking or biking or kayaking or whatever you’re–

**DAVID BAKER:** That’s right. That’s right. And that’s part of the reason I’m here, so, yeah.

**KEVIN SCOTT:** That’s awesome. Well, this is amazing. Like, thank you so much for taking the time to chat with us today and more importantly, thank you for what you’re doing. Like, I don’t know whether you think about your work as, like, this great public service, but it very much is.

And so, on behalf of many of us, like, I just want to express real appreciation and gratitude for – for the work that you and your students and your colleagues are doing.

**DAVID BAKER:** Well thanks, Kevin. This was a lot of fun. And honestly, what I – I’m not a surfer, but I just feel like we’re riding the wave and we want to – you know, the longer we can ride it, the better – that we can make the world a better place, that’s really what we’re trying to do. So, yeah, this was a lot of fun. I enjoyed our conversation.

**KEVIN SCOTT:** Awesome. Thank you so much.

[MUSIC]

**CHRISTINA WARREN:** Well, that was Kevin’s conversation with Dr. David Baker. So, what stood out to me about your conversation was just how fascinating everything that’s happening in this field is, like, I honestly – I’m going to be honest with you, even after you said that this is what you would study in grad school if you were in grad school right now, I – in my mind, I’m, like, I’m not a traditional sciences sort of person. I don’t know how fascinating any of this will be. And I’m just riveted by all the cool stuff that is happening in this space.

**KEVIN SCOTT:** Yeah, it’s really crazy, like, how fast things are moving right now. You know, I think one of the things that he said that was really interesting and very, very true is that scientific revolutions, technological revolutions, tend to happen when you have multiple things that are moving very quickly and have had their own transformations come together at the same time. And he, you know, named off six of those in the course of our conversation.

And, you know, it’s one of those places where because it’s moving so rapidly and because every day we’re learning more and more and more about how to push things forward even faster, this is just where so much of the interesting things are going to be happening in the world over the next couple of decades is in this particular discipline – in digital biology, synthetic biology, computational biology, where we really are trying to get this, like, higher – high resolution and more accurate picture of what happens in biological systems. And then, being able to engineer those systems to solve–

**CHRISTINA WARREN:** Yeah.

**KEVIN SCOTT:** –really, really tremendous problems.

**CHRISTINA WARREN:** Yeah, no, I mean, that’s what struck me. I mean, like you said, he was talking about how all these different things kind of need to coalesce to have this real innovation and when he was saying that some of the stuff that they were – that the industry has been doing and the scientific community has been doing with coronavirus, wouldn’t have been possible with computers from – and technology from a decade or 15 years ago really struck me.

And when he was talking about how the way that the engineering and the technology is working now is that it’s intentional, whereas before, you know, you’d look to nature, and now you are intentionally and having this intentionality about saying these are the problems we want to solve, and we’re going to engineer a solution rather than looking for something that might already exist that can solve that problem.

**KEVIN SCOTT:** Yeah, I mean, it – and in a very real sense, like, many of these areas in biology now have a real engineering discipline that goes along with them in addition to the normal scientific practice. Like, we understand enough about the systems where we can start designing them in ways that serve purposes that are different than the ones that nature strictly designed them for through the process of evolution.

And, like, to me, that is the most fascinating thing. And I think, you know, the interesting – interestingness about this particular moment is we are all at a heightened level of awareness about both the upside and the downside of biology because of the COVID-19 pandemic. Like, we know what one little molecule can do to you know impact hundreds and hundreds of millions of lives and, you know, just sort of trillions of dollars’ worth of economic damage.

And, like, we also know that we can harness this greater understanding that we have about biological systems to – in an unprecedented way – design therapeutics and vaccines for the pandemic itself. And, like, all of that just gets better in the future.

**CHRISTINA WARREN:** It does. And it makes it exciting, I mean, it make – it’s a little bit harrowing in some sense, and if you wanted to become really dystopic about it, it could be you know sort of concerning in that respect. But it’s also so exciting because it really does feel like the things that we’ve thought about in the past of being science fiction are really going to be things that not necessarily, right, like, that actually could be reality, which is I’m going to be honest, I think if nothing else – I mean, I think it’s exciting, but if nothing else, is really interesting.

**KEVIN SCOTT:** Yeah, I do think it’s exciting, you know, I keep saying that I’m an optimist, even though, you know, my wife would look at me and say I’m a grumpy – grumpy old cynic. But I’m very optimistic about the choices that we will make about how these tools and this greater scientific understanding of biology will get used, like, our – and I think you can absolutely see it with, you know, with COVID-19.

Like, we have just had our scientists and engineers come together in exactly the way that you would hope to, like, just pour time and energy and expertise into getting us past the misery of a global pandemic as quickly as possible. And I think not just the science has been a shining light, but the way that we’ve come together as a species has been a shining light for me.

**CHRISTINA WARREN:** I agree. I agree. It’s actually been pretty remarkable to see and to see what’s happened in this relatively small period of time, all things considered. Anyway, this was a great conversation. I love hearing about what Dr. Baker is working on in his work.

That’s it for our show today. We are so grateful to Dr. Baker for joining us and you know that we love hearing from our listeners. So, contact us anytime at BehindTheTech@Microsoft.com. Thanks for listening.

**KEVIN SCOTT:** See you next time.