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Mark Zuckerberg: Hey, everyone. We're here today to do the next in the series of challenge discussions on the future of technology and science and society. Today, we're going to be focusing a little more on medical research and biological research, overall; so, taking a little bit of a break from some of the Internet policy topics that we've largely focused on so far. Today, we're at the Biohub in San Francisco. And I'm here with Professor Steven Quake and Joe DeRisi, who are co-

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presidents of the Biohub. And the Biohub is-- it's a research lab that is basically a collaboration between three of the top universities in the area. So, you got UCSF, Stanford, and UC Berkeley. And we, actually through our philanthropy at the Chan Zuckerberg Initiative, helped set this up initially and we're really proud of all the progress that they're making here so far. But, you know, we've gotten a chance through this to get to

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know Steve and Joe who are, you know, two of the most talented and accomplished scientists in the field. And I'm really excited to just have the opportunity today to talk about some of the things that you're excited about, but also some of the challenges in science and how some of the broader policies, issues, and trends going on in the world and challenges that society faces are impacting science as well. So, today, we have Steve Quake is here. Steve is probably best known for his work

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pioneering a technique that, I guess, is best-called liquid biopsy. So, the basic idea is that you can take some blood in a blood test and now you can sequence the blood. So, you'd basically have a sense of what the DNA of the person is, the sequence of the person who you've taken the blood from, but, at the same time, you can also sequence the DNA of fragments of whether it's viruses in the blood or cancer cells or other

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things that might be going on in a person's body to get a sense of what else is going on in there. And it's a very-- it's a really important technique that is going to help in diagnostics around a lot of different types of diseases. I'm sure we'll talk about this a bit today, but probably the biggest advance that this has created so far is replacing amniocentesis for a lot of pregnant women, right? It used to be that you had to get this big needle put in in order to do a Down Syndrome test to get some cells from the fetus, but now you don't have to, thanks to

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this advance that Steve and a number of others have made. You can just take a blood test and from there, you can separate out what the mother's DNA is from what the baby's DNA is and, from that, get a sense of "Is the baby going to be healthy on a number of fronts?" So, it's really exciting work. That's, of course, only one of the things that Steve has done. And I'm sure we'll get into more detail on that and some of the challenges around that. Joe is also extremely talented and has done-- has focused his career on-- more in the area of infectious diseases.

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Right? So, it's a similar focus on genomics and a bunch of the areas where you've been very involved in building chips that have helped diagnose different infectious diseases, including SARS when that was first becoming a big and emerging threat-- I guess this was more than a decade ago. But, more recently, you

know, a lot of the work that you're doing is applying some of these techniques of kind of broad genomic sequencing, similar to the liquid biopsy stuff that we just talked about, to

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identifying infectious diseases in developing countries, both for public health and for medical research. And that goes to this IDseq project, which you've pioneered, but we're also working on as a collaboration with the Chan Zuckerberg Initiative engineers to bring that out. So, I'm really excited to be here with both of you guys to go through some of the work, but also a lot of the challenges. So, I'm curious though to start off with-- you know, maybe you could each just go into a

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little bit of detail about what you think are some of the most exciting developments that are going on today. It could be some of the stuff that we just touched on and how that could extend in the future or it could be something completely different. So, I don't know if you want to kick us off. Go for it.

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Steve Quake: Sure. Well, just to pick up the cue from what you were saying, I think this field of liquid biopsies is poised to really emerge and transform healthcare in a way that creates health equity. You know, right now, you know, if you're lucky enough to live near a major hospital with high-end doctors, you could get the benefit of that. If you're in a rural area, it's much harder to access that quality healthcare. And these liquid biopsies bring genomic technologies sort of to everyone, because blood can be drawn anywhere in the country and sent into a

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testing lab and it helps everybody realize the benefit of this work. And, as you mentioned, the sort of first and, thus far, most successful one has been around non-invasive prenatal testing and that is now millions of women a year who are getting that test worldwide. And many thousands of lives saved if they're all--

<overlapping conversation>

Mark Zuckerberg: Yeah, Priscilla got that test and that's how she got her tests when she was pregnant.

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Steve Quake: Yeah. Yeah. So, yeah, I got interested in that area when I became a parent. And, you know, we were in visiting the doctor and the doctor says, "Do you want amnio? We recommend it." And it sounded like a theoretical question; we have time to think about it. And we kind of-- my wife and I looked at each other and said, "Sounds like a good idea." Next thing you know the guy was turning around with a huge needle and-- whoosh!-- right in the belly! It was really terrifying. And there are negative health consequences for some people. So, that's the first of what are, I think, going to be many tests. The next

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one I was involved in was for organ transplant recipients, heart and kidney and lung transplant, as another way of replacing invasive biopsies for people that had those transplants, and the doctors want to monitor the health. Infectious disease, I think, was something we both worked on and that's clearly going places. And cancer is another one which is probably a little earlier on, but in the next five years I think you'll see these sorts of tests very widely used in all sorts of aspects of cancer care.

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Mark Zuckerberg: So, what's it going to take to get there on cancer? I know when you first started working on some of this, I mean, the hope was to do early-stage cancer diagnostics, because, of course, cancer has the property that a lot of times it's not identified until it's really too late to do something about it. So, if you can bring the diagnostic in and do it sooner, then you can usually handle it before it's going to be fatal or cause a lot of damage. But I'm curious: What are the gates or the challenges that make it so that this approach, which is already so accurate for detecting Down Syndrome in

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babies or before they're born, what needs to happen on cancer?

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Steve Quake: Yeah, so, I think you're right. And there's other ways in cancer treatment it can be used, but the most important would be early detection. And that's a tough one and you sort of have to decide how good you want the test to be and there's sort of challenging questions there. If you look at current early detection tests, like mammograms and PSA, their performance is really not that good. So, it's not hard to beat them in performance, I think, for these liquid biopsies. But then the question is, you know, to be a really good test, how-- and the

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performance level goes up sort of another order of magnitude in order to reduce the number of false positives: The real question is you want to reduce the number of false positives so that people don't get a test-- healthy people don't get a scare, basically. And that's hard to get it to the level where, like, less than half the test positives are false positives. That's difficult and that's the challenge of the field, I think.

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Mark Zuckerberg: Yeah, so, I mean, to kind of paraphrase this and let me know if I'm getting this wrong, I mean, part of the issue on false positives is that someone once described this to me, that, basically, in our bodies there's always, like, a little bit of cancer growing almost, that our body's naturally just going to beat it back, right? Our immune system is going to beat it back. But if you did a test that was perfectly sensitive and could identify any cancer cell or mutation anywhere, we'd all just get told that we had a lot of cancer all the time, yet most of it was not actually going to be an issue and our body

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would have dealt with it. So, you need to kind of get it at the stage where it's sufficiently problematic that we need some kind of external intervention and not so early that we're just all getting scared about what's going on in our body that it'll naturally take care of. Is that kind of right or do you think that's overstated?

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Steve Quake: That's the most interesting part of the false positive problem!

<laughter>

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Steve Quake: There's also technical issues around false positives that have to be managed. But, yeah, I mean, that's the deeper, I think, sort of biological or physiological aspect that the field's going to have to

grapple with that they haven't had to before, because they just haven't had measurement tools with that sensitivity.

Mark Zuckerberg: Yeah.

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Steve Quake: And we can see those are going to be coming and it's going to be a lot of interesting frontier research to sort all that out.

Mark Zuckerberg: Interesting. All right, so, Joe, what do you see is most interesting on the horizon?

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Joe DeRisi: Yeah, well, you know, I'd riff on topics that Steve mentioned: Measurement tools are really important and our ability to have accurate measurement tools changes what we can see and how we can see it. And I don't think anything has changed in the measurement-tool area in biomedical science more than genomics in the last few decades; specifically, our ability to sequence RNA and DNA. And while many people are familiar with sequencing DNA to find inborn genetic mutations and things like that, the same concept of precision medicine can be extended to

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infectious disease-- something I'm very much passionate about-- and cancer and other things, as we discussed. And we could comment more on those afterwards. But in the area of infectious disease in particular, it really begins to flip the paradigm when you use these new measurement tools. Instead of having kind of the old model where you go to the doctor, you get a patient history, and the doctor sort of has to take that all into account and make some targeted guesses about what you might have, if you've been exposed possibly to an infectious disease, and then send out for those assays kind of one at a time

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hoping they hit the mark; instead, genomics allows you to take a data-driven approach. An unbiased approach. That is, take the sample, look what's in it, and actually separate everything out that's from human from everything else and ask the simple question of "What isn't human?" and get a completely unbiased view of what's in there. And that can really, fundamentally end diagnostic odysseys that many people find themselves on, whether it be a rare infection or something the doctors just never considered.

Mark Zuckerberg: Mm-hm.

Joe DeRisi: I can give you a small anecdote, for example.

Steve Quake: Yeah, go for it. Go for it.

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Joe DeRisi: You know, we had a guy come to the UCSF clinic, he was a construction worker, he had immigrated from Nicaragua some number of years ago, and he just had double vision and a really bad headache. And it's hard to work when you have double vision and so on. And I did sort of a neurological example and, sure enough, some of his cranial nerves were not acting appropriately. But that doesn't tell

you want it is. There might be some kind of infection that's hurting his brain, giving him meningitis, infection of the covering of the brain infecting some of those nerves; but based on his patient history I

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said, "Well, maybe this is TB." It could be micro-bacteria tuberculosis in the brain; put you on a large regimen of antibiotics and some steroids. And for a while he did okay. Got a little better. But then he got worse and he got worse and worse. And he began to lose facial muscles, ringing in the ear, vomiting. He just declined precipitously. Repeat examinations of him and send out tests over and over again over the course of a whole year failed to identify anything that was wrong with this

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guy: MRIs, imaging, dozens of PCR tests. And, so, ultimately, that activated a protocol we have that I had in my lab, which is, basically, we can accept patient samples that nobody can figure out and then we can see if we can do a better job and then return those results and confirm them with another assay. And, so, what we did is we actually took his cerebral spinal fluid-- so, basically, the fluid that coats the brain and around the spinal cord-- drew a little bit of that, and then sequenced

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the heck out of it. Basically, sequenced all the RNA and DNA without regard to what's in there. Just do it all and then let the computer sort it out: What is human, what isn't? Just separate it out. Find the needle in the haystack. Now, in this case, there was a lot of needles in the haystack. It wasn't really hard to figure out what this was wrong. Within about 20 minutes of getting the data, we knew exactly what this guy had and it was sort of a good news-bad news situation for the guy. So, at the expense of potentially grossing people out--

Mark Zuckerberg: It's okay, go for it.

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Joe DeRisi: This guy had pork tapeworms in his brain.

Mark Zuckerberg: Oof!

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Joe DeRisi: And that is actually a far more common problem worldwide than people realize. It's a global neglected disease. It's a disease called taenia or neuro-cysticercosis and you can get it by eating contaminated material that has the larva of the tapeworm in it. And it causes actually a great proportion-- maybe a third of the world's epilepsies is caused due to this. And he had immigrated from Nicaragua where pork tapeworm is endemic. But because he was seen here in San Francisco he was out of context. No one actually thought that, "Oh, maybe this is

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pork tapeworm." Now, the good news is it's totally treatable. There's a drug, albendazole; he got on it right away, he's returned to work, he's leading a normal life, he's back to being himself. And, so, it's a story that's representative of a lot of stories that we have run in our lab where you think you're looking for something, but it's something completely different. And instead of using intuition or being beholden to your own cognitive biases, you just let the data do the work, let the

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computer figure it out. Because with this new measurement tool, we can really just scorch the Earth and sequence everything.

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Mark Zuckerberg: Mm-hm. Yeah, so, I think that there are a bunch of different interesting trends in there. And one-- different points that you're making. One is, I think, for a lot of diseases we already have cures or ways to treat them, but a lot of the time the hard thing is just figuring out and doing the diagnostic, figuring out what the disease is. And then the vision that you've talked about a lot, around hypothesis-free diagnostic, right, the idea that today if a patient goes to a doctor, the doctor tries to come up with a guess of what you have, and then they run specific tests to see if you actually do

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have what they think you have, and then figure out how to treat it; part of the goal of the work that you're doing is to make it so that when you do a blood draw you sequence everything that's in there. And then, without having to come up with a hypothesis ahead of time, you can basically just have a computer spit out the results of "Here's what I found: Here are the viruses, here's the--" eventually, cancer types or different types of issues that are there. So, that's a very promising vision for the future once we can work through a bunch of the issues in there. Now, I'd like to kind of transition to talking about how

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there are a bunch of broad trends across society that I think are having-- they're having impacts not just on science, but a lot of different parts of society and policies and things like this, but they also impact science. So, it's everything from advances in technology and computing to social issues like the erosion of a sense of truth and trust in experts-- I mean, that's obviously something that hits science a lot-- to

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even things like the trade war that's going on right now and the tension between our country here in the U.S. and China and others and how'd that effects something like science, which is a very--it's globally collaborative. So, I'm curious to go through these and if you have other things that you think are interesting, global trends that we should cover as well. But I think that the impacts on science and how science can maybe contribute to making-- to addressing some of these problems may be somewhat counterintuitive to a lot of folks. So, maybe let's

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start with what might be the most-- the simplest of it is just the impact of technology and compute on scientific progress. You know, there are a lot of people who argue that with more compute power we can do a lot more. There are also-- I've seen arguments recently that some people think that the pace of scientific progress is slowing down. So, I'm curious what you guys think about this. What's the broad trend over the last 20 years or so, what can we do now that's better than it used to be, and what's harder.

Steve Quake: In the pace of scientific progress generally?

Mark Zuckerberg: Yeah. Yeah.

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Steve Quake: Well, that's a really tough question, because different fields go at different rates, right? It's not like it's all moving in lock-step. And 20th century was great for physics; 21st century is going to be great for biology. And even though physics has largely slowed down, there's areas of it that are exciting and areas that have been open problems for a long time. And a lot of excitement around gravitational wave observatory, for example. That's a bright spot in the physics,

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but on the other hand it's one where it's not that surprising. I think most physicists sort of expect the unseen [ph?]. It's a prediction from a hundred years earlier.

Mark Zuckerberg: I should say, you're background is actually as a physicist.

Steve Quake: Correct.

Mark Zuckerberg: Right? So, yeah.

<overlapping conversation>

Steve Quake: Correct.

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Mark Zuckerberg: You just transitioned into biology because you thought it was more interesting at some point, but-- or--

Steve Quake: I felt like the frontiers were expanding more rapidly.

Mark Zuckerberg: Yeah.

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Steve Quake: And I feel good about that decision. That worked out for me. And within physics there are probably areas that would have been smart to go into, that had that same property, but not the whole field in general. And within narrowing it down to the last decade or so, in biology, you know, as Joe was saying, genomics has been a transformative technology and there's been ten years of just absolutely revolutionizing the field of genetics. And it has moved an incredible distance, thanks to genomic technologies. But those technologies are now going to be put into service to other areas of biology. Joe talked about infectious disease as one. Another example that

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we're also very interested in here at the Biohub is cell biology. We feel like measurement of phenotype is going to be transformed by RNA sequencing and other sorts of epigenic analyses of cells. And we're at the beginning of that. And that's an area that's accelerating enormously.

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Joe DeRisi: Compute is really accelerating a whole array of different technologies and, without them, we couldn't do what we do. Most of the things I just described are made possible by advances in compute. And take an area that I'm not directly involved in, but just watching next to it is just amazing to see is cryo-electron microscopy. The advances in compute there let people understand the molecular structure of proteins and molecules at a pace orders of magnitude faster than in the last

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decade, and that's going to drive drug discovery, drug design, our understanding of underlying mechanisms of disease and everything, and that's fundamentally electronic, mechanical engineering advances but really compute is at the heart of all of it.

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Mark Zuckerberg: Yeah. So I guess there are a couple of trends that you're talking about here. One is just the speed and price decrease in sequencing, right? So I guess when the first DNA was sequenced this was in the 2002?

Steve Quake: The human genome [ph?]. Yes, human genome.

Joe DeRisi: No. I was about to say and our first DNA -- the first human genome --

Steve Quake: Human genome now.

Joe DeRisi: Yeah 2002.

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Mark Zuckerberg: The first yeah, yeah, okay. So 2002. Human genome, sorry, thank you for correcting me on that. And that was a--

Steve Quake: That was a billion-dollar effort.

Mark Zuckerberg: It was only a billion? I thought it was three. Yeah. Multibillion dollar effort and took many years to complete.

Steve Quake: It's an order of magnitude estimate. <laughs>

Mark Zuckerberg: There you go. All right. So but now we're here though. It's on the order of less than 20 years later, and now sequencing a genome--

Joe DeRisi: Couple hundred dollars.

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Mark Zuckerberg: Okay. Yeah. And it's on its way down to tens of dollars, right? And it's now at the point where you can do, I mean that's the--

Joe DeRisi: It's a million-fold decrease.

Mark Zuckerberg: It's the fundamental-- but that's the ingredient to do the liquid biopsy type work that we're talking about or the IDC quirk that you were talking about is that all that stuff starts with you take a sample of blood, you run the sequence, you can do it quickly. I mean how long does it take now? It's hours? I don't know, days?

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Steve Quake: These tests are turning around in a day or two pretty much.

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Mark Zuckerberg: Okay. And so both it's getting faster and cheaper, and that will continue, but then you end up with a different bottleneck which I guess is what you're saying which is now what-- like so you get the data coming out of this and it's what? It's like gigabytes, right? For one sequence. So and it's at the point where-- I mean I'm on the board of the Biohub, right, because the Chan Zuckerberg Initiative is kind of the primary founder of it although not the only founder-- there are folks like Reed Hoffman who have also given millions of

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dollars to the effort-- in our Biohub board meetings I mean one of the things that we talk about is the cost of the compute, and our AWS bill for example is like one of the specific--

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Steve Quake: You'll hear more about that at the next meeting unfortunately. <laughs>

Mark Zuckerberg: Well that's okay. We'll call Jeff up and ask him about this, but it's interesting that the bottleneck for progress in medical research at this point, a lot of the cost in it is now on the compute and data side and not strictly on the wet labs or how long it takes to kind of turn around experiments, although that's obviously still going to be a big thing for a while as well.

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Joe DeRisi: This is no more apparent than in the developing world or low-income resource settings where actually the cost of the sequencing and the lab work has gotten to the point where you can do this almost anywhere in the world, it's gotten that cheap. However, the compute to be able to analyze that data is unfortunately not accessible to the vast majority of the people that do that. So it's very often the case you'll go to one of these low income resource settings they'll have a sequencer-- it's collecting dust. It's collecting dust because they can't compute, they can't actually do the compute side of it, and even

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if they could access the cloud which many of them can, they can't afford that, and so one of the primary initiatives that we've had here at the Biohub is to be able to address that bottleneck, to be able to overcome that compute barrier by providing really hardcore bioinformatic tools for these kinds of sequencing analysis at no cost as well as training them how to use them.

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Mark Zuckerberg: Yeah. And that's why a lot of the approach at the Chan Zuckerberg Initiative has been around engineering, right? It's taking some of the lessons that I've learned from the experience in building Facebook and try to build a world-class engineering team that can help crank on some of these problems and make it efficient, but even then we partner with folks like the Bill and Melinda Gates Foundation for your project in I.D. seek that to do the public health part of this, right, because it's expensive to do the compute and to get the equipment out and do all the pieces that you need to. What

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are the other trends or what do you think are the things-- so maybe on the negative side of this, what is slower today or the biggest headwinds either from technology or just facing science more broadly that weren't in place over the last 20 years?

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Steve Quake: Yeah. I think technology is largely an enabler of science, and that's been true not just for the past few decades but going back five centuries essentially-- many stories about that-- and the headwinds we're facing now are more societal. You touched on some of them in your comments. Issues of international collaboration are becoming very challenging now, and the trade war hasn't helped in that, and science has been a little bit swept up in that, and it's been-- certainly I hear from my colleagues they're frustrated with sort of publishing

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with authors internationally, having collaborations especially in China but not exclusively in China, and that's starting to put a chill on what has been a very powerful set of international relationships.

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Mark Zuckerberg: So maybe go into a little more details or specifics if you can because I would bet that most people who are watching this are not familiar with how the trade or a strained relationship with China would filter down into policies that make scientific research harder. So maybe just go into a bit more detail on how that works.

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Steve Quake: Sure. So science is a global enterprise and it transcends borders. We train people from many different countries in our labs, we visit labs in other countries as scientists, we publish papers together, and so it's sort of both the teaching and sharing of the knowledge we get with each other that advances the whole field, and now the trade war has sort of started to limit that in the sense that China has been a very actor industrially. I think no one is debating that that the

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commercial terms which they've engaged with other countries, stealing technologies, inventions, things like that have been really negative and not helpful, and the U.S. is justified in being concerned about that, but with science at the end of the day there are no trade secrets. We publish everything we do, we share freely, and a large part of what we want to do is accelerate human knowledge, and so there's not as much to be afraid of there, and in fact it slows down science when it

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becomes harder to talk and collaborate, and so simple things like you publish a paper, you sort of have an obligation to share your reagents with people, they write you and ask for them, I'd like this plasma or whatever, and now some of the funding agencies in Washington are making that much more burdensome like you need to get their approval to send it out. There's places they don't want you to collaborate with, and so there's kind of new sets of regulations coming down at a very granular level that's kind of inhibiting people from full and open collaboration.

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Mark Zuckerberg: And I mean so you mentioned some of the industrial issues in the U.S.-China relationship, but I mean one of the concerns that I think has come up on the science side is that there's a question around ethics and will advances that are being made be applied ethically and with the same standards in these different countries around the world. So what's the kind of case on the other side, or I don't know if you just think that this is too farfetched for how you'd handle some of those

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issues if not to try to put friction into the collaborations overall.

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Steve Quake: Yeah. So I mean that's a legitimate question to worry about because sort of ethical bodies are sort of done in each country specifically and there's not a global scientific ethics thing, and so there's sort of different standards for sure, and I think the systems in place are pretty good so if you're in a collaboration that involves human subjects or something like that, your university is going to look at what

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you're doing as part of this collaboration, so your part of it is going to be looked at with U.S. standards.

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Mark Zuckerberg: Yeah. So and what are you seeing as the implications of this on collaboration outside of China? So I mean the Chan Zuckerberg Initiative we do a number of collaborations I think with folks across Europe. I don't know if we do much in China, but those seems to be going well, right? I mean those are kind of good partnerships. We value working with-- some of the top institutes in the world are in Europe. How is that going? Is that being impacted too from your perspective and what you see, or do you think that this is primarily a China thing?

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Steve Quake: It's hard for me to know totally. I mean my sense is those are going to be impacted because the regulations that are coming are for all international collaborations, but most of the cases that are coming up are China related specifically so there are obviously very complicated, high-level politics going on around all that.

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Mark Zuckerberg: Yeah. All right. So maybe moving on from the topic of kind of trade and how that impacts science to this question around just truth and trust in experts, right, which of course we see affecting a lot of different parts of society. I mean there's a big crisis and a lot of questions around

journalism and high-quality journalism. I mean obviously Facebook in the work that I do most of my life is at the center

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of a lot of these questions around what is the role of social media in combatting misinformation, but there's the version of this for science too which it kind of plays on both how do we trust science, and how do we in the work that we're doing build trust in science so that way people can have faith in the work that's being done, and I guess that there's this broader trend of people probably trusting experts a little bit less now than they would have 10 or 20 years ago in general. So I'm curious

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what you're seeing on this. What responsibility do you think scientists have or people who are leading scientific institutions like you are, or funders of science which we are, what responsibility do we have and how can we best kind of combat this trend which I think is a really important and negative one?

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Steve Quake: Yeah. Absolutely. Distrust in science is something that's been gnawing at me for some time, and it's obviously a very complicated issue. I think that there are many things that influence whether you trust something in science or not. One of those things is just being scientifically literate, being able to understand the information that you're given, and then fundamentally do you have access to that information. I mean I think it's pretty obvious that if you don't have the facts or have the information you're not able to make sound

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judgment or objective decisions about that information itself, and so actually just having the facts is a big deal, and in science frankly I think we're headed toward a big reckoning here because where do you get your facts. If you have a family member that has cancer and you want to know more about that cancer or a clinical trial or how that drug performed you want access not to what a panel on T.V. said about it, you might want to look up the actual facts and research the primary literature,

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and the fact of the matter is today is that much of our scientific record is held by for-profit publishing companies as their private property in perpetuity behind paywalls even though your tax dollars paid for that science, and so what we're headed towards now is a reckoning with this issue and that the trend towards publishing things open access, that is not behind a paywall, I think is really going to be critically important for

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the advancement of scientific literacy and building trust in science, and so this is a big deal, it's been the case for hundreds of years that these publishing companies which served a much more legitimate purpose in the past when it was printing paper and distributing journals and things like that is very different now in the electronic age, and it's hard to justify what they do and their profit margins in today's world. We need to change that.

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Mark Zuckerberg: Yeah. Yeah. No I mean I think there's a lot of issues around this and I know one of the projects of the Chan Zuckerberg Initiative that we funded is bio archive and the whole pre-print movement to make it so that even-- I mean you're talking about one part of the issue which is the closed

nature of the publication. The other part of course is that it's slow, right? You go and you publish something and then by the time that it gets reviewed and one of these companies gets around to publishing it you might have burnt a year of other good scientist time studying a similar thing when you already had the

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result to what they were studying. So the pre-print not only makes it open but makes it so the turnaround time can be a lot faster and iteration time matters a lot.

Steve Quake: Absolutely.

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Mark Zuckerberg: One of the ways that I've kind of thought about this issue in trust in science is you have-- this may be oversimplified, but I think there are some people who say okay well you should always follow what the current state of science is saying, and then there are a lot of people who say hey scientists get it wrong, and it seems to me like the reality is somewhere in the middle. The current state of science is our best understanding of the world, but a lot of it is likely going to be improved upon or proven to be not wholly right in the

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future. Yet still your best bet when you're making medical decisions for your family or kind of decision in any part of your life, it doesn't have to be medical research, is your best bet is to basically go with what the leading research has been at that time even knowing that some of it will end up being proven false in the future because other than that you're just kind of going randomly. So one of the things that I guess I worry about, and I'm curious if you share this, is I do think in

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those two sides of the debate, some folks are you should always follow and like science is accurate all the time versus a I don't know if we should trust this, I do wonder if there's a responsibility on the part of science to sometimes not-- to make sure that we don't overstate things, right, and I know that this is something that you've talked about a bit in our conversations about how-- well I'd love to hear it in your words, but an issue that you've observed in the field over the last decade or so.

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Steve Quake: Yeah. There's a lot to unpack there. I mean I worry that this loss of trust in experts when it comes to science is a loss of trust in objectivity and in the process of science, and it's a different thing. So within science you should always be skeptical. This is a sort of fundamental tenet of science, to be skeptical. My mentor used to tell me never trust anybody, especially not yourself. <laughs> And there's a lot to that. You question, and this is how science advances by

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questioning other people's results, you question your own results, and that's just an essential part of what the field is, and so it's not that you're saying trust experts, it's saying trust the process of science, and another way <laughs> that's sort of frustrating right now that I think we could communicate better to the general public is around that, and Bob Phillips at Cal Tech has a very nice way of saying. He says, "Science is not a buffet." All right. You don't get to pick and choose what you believe, and there is truth and if you want to have jet

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airplanes that get you around the world and you want to have cell phones and you want to have the internet, well you've also got to accept vaccines and evolution and climate change. It's all the same intellectual edifice, and I think that's been lost right now. We failed to communicate that to the general public as scientists.

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Mark Zuckerberg: And what are some of the issues where you feel like a result gets overstated, because I think part of what might hurt trust is that, but I mean there are the advances that led to the internet or to jet engines or vaccines were obviously huge advances that when those things were figured out it had a many-fold improvement over whatever the current state of the art is. Yet a lot of what I see on a day to day basis is people

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publish results that might be a small percent improvement over something with not a lot of-- often it's very hard to reproduce, right? So it's hard to know if something was idiosyncratic to the data set that they used, and a lot of time it gets picked up and characterized and summarized even if not by the scientists themselves but by people covering it as like as if it's some

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kind of definitive proof of something even if the effect size was small, and I wonder how do we push back on that because it seems like you want to separate between the things that are truly transformative and major improvements and things that really might be marginal or might be nothing and likely were overstated, and I think that that's kind of-- when people hear about this, if something gets overstated and then it ends up not working out then that's how people lose trust.

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Joe DeRisi: Yeah. We've got to do a better job in science communication. It's about science literacy and science communication, and the way that science is communicated to the public now is really important. My daughter reads something in the popular press, "Hey daddy, they discovered something about this," and my first question is did someone else reproduce it? Is there another lab that confirms it?

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Steve Quake: Or where does it fit in the context of the hundred other papers on that topic. This is often where things get out of balance, right?

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Joe DeRisi: And those are often not communicated in the style of the common media, and I think we could do a lot better on how we communicate science to the public in the nuance and in speaking to the truth about reproducibility and the fact that things have to be done over and over again.

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Steve Quake: And I think it's a responsibility of the press as well and not trying to sensationalize the latest paper that came out and overstating it and forgetting the context in which it sits, often a literature of many histories. You were mentioning vaccines, and that's one where they're, these issues, are coming

up all the time right now, and all these elements are part of that story. So the whole vaccine autism sort of--

Mark Zuckerberg: Debacle.

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Steve Quake: --misconception, debacle, yeah. This started from one paper, published by Andrew Wakefield, with a very small number of participants. It was a result that disagreed with hundreds of other papers, people that studied for decades the effects of these vaccines, and that one paper the press jumped on, you know, didn't put it in context with the rest, so then popular culture picked it up and it created a situation where now lots of people aren't getting vaccines is really detrimental to society.

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Joe DeRisi: You know, it speaks to this concert, this concept, of sort of expert consensus, right, and it ignored the expert consensus. I think Lewandowski and others have written about this, but basically if you're approaching a bridge and 97 percent of bridge engineers say, "Hey, the bridge is unsafe," should you drive across the bridge? Right. If there's that one percent, that one paper says, "Well, maybe the bridge is okay." <laughs> You're not to-- you know, most people, most rational people, would probably take the consensus result, say, "Ah, maybe not today I'll cross the bridge."

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Steve Quake: And there's no room for nuance in a discussion either, because, you know, as I think you were hinting at, not all vaccines are equally efficacious, right, and some work really, really well. Most of the ones we're supposed to get are really tremendous. I'm up-to-date on measles, <laughs> tetanus, typhoid. You know, in the last year those are all ones I've had because they work really well.

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Joe DeRisi: You know, and measles encephalitis can ruin your whole day.

Steve Quake: Yeah, the disease, not the vaccine. <laughs>

Joe DeRisi: The disease, yeah. Yeah.

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Steve Quake: The vaccine is terrific, and with the uptick of people not doing, getting vaccines and uptick of measles cases, everyone should be looking. I got measles as a child, and my doctor had my titer checked-- I had the-- sorry, the vaccine as a child. Doctor said, "We better check your titer." No sign left, so I had to go get a booster.

Mark Zuckerberg: Interesting.

Steve Quake: But--

Mark Zuckerberg: Yeah. Got my flu shot yesterday.

Steve Quake: Yeah. Well, that's one where it's--

Mark Zuckerberg: Just a shout out to everyone watching. Go get your vaccine. All right?

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Steve Quake: <laughs> Yeah, that's one where it performs less well though. I think flu in comparison to the whole rest of the battery is significantly poorly performing, and it's not good if we don't acknowledge that as well and say that, "This is an area where we can do better," and we should be putting a lot of effort--

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Mark Zuckerberg: But when you say performs less well, you mean the measles vaccine definitely prevents measles. The flu vaccine at the beginning of the season, the scientists and people in charge of managing infectious disease have to kind of make an educated guess at what strains are likely going to be big, and then they put it into the vaccine, and then you could vaccinate against those. So they might be wrong, but it's not going to harm you.

Steve Quake: Generally not. That's right. Not harmful.

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Joe DeRisi: Yeah. Yeah. Yeah, and may have some beneficial effect for some segment of the population. It's better than none. You know, this is a really important point, and the important point is that these are the kinds of things that are a public health issue, and they're-- and it's one of the areas that I really feel strongly about. In fact, that I think that we should recognize the fact that if you want public health policies to succeed, they basically have to be mandated. You cannot leave it to the individual to enforce those public health policies or they will fail.

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Mark Zuckerberg: Hm. Interesting. All right. So I want to move on to another topic, off of the broader issues and maybe little more futuristic. So let's talk about wearables and implantable technologies. This is something that I work on and I'm interested on on the Facebook side too. We've also had a bunch of conversations on the science research side. You know, Facebook recently we made this acquisition of this company, CTRL-Labs, that basically is a wristband that can pull-- it can digitize signals that are coming down from your motor neurons,

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so the goal is to eventually make it so that you can think something and kind of control something in virtual or augmented reality with it. They actually have a dev kit of this working already today, so it's not like far-off science fiction. But one of the big questions, and I mean, they have a great team of computational neuroscientists, and they really believe that the best approach to neural computing is wearable, versus putting something inside you. Now, other people-- I think that there's-- there's Neuralink is the company, for example, are

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experimenting with approaches that are implanting something in you, like, literally drilling holes in your head, putting something in your brain, trying to pull signals that way, and of course, it's not just getting signals from the brain. I mean, there're things for managing a number of health conditions, and I'm curious, just I think it would be useful or interesting, to have the, to hear your thoughts, on where are the boundaries between where something is better as a wearable versus

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implanting in you? What are kind of the challenges that need to be overcome with implantables and kind of how do you think about that broadly?

Joe DeRisi: Oh.

Steve Quake: Want me do it? All right. <laughs>

Mark Zuckerberg: You go first. <Inaudibles 00:05:06>.

Steve Quake: I'll go first.

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Joe DeRisi: I have my own thoughts on this and they probably will differ from yours.

Steve Quake: Okay. You know, it's definitely a higher barrier to get to an implantable, I think, and, you know, my personal--

Mark Zuckerberg: I would hope so.

Steve Quake: Yeah, exactly. Because of the risk. There's a health risk involved in the procedure.

Mark Zuckerberg: Yeah, of course.

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Steve Quake: And, you know, I think those are probably most useful in cases where you've already got a medical condition, usually chronic conditions and things like that, that need to be monitored and managed in ways that you can't get the information any other way. If you could get it from a wearable, I think that'd be your first choice, but if you've got to measure pressure in, you know, in your coronary system or something like that, your pulmonary system, sometimes you've got to be inside to do that, and there's devices that do that now and they're going to probably be more broadly used over time and you'll see,

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I think, their role in management by talking to external devices and things, get a lot more sophisticated. But I think for the largest number of people, the wearables are going to have the most impact, because it's just noninvasive and it's easier to do.

Mark Zuckerberg: Yeah. So what are the problems though that you think you need to be inside the body to get?

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Joe DeRisi: Well, one of the obvious ones is getting direct access to neurons, and I think some of the most dramatic advances that we've seen over the last year in this area, for example, Eddie Chang's work at UCSF, where, again, you have to take the skull off, but an implantable sensor array can actually decode in real-time inner speech. So think about aphasic people, people who can't talk because they've had a stroke. This sensor array can literally decode inner speech. So you think a sentence and with very high accuracy in real-time it can read it out, and those kinds of accuracies and that kind of

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detailed real-time information has never been possible from surface readings. You actually have to get under the skull and touch neurons, and I would say that the same is going to be true for certain kinds of neural prosthetics, for very complicated motions. Playing the piano, for example, is going to require direct interaction with neurons.

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Steve Quake: These are people who are very sick though, who are paraplegic, paralyzed in some way, right.

Joe DeRisi: Yeah. Well, like I said, aphasic, not able to talk.

Steve Quake: Exactly, so--

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Joe DeRisi: I mean, the worst one that, you know, I've ever heard of is called locked-in syndrome, where you're completely paralyzed but you're cognitively active. So, you know, imagine those people, if you could provide access to the outside world through a neural link.

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Mark Zuckerberg: Yeah. Well, especially if your brain is not able to send out motor neuron signals. I mean, part of the theory that the CTRL-Labs team has is that, you know, it's pretty much all animals have motor neurons, right, and it's-- before, I mean, humans are somewhat unique in having the neocortex and the thinking part, the reasoning, but, you know, every animal moves, and because of that it's actually one of the areas of our biology that has the most redundancy, right. If, like, a neuron gets damaged there's plasticity and your body can

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remap it to something else, which means that your body also has excess capacity to be able to, you know, just like I can move my hands around, I have enough kind of neural capacity in my motor neurons to probably control another extra hand and it's just a matter of training that, and then they can pick up those signals off of the wrist. But obviously, if your ability to translate things that are going on in your brain into motor activity is limited, then you need something implanted, but--

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Steve Quake: No. I think you're right. This, the peripheral nervous system, is going to be really useful for wearables. Scott Delp at Stanford has been developing wearables to control tremor diseases and things like that, handshakes and using feedback based on measurements of a wearable on the peripheral nerve, and that all looks very promising.

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Joe DeRisi: In fact, one of our Biohub investigators, Rikky Muller, is doing implantable, closed-loop deep brain stimulation. You know, in fact, deep brain stimulation's one of the areas where people are walking around today with implantables in their brain for-- mostly for motion disorders but also now for depression and many other things, and actually having a closed-loop system, like Rikky works on, that can actually monitor what's going on in the brain and then modulate that activity in real-time, I think is very powerful and it makes a strong case for an implantable that's below the skull, and depression's not exactly, you know, infrequent either.

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Mark Zuckerberg: Yeah. So what about outside of the brain? What do-- I mean, so you mentioned the heart, but, I mean, what do the-- I mean, some of these things-- well, I'm curious if you have examples in mind that you think would be interesting, but I'm mostly curious to go through some of the challenges of this. I mean, it's-- our body basically treats anything that's foreign as something that needs to be quarantined and kind of boxed off, right. So what are some of the-- so where do you think this would be useful, and what are some of the challenges that need

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to be overcome to make this something that can actually happen over time and have a lifespan that's beyond, you know, a year?

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Steve Quake: Well, you know, some of the best examples are stints and pacemakers, right, which will-- stints will go in for 20 years or more, and they're passive devices, so don't need power or anything like that, but they're able to be there in the body for very long periods of time and not be completely rejected. Pacemakers similarly have fairly long implantation times, and so those are examples of, you know, what you can hope to aim for, more complex devices, and I think you'll see them in areas like pulmonary and cardiovascular disease for sure.

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That's where there's been the most history, most medical need, and where there's a very bright future.

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Mark Zuckerberg: And how do we deal there with the problem of the immune system attacking foreign objects in the body? Why do those last for 20 years but other things that might be implanted have significant bigger challenges?

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Steve Quake: A lot of it's the material science of the devices and what you can do around that to control and, you know, if you want the device to be sampling from the body then you have interfaces that are harder to control, and so lot of it is design specific, I think. Other parts of it, I think, are lifetime related with batteries and--

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Mark Zuckerberg: I see. I see. So your point is, if you want to have something in your blood-- right. So take for example, like, the liquid biopsy thing that we talked about before but some version of this, like, 30 years from now that's not just a one-time test but like a permanent thing in your body that, I mean, I don't even think that there's any roadmap to be able to get to this in 30 years. But in theory you would want something that could on an ongoing basis monitor what's going on in your body and alert you if there's something that you need to go deal

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with, but in order to do that, in addition to, like, many other problems that you'd need to deal with on the path to that, it would have to have an open interface to the blood and when something has an open interface like that it's just more-- when the, I guess, when the immune system tries to box it off, which I'm sure there's a more technical term for than box it off.

Joe DeRisi: Yeah, biocompatible.

Steve Quake: <Inaudibles 00:11:56> growth, yeah.

Mark Zuckerberg: Yeah.

<laughter>

Mark Zuckerberg: It's tough to keep those interfaces open, all right, so--

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Joe DeRisi: You know, biocompatible material science is where it's at, and being able to have these electrodes or interfaces stay fruitful for a long time is really a huge challenge. The arrays and sensors that are-- we have today have a very short half-life. They get blocked off, as you say. They lose functionality until that is solved and it's really a biocompatible material science problem, and I would also say that you're going to want to have these things passively powered. You can't have batteries in there. That's sort of unrealistic, and so how do we get passive power transmission, whether--

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Steve Quake: Well, Ada Poon, one of our investigators, has been--

Joe DeRisi: I was just about to mention her.

Steve Quake: --new field charging [ph?].

<laughter>

Steve Quake: Oh, there you go. Sorry. You're setting it up. <laughs>

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Joe DeRisi: Yeah, you jumped the gun. So Ada Poon, one of our investigators, is developing new ways to harness ambient Wi-Fi and other power transmission modalities to power nanodevices, in which case you don't really need long-live batteries underneath the skin, and that's going to think be really critical.

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Mark Zuckerberg: Yeah, that's really interesting. All right. So maybe one more topic before we wrap. You know, so the Chan Zuckerberg Initiative for science, we kind of have this very long-term goal, which it's going to take a very long time to get to, but the hope is to help the field of science to cure, prevent or be able to manage every disease hopefully within our children's lifetime or, you know, by the, you know, maybe by the end of this century, and that's, I think, there's a lot of

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debate about whether that's possible to get to. There are kind of broad-- there's a lot of different diseases, but there aren't that many different categories of diseases, right. So we've talked about infectious diseases, cancers. You know, people die from accidents. There's obviously the neurological and neurodegenerative diseases. I'm curious from each of your perspective, what do you think needs to happen over the next, I don't know, 20 or 30 years to get us on the path to being able to achieve that goal? Yeah.

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Steve Quake: Okay. So when you look at the global burden of disease, around the world right now sort of by whatever statistical metric you care about, they're sort of dominated by two broad categories. One is infectious disease. The other are diseases that relate to disorders of the cell, and there's-- a lot of what you just mentioned fall into that, and so if you're thinking a hundred-year time scale to reach that second category, what you should be investing in now and what we decided to do with the Biohub was make a very strong investment in understanding cell biology. You understand the basic biology

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of cells you'd be able to then use that to understand and hopefully correct and cure these diseases, and that gets a big piece of the puzzle right there.

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Joe DeRisi: Absolutely, and investment in tool building. Like, having tools that let you do that next thing at a accuracy or proficiency logs better than you can do now is critical. So how do we make vaccines, how do we design vaccines? In the past it was, you know, sort of hit or miss. You know, get the bug and activate it, make it immune respond to it. That works for some things, and for polio and measles, many other things, it's been a huge success. For other things like malaria, it's been a lot tougher, and we need to be smarter about how we do that. It's

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going to be limited by our ability to see the molecules, it's going to be limited by compute, but if we can design immunogens, the thing that elicits the immune system, to create antibodies that we already predetermined, broadly neutralizing the antibodies, for example, antibodies in your immune system that can actually prevent HIV or prevent forms of dengue virus or whatever infectious disease you care about, that would create a whole new area of vaccinology and immunotherapeutics that we

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can't even imagine right now today. But we know that the power's there to do it. Human beings naturally generate these antibodies. If we can understand the fundamental rules about how they do that, when they make a good antibody from a bad antibody, we can play the same game.

Steve Quake: It'd be a game changer.

Joe DeRisi: Total game changer.

Steve Quake: It'd be totally transformative.

Mark Zuckerberg: So how do we get there?

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Joe DeRisi: So one is to understand how the, you know, when a rare individual does make that one-in-a-million antibody that tends to be, like, really good and neutralize all the forms of dengue virus or HIV-- HIV's been one of the toughest ones to do-- or malaria, a parasitic disease, we have to understand what were the rules by which that immune system evolved to that point? How did it get there? And if we can create a molecule that can walk the immune system down that same path to end at the same antibody, then we can help everybody's immune system do

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the job itself rather than giving people a medicine or small molecule, which are also very important, don't get me wrong.

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Steve Quake: And Peter Kim, who's been our lead adviser on the infectious disease project, has really fantastic ideas there and is taking the steps down that path, right. Super-exciting.

Joe DeRisi: Absolutely. He calls it immune focusing.

Steve Quake: Yeah.

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Mark Zuckerberg: Yeah. So you mentioned the strategy of building tools, right. So if the goal over a, you know, 80 or 100-year period is to dramatically accelerate the rate of progress, and part of how you do that is by giving scientists better tools that they can inspect things in more detail, can do the computation that they need to faster, et cetera, and obviously, at the Chan Zuckerberg Initiative we're not actually, you

know, doing the science directly. Our home mission is around empowering scientists to make these, to make this

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progress. I'm curious, what are the things that you think need to happen to accelerate scientific progress the most? Whether it's like specific tool development, things that you'd like to see in the field, or just overall in order to kind of get closer to this, to this mission.

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Steve Quake: Well, you touched on it earlier, I think. You know, one of the ways-- we spent a lot of time thinking about how to accelerate science as we were all planning the Biohub together and, you know, accelerating communication through preprints. I mean, that's a big experiment we're doing, and all the research we do and all the research we fund people have committed to accelerating the sharing of the results through preprints, which if you do the back-of-the-envelope calculations could be even a factor of five increase in the speed of discovery over a decade or two. So that, we think, we're really

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interested in seeing how that works. But also I think just really recognizing that science, scientific discovery, is often driven by the development and application of new technologies and, you know, sometimes in the narrative, that gets a little bit swept under the carpet, but I think bringing that out and recognizing it and saying, "We're going to explicitly invest in that and try to develop the next generation of tools," whether it's compute-based or novel forms of microscopy or the next generation of genomic tools, and helping people use them in their research.

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Joe DeRisi: I'd make a pitch for fundamental discovery of basic science and curiosity too. That, you know, sometimes you're studying something or you have a scientists that's studying, that's very basic, it's not obvious to see how it'd ever be applied in the real world, but sometimes that fundamental investigation, that discovery or that, you know, dissecting of really basic mechanisms, can lead to quantum jumps that no one ever expected. I mean, just in the last decade, Jennifer Doudna and others have, you know, studying phage, you know, viruses that infect bacteria. No real obvious play on how that

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would affect human health or disease in any real way. Unleashed the revolution of CRISPR and gene editing, and that came from basic science without an obvious applied goal, and so there's a role for fundamental curiosity-based investigation in everything we do.

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Mark Zuckerberg: All right. Well, I think this has been great. I think we hit a lot of topics. I'm real excited about the work that you guys are doing. Thanks for joining me today.

Joe DeRisi: Thanks for having us, Mark.

Steve Quake: Thank you. Yeah.

Joe DeRisi: Yeah.

Steve Quake: It was fun.

Mark Zuckerberg: All right.

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