

Disruptive: Synthetic Biology

Host Terrence McNally interviews Pam Silver, Ph.D., and George Church, Ph.D.

Terrence McNally:

Hello, I'm Terrence McNally and you're listening to Disruptive, the podcast from Harvard's Wyss Institute of Biologically Inspired Engineering. The mission of the Wyss Institute is to transform healthcare industry and the environment by emulating the way nature builds with a focus on technology development and its translation into products and therapies that will have an impact on the world in which we live. The Wyss is not interested in making incremental improvements to existing materials and devices, but in shifting paradigms. Today's episode of Disruptive, synthetic biology.

"We have within our grasp the technology to change evolution. This could change the course of biological life." Those are the words of Paul Berg, Nobel Laureate, and a pioneer of genetic engineering. What sorts of breakthroughs are possible by modifying an organism's genome, something we're now able to do evermore cheaply and efficiently. The basic idea behind synthetic biology, according to one of today's guests, George Church, is that natural organisms can be reprogrammed to do things they wouldn't normally do. Things that might be useful to people.

Researchers have learned not only how to read an organism's genetic code, but also how to write and insert new code into that organism. Did you know that we're already able to program microbes to treat wastewater, generate electricity, manufacture jet fuel, create hemoglobin, and fabricate new drugs? What sounds like science fiction to most of us might be a reality within our lifetimes. The ability to build diagnostic tools that live within our bodies or treatments to eradicate malaria from mosquito lines or possibly even to make genetic improvements in humans that are passed down to future generations. These can be game changers.

In pursuit of these high impact benefits, what sort of risks are we looking at? Will there be unintended consequences to humankind or to our ecosystem? When will we know the effects as they play out over generations? This conversation about the promise and the risks of synthetic biology has come to a head recently with the publication of two public letters. The first, signed by a small group of prominent researchers posted on March 13th in the journal, *Nature*; the second, signed by 18 leaders in the field, most of whom had gathered in Napa, California to come up with a path forward posted March 19th to the journal, *Science*.

The Napa group wrote of unparalleled potential for modifying human and nonhuman genomes to cure genetic diseases in humans and to reshape the biosphere for the environment and human societies, and they warned of unknown risks to human health and wellbeing. Bottom line, how do we make this work so that humanity enjoys the benefits of the breakthroughs without suffering unintended negative consequences, and what do we need to do now to move in that direction? We'll explore these questions with Pam Silver and George Church,

one of the signers of the Napa group letter. Among the many positions and titles they hold, both are founding members of the Wyss Institute.

Pamela Silver, Professor of Systems Biology at Harvard Medical School received her BS in chemistry and PhD in biochemistry from the University of California and did post doctoral work at Harvard. Pamela is building cell based machines, designing novel therapeutics and re-engineering photosynthetic bacteria to produce hydrogen and other fuels. She's won many awards and grants and serves on a number of private and public advisory boards. Most recently, she was recognized with a large award from the department of energy to develop electrofuels. Welcome Pam Silver to Disruptive.

Pam Silver:

Hi Terry. How are you?

Terrence McNally:

I'm good, I'm good. I'd like listeners to get a feel for the people behind the work and the ideas that we talk about, Pam. So can you take us back and tell us a bit about your path to the work that you do today and feel free to mention mentors, turning points, moments of decision.

Pam Silver:

Sure. I love to talk about myself and this could take the whole hour by the way. Let me begin by saying that I actually grew up in California in the Silicon Valley area during the birth of the personal computer. My family was intimately involved in that. My best friend's father ran one of the biggest computer companies. So, science and engineering were heavily encouraged in that environment. I actually had precocious math ability as a girl, which was considered unusual at the time. I think I actually became the subject of someone's PhD thesis at Stanford because of this. And I won the IBM math contest. The prize was a slide rule, if anyone knows what that is anymore.

Terrence McNally:

Actually Pam, I love the fact that I used to sort of feel intimidated by the folks who had slide rules in high school. When I realized that they had become obsolete, it was like a sense of personal triumph.

Pam Silver:

Well, they became obsolete in part because of my best friend's father, who was one of the inventors of the first calculator. I remember once being at their house doing our P chem homework and he came home and threw down the first programmable calculator and said, "Here girls, try this." So the environment was right for me in terms of innovation and being in the right place in the right time. I first started in math, migrated to physics and realized at the time in physics that the choices were either to work on chaos theory or work on high energy physics.

The trouble with high energy was that you would have to work at an accelerator and you only got to do an experiment once a year if you were lucky. And then if the pen broke on the readout, you were screwed. So that was out because I really wanted to do experiments. So I ended up migrating to chemistry. And then I think a key event for me was being sort of at the right place at the right time during the molecular biology revolution, which was just absolutely transformative. I think looking back and looking at the history of synthetic biology, of course the precursor of that is molecular biology where we learned how to engineer single genes at a time.

Molecular biology was very important in telling us that biology was fundamentally modular and that is one of the underpinnings of synthetic biology. What do I mean by that? The gene was the original modular unit of biology. You could transfer a trait with a gene from one organism to another.

Terrence McNally:

What year is it that we believed this?

Pam Silver:

Oh well, this was the work of Mendel. This goes back early 1900s-

Terrence McNally:

And it holds until.

Pam Silver:

Well, then once people, like you mentioned, Paul Berg and others were able to start cutting and pasting DNA of organisms in particular bacteria at the time, it became evident that there was modularity that extended beyond the gene. We could take parts of genes and move them to other genes and they would function. There's something called a promoter. You can move that promoter around and it will regulate different genes. That's the definition of modularity, being able to take something out of its natural context and move it somewhere else and have it function in the way it's supposed to.

Pam Silver:

Let me preface that by saying that this goes back to what I consider this so-called founding of synthetic biology, which I was involved in here in Boston in about 2002. I got together with a group of computer scientists and bioengineers at MIT when we called ourself the synthetic biology working group. I was the token biologist, and the premise that they had was that biology should be as easy to engineer as it is to build a computer chip, and why isn't it? That was the underlying premise.

And then what led to this idea of employing modularity of biology is much the same as what an engineer does or an electrical engineer where they build a circuit and they use different parts to build that circuit on the chip and they know the

characteristics of those parts so they can predict how the chip will behave. This is how the computer industry works.

Why is biology the best engineering material? Life can do a lot of things and it can do it better than what engineers can often do, or it can do it in ways that are more compatible, say with interface with ourselves or with the rest of nature. So, one of those is this exquisite sensitivity of biology. I'll use as an example the olfaction system, your ability to smell. Your olfactory system can sense a single molecule. There's very little that can do that in real engineering.

We already discussed the ability to use modules. Much like electrical systems, biology is capable of sending and receiving signals. Of course in the nervous system, this is standard, but there's also cell cell communication that occurs in all parts of your body, in all parts of nature. Between different bacteria in your gut, they're talking to each other. What's that conversation about? We need to understand that and once we can understand that we can use it to engineer, for example, your gut. This is a project we're working on where we want to reboot your gut bacteria.

And then lastly, of course, biology unlike machines can duplicate itself. Now, as synthetic biologists, part of our responsibility is to make sure that duplication is accurate, doesn't cause mutation or things to go haywire. This is part of our responsibility to make sure that when we build these systems, they don't go wild, they don't go out of control and they don't integrate into the natural world.

Terrence McNally:

Yeah. In other words, the phenomenal opportunities that we face here once we are able to tap into biology to work with us and for us lays with it that responsibility.

Pam Silver:

Yes. But keep in mind that we have already been employing biology in our service for ages. For example, we engineer plants through evolution. We evolve them to have certain phenotypes or certain characteristics. We as humans have been evolving plants to do what we want: grow with certain fertilizers, grow in a more drought like conditions, grow in more crowded conditions, have better yield, be insect tolerant.

We've been doing this and if you look at the original corn that Indians had, the corn we eat today looks completely different. So, as humans, we've already been mucking around with nature. So, I think it's important to keep that in mind. That was using evolution, but using it for our benefit. Now we're just better at it.

Terrence McNally:

Right. We know more and we have much more powerful computational tools to work with.

Pam Silver:

It is that about 50 years of molecular biology which culminated in the sequencing of the human genome and now what we really call citizen science where essentially anyone can sequence anything. It's cheap enough. To do DNA sequencing now of genomes is one of the cheapest commodities you have in science and can be done on a bench top. So, now that we have all this information close at hand, we can employ that to start engineering organisms, and that was brought to us by this essentially 50 years of molecular biology.

And so it's in a wonderful deep history. Many of us were heavily engaged in that and now to be able to see the fruit of that, to think about this idea that we can use biology in a predictable, cheaper and faster way to engineer it to do good is really the definition of synthetic biology as you pointed out at the beginning. It is not about whether we can make whole new organisms. That's an approach to synthetic biology. The goals really are this faster, cheaper, more predictable engineering of biology for good.

Terrence McNally:

On your website, you say we seek to implement design strategies used by nature as well as to go where evolution may not readily go. Now that's something which might make someone nervous. Could you say what you mean by that because I think it's pretty interesting.

Pam Silver:

So evolution, if you believe the standard theory, would be selection of the organisms that can thrive in a certain environment, right? And they do that simply, the others die and the good ones grow. So what you can do is apply artificial evolution. I could say, for example, I want to make a plant that can grow without hardly any water. So I set up an experimental condition in the laboratory and then I put lots of plants out there and I look for the guys that can grow. So that's imitating a condition and allowing evolution to occur in the laboratory. You can also accelerate it in different ways by using the tools of molecular biology to help accelerate evolution. But that might not be a case where you would be able to find that drought resistant plant out in nature.

Terrence McNally:

So that's where you take a path nature is on already and you find things you've learned to actually accelerate the pace of evolution in a direction that you choose.

Pam Silver:

Not only that, but you also can apply... I used a real world example that might resonate for people, but you could also pick other unusual conditions like an unusual drug or something like that, that you really want organisms to be able to grow in the presence of where they normally don't. So, you can apply in sort of an artificial evolutionary condition as well that might not be seen out in the real world. Or you might anticipate... say you want to send things to Mars, so you might

anticipate, "Okay, here's what it's like on Mars, can I evolve some organisms here on earth that might live on Mars?"

Terrence McNally:

Now that we've defined some terms and laid out some history, can you talk a bit about what you're working on these days?

Pam Silver:

I can talk about the two that are the most exciting to my laboratory right now.

Terrence McNally:

Absolutely.

Pam Silver:

One I just mentioned was engineering the gut so that it can respond and possibly act as a therapeutic, both a diagnostic and a therapeutic. Imagine first of all the real world problem and I will take it to the human level for a moment. So here's a real world problem. If you have a chronic disease of the gut. You're living, you're not going to die from it. But it's a chronic disease, you are in pain all the time, for example, with Crohn's or inflammatory bowel disease.

What if you had a bacteria that was native to the gut but have been engineered so that when you have inflammation, it can sense that inflammation and then secrete or let something out of it that will treat that inflammation. It's like a Sentinel. It's standing there in your gut ready, on alert, for when something bad happens. And we can do this now actually. This will be fairly short term.

Another one, a huge cost to the military and to the world in general is traveler's diarrhea. In point of fact, when troops are deployed overseas, they're down for three to five days and the cost to us, the taxpayers, is huge. Many people do not realize this. Imagine if you could create a therapeutic gut bacteria that would prevent traveler's diarrhea. So that's ongoing. That is research that is ongoing in our laboratory by trying to create artificial communities of bacteria that you could regulate on demand.

Terrence McNally:

How far away is that?

Pam Silver:

If DARPA has its way, two and a half years.

Terrence McNally:

The evolution of antibiotic resistant microbes through the overuse and abuse of antibiotics could lead to the end of the antibiotics era that we take for granted. I suffered a staph infection, a pretty severe staph infection couple of years ago, I

take that threat seriously. You've engineered this natural gut bacteria we spoke about that can remember exposure to antibiotics in mice. How is that going to help us with this threat that we face?

Pam Silver:

Well, first of all, that system is highly modular, so I can make it respond not just to antibiotics, but to inflammation, to other drugs. It's the perfect example of a synthetic circuit that's highly modular. So it's very useful. What it could do is help reduce the amount of antibiotics that's being used because it can not only register whether you've been exposed to antibiotics or not, but how much, and it can also act as a counter and say for how long you've been exposed to those antibiotics. So in that way, it's acting as a probe, as a diagnostic.

But let me give you another potential real world application that could happen now. So as you know, there's a big issue around use of antibiotics in the livestock industry and perhaps this is impacting on our own health and our own resistance. So, in the poultry industry, don't laugh, there's a lot of inflammation that's a problem. Oftentimes they sample only a few chickens in the flock. So if you could use our bacteria in a contained environment to diagnose those chickens, you would know what's going on in the whole flock. And so that's a relatively cheap, fast way to engineer the poultry population without having to directly engineer every chicken.

Terrence McNally:

Right. And if I'm following you, right now they just blanketly use a lot of antibiotics for the fear that some of them might have problems, right? What you're saying is, using as a diagnostic, you could select, you could say, we don't need to give it to everyone.

Pam Silver:

Right.

Terrence McNally:

You've set some very important goals for synthetic biology. One is to get beyond the dependency on petroleum and the other is to design a sustainable earth. I like both of those. They're big and they're enormously positive. How are you working toward those two goals right now in the lab?

Pam Silver:

Let me tell you about the bionic leaf.

Terrence McNally:

Yes. I love the bionic leaf.

Pam Silver:

This is the thing I am most excited about today. Let me preface this story by saying this is a case where a wonderful collaborative effort, I met Dan Nocera who used to be at MIT and is now here at Harvard in the chemistry department. I literally met him in a cocktail party and he had just moved to Harvard and he said, "I've been wanting to meet you," because he had developed something called the artificial leaf.

He's an inorganic chemist. He has developed a catalyst essentially that will act like a leaf. It will do what's called the water splitting reaction, and it will do it cheaply. The water splitting reaction generates hydrogen and oxygen. That's the front end. So you've got a solar panel hooked up to his magic artificial leaf.

What do you do with that? It's the age old problem of, how do you store solar energy? Now, Dan's original concept of this, and I was interested in this as well, is a hydrogen based economy. Now, that comes and goes in terms of popularity. Hydrogen, by the way, is a clean burning fuel. So it has that advantage. But he was sort of stuck with, "Okay, now I've got something that makes hydrogen, what do I do with it?" Okay, there's some hydrogen-based cars. But at the time DOE was pushing the electrical cars. So what are you going to do with this thing?

So we said, "Well look, there are bacteria that can live on hydrogen. They eat hydrogen. All they need is CO₂ and hydrogen." And so we then interfaced these bacteria together with the artificial leaf so that the bacteria live in the presence of the artificial leaf and they make stuff, in this case, a pseudo fuel.

So this is a way of taking sunlight and converting it into biological carbon. It's a drop in, that means you can just essentially put it in water. It could be used in the developing world, it can be scaled up. We also call it the bionic leaf because it's the interface between the inorganic and the living system that has been engineered.

Terrence McNally:

And one of the things that you point out about this is that just in the same way that nature has decentralized local energy, once we deploy this technology, we can also look toward local decentralized energy rather than depending on massive powerful companies with grids.

Pam Silver:

When I was working on this early on several years ago, I owned the domain name personalized energy because I wanted to think about it that way. That you would, for example, grow a bunch of bacteria on your roof and they would make stuff for you. So, that's how Dan and I think about it, is this idea that... and in a way, people who have solar panels are already doing this. They're already decentralizing, even though in some cases they're selling it back to the grid. But imagine if you could use that to drive production in your own home of either energy or make your own commodities. You need a certain drug, what if you had the bacteria program to

make a drug? I mean, this is getting way out there in the future, but this gives you the front end to do that.

Terrence McNally:

Photosynthesis is, none of us would be here without it. When I've looked into all this, photosynthesis is the only free lunch there is. Sunlight comes and photosynthesis converts it and suddenly we have things happening. When you begin to tap into that power and that ability, that is really enormous.

Pam Silver:

Well, this is why I've called the engineering of the photosynthetic machinery, I think it should be a grand challenge because right now, as you know, plants are the least efficient at harvesting sunlight. It's about 1% or so. Photosynthetic bacteria get a little better and algae I think hit the peak at 5%. Actually there may be some bacteria that can get up to 8%. Our leaf as of right now is doing about 5% which makes it equivalent to algae, which is huge. I know it doesn't sound like a lot, but we're doing better than a real leaf and we're doing almost as good as the best thing on earth.

Terrence McNally:

Right. I have a quote from Dan here and I've seen him make a presentation on this which is one thing that got me interested in all of this. He says, "There's been 2.6 billion years of evolution and Pam and I working together a year and a half have already achieved the efficiency of photosynthesis."

Pam Silver:

Thanks Dan. Well, the evolution is an interesting question in and of itself, which I don't want to get too close to because many people have different opinions on it. But going back to your thing about evolving organisms synthetically, there's another way to think about this problem. We have engineered something that is potentially scalable and more efficient. It has the potential to be better. But, what if we go back to life and say, "Can we now make living photosynthesis better?" And I still think that should be a grand challenge.

Terrence McNally:

Are there unique challenges to the field of synthetic biology? You've made the point a few times to do things for good so that things don't get loose in the wild and so on. I would think predictive, ethical, political, cultural, some of the challenges that synthetic biology faces. Could you speak a bit about that?

Pam Silver:

A little bit. To be honest... I've been very impressed with the community in that it has caught the fascination of not just engineers and scientists, but also ethicists and policy people. And so, the community has sort of grown together and we have a lot of people thinking about ethics and policy. I think MIT may even almost have a department of it. And that's a great thing because I am not a policy person, although I just got back from the White House, and I'm learning more about it, but

I'm a scientist and I like the idea that there's this community that I can go talk to and learn more about what these issues are and what real people think about. So, I think that's one way that some of these challenges are being addressed.

It's also being addressed by the press quite a bit which is a good thing and sometimes a bad thing. But again, the discussion is quite open and I think it's certainly caught the fascination of young people. I have more students that want to work in my laboratory than I had when I worked on cancer. And this has just caught the imagination probably much in the way that the IT industry catches the imagination of young people. I think synthetic biology has also caught their imagination, and we should not lose that over issues of policy or issues of fear. We should somehow understand how to nurture that.

Terrence McNally:

Let's talk a bit about the fear. You've been working in this arena for quite a while. When you're looking at experiments and research, how do you deal with the possibility that something could go wrong?

Pam Silver:

Well, I would say for most of my scientific career, I worked on laboratory organisms that are contained and are not pathogens and the recombinant DNA aspect had been already dealt with with the Asilomar meeting in the early days, and there was a moratorium in Cambridge.

Terrence McNally:

Asilomar was back in 75.

Pam Silver:

Yeah, that was the mid 70s and to be clear, that was the product of scientists talking about the dangers of release. They did not talk about malicious behavior. They did not talk about bio warfare. They simply addressed the issues of release.

Terrence McNally:

So if I can say involving no bad actors, it's just even doing our best, could something go wrong?

Pam Silver:

Right. What came out of Asilomar were the biosafety rules which we still live by. So we have carefully controlled facilities if I want to... I've worked on HIV, there's a biosafety containment lab here at Harvard where we can work on HIV. So this is the mechanism that we've lived with and it's worked. The data's there, it's worked. However, now that we are starting to do things... so you asked about me personally, I bought into, in general, recombinant DNA is safe based on the many years of experience and the biosafety rules.

However, moving forward, as we start to explore, this ability to sequence anything is powerful and the ability to potentially manipulate anything is powerful. So as we move forward, we start to get into the realm of organisms that we don't normally handle and we don't even know if they can be pathogenic or not. For example, for working with the gut microbiome, there may be organisms in someone's gut that could be bad for someone else, right? And so, this is where I pay attention to my students and that they are actually following the rules for containment. It's not a game.

Terrence McNally:

How would you define responsible conduct and is that something that is only up to one or is that part of a partnership and a collaborative sort of nature of responsibility?

Pam Silver:

I think it's like everything. First of all, there's personal responsibility. You have a personal responsibility to protect yourself and to protect your neighbors, in this case in the laboratory, and to be open about what you're doing. I think there's a need for openness about the research you're doing, not just to your neighbors but to all the people around you. And we should have more open sharing of what people are doing.

Then there's this issue of citizen science where people are going to start experimenting on themselves and/or obtaining their own genomes and thinking about that. And so, I think that's where we need, and I hate to sound trivial, but we really just need more science education. The infamous Larry Summers said, "I don't want anyone to leave Harvard without knowing the difference between a gene and a chromosome." I don't know if that ever came to be true, but if this is the technology of the future, which I believe, or it's the technology of now, then I think people need to be a little more educated in it. They don't have to know everything, but they should be more educated.

Terrence McNally:

If you had a final word to listeners who've tuned into this podcast, what might that be in terms of both what they might be looking for, what they might be thinking about, et cetera?

Pam Silver:

Simply put, biology is the technology of this century. It's not Silicon, it's biology.

Terrence McNally:

Okay. Thank you very much Pam.

Pam Silver:

Thank you.

Terrence McNally:

You're listening to Disruptive, synthetic biology. I'm Terrence McNally and I've been speaking with Pam Silver. We'll be back in just a moment with another founding member of Harvard's Wyss Institute, George Church. Welcome back. I'm Terrence McNally and you're listening to Disruptive, the podcast from Harvard's Wyss Institute of Biologically Inspired Engineering. On this episode of Disruptive, we're discussing the enormous promise as well as the potential risks of synthetic biology.

You're about to meet George Church, another founding core faculty member of the Wyss Institute. George Church is Professor of Genetics at Harvard Medical School, Professor of Health Sciences and Technology at Harvard and MIT and a Director of PersonalGenomes.org. Church is Director of the NIH Center for Excellence in Genomic Science and has co-founded at least 13 companies. He earned a bachelor's degree from Duke University in two years and a PhD from Harvard. Honors include election to the National Academy of Sciences and the National Academy of Engineering. He's coauthored hundreds of scientific papers, 60 patents and the book *Regenesis: How Synthetic Biology Will Reinvent Nature and Ourselves*. Welcome George Church to Disruptive.

George Church:

Thank you. Great to be here.

Terrence McNally:

So George, I've highlighted some of your achievements, but can you take us back. Tell us a bit about the way you see your path to the work you do today.

George Church:

When I was a kid, I was interested in computers and medicine. My father was a physician. Computers were really out of my capability, but I was interested in them and I looked for ways to merge those two. The first real good opportunity occurred in my second year and final year of college where somehow chem was a crystallographer and these two things came together and then... that was one of the few automated components of biology or chemistry for that matter and it inspired me to try to apply some of the concepts of biophysics and automation to other parts of biology, including genomics and proteomics, and when I later started up my lab.

Terrence McNally:

I've read an interview where you talked about, going back even further, George, when you talked about your visit to the New York world's fair and you were a kid from Tampa, Florida, I know. What did that visit, that vision, inspire in you?

George Church:

Yeah, that's a really excellent point. That was transformative for me and I think I didn't really even realize it until just a few years ago when I was reflecting getting ready to go back to that site again for a "family reunion" soon. But it was

transformative in that I saw a world that was very different from the world in Florida, for that matter is different from anywhere else in the world. But I thought the future had arrived when in fact it was kind of a heir set's vision into the future.

They had things like touch pads where you could draw things and then a computer would print out a fabric of exactly what you drew instantly. There were robots that looked like people, like Abraham Lincoln. And just as soon as I got back to Florida and realized that the revolution was not really there, I think I sort of subconsciously said, "Well, if I need to make it, I need to be part of making it become true because it seemed very attractive."

Terrence McNally:

And how old were you at that point?

George Church:

I was 10 years old.

Terrence McNally:

10 years old. But I mean, to some extent, that vision that if the future isn't going to come to me, I'll help create the future, has really been something that's been a thread ever since. Is that true?

George Church:

Absolutely. There's still things that I feel should have happened by now or would be better off if we at least cautiously explore them. And so, yeah, there's quite a few things left on my bucket list.

Terrence McNally:

Very good. Let me read one quote which I found wonderful when you spoke Reference that you said, "Very often as I wander through life, I'll get that old feeling that I've come back from the future and I'm living in the past and it's a really horrible feeling."

George Church:

Right. Yeah. There's element of that. Yeah.

Terrence McNally:

One other thing I've heard you say, "It's all too easy to dismiss the future. People confuse what's impossible today with what's impossible tomorrow." Could you talk about that?

George Church:

One of the things that I try to instill in our laboratory, which is clearly unusual atmosphere, is that many creative people think of ideas, but then they quickly say, "Oh, that's implausible, impossible, too expensive," and then they stop thinking

about it. Well, I try to encourage people, my group to think about it a little bit longer, talk it with a few people, maybe do a really easy paper or a real experiment before you completely drop it.

And even then, put it on the shelf and bring it off the shelf from time to time to re-examine it; because if it's not really ruled out then you should be considering it. And a lot of the creativity comes from having a lot of things that are partially working, a lot of things that you've never fully rejected available at your fingertips and you put them together in new combinations. And the fear of failure is another thing we try to make that so that's not such a big deal as well. Not dismissing and being capable of failing quickly is a good thing.

Terrence McNally:

And within your lifetime or even within your career, some of these timeframes have shrunk enormously, right? Things that were considered decades off actually ended up being years off or that sort of thing.

George Church:

Right. An affordable genome, it was predicted to take maybe six decades to go from \$3 billion to affordable, and it took more like six years. That's genome reading, and then genome writing, we have a revolution that's measured in two years now called CRISPR. So, six to two years is the new infinity.

Terrence McNally:

Yeah. You say we are poorly adapted to our current environment. What does that mean to you and what questions does that raise for you?

George Church:

In a biological sense most species take a million years to speciate and become adapted to a new environment thoroughly. Even our upright stance, we still have back problems and other consequences. But more recently than that, moving into cities just in the last century or two, we've gone from less than 3% of the population in cities to most of us, more than half of us in cities. That's an incredibly high population density that normally is associated with stress and so forth. And then we've also changed into a sedentary nature.

Instead of using 12,000 calories a day, we are down around 2000, is what we should be eating. But then we're completely surrounded by all kinds of really, really tasty food while before you might have to chew on your food for several hours to get a few calories out of it. Now you can just shovel it in or slurp it in. And I think those three things: living in cities, the sedentary life, and the food are just among a few of other things, high speeds, physical speeds and intellectual speeds, toxins. There's just a whole variety of new things that we're not ready for.

Terrence McNally:

You reprogram natural organisms to do things they wouldn't normally do. How do you do that?

George Church:

It has certain things in common with other fields of engineering where you have a discipline of a collection of parts that you trust and principles that can be used, safety engineering and equations and so forth. But the main thing that's different from other fields of engineering is that we benefit from having a set of parts that came from all of time in terms of evolution and a vast amount of space and organisms involved.

So we have these very highly tuned devices that do amazing things like DNA polymerases that copy DNA and act as a tiny motor and all these atomically precise parts. So we the benefits of past evolution plus we can do current day evolutions. So instead of, in typical engineering you might make one prototype for a bridge or a car, in molecular biology lab evolution, you can make trillions of prototypes, design them on the computer and build them fairly quickly and then test them out. So that difference between one prototype and trillions is another big advantage of synthetic biology.

Terrence McNally:

Based on your ambition, your vision, you want to see ideas translate into action, into products. What are some of the things that you're most proud of having been involved in and most excited about working on now?

George Church:

In terms of translation of not just incremental improvements, but of transformative or sometimes positively disruptive technologies, we've been involved in almost all of the so-called next generation sequencing methods, new methods that have brought down the price of the human genome and other genomes by 10 million fold. Similarly, we've been working on many different ways of writing the genome engineering, genomes of micro organisms as well as human cells since the 1980s. The most recent one that we helped bring into being as a technology and also improve the specificity is the CRISPR method that you mentioned which seems to work in every organism. Other methods we have are restricted to a particular organism, like the MAGE method works well in E. coli K-12.

So, each of those has been translated into some sort of commercial context. There are other things that are more appropriately done in a nonprofit way, such as the personal genome project, which allows us to gather together big data sets about individual people and share them broadly as is sort of the mandate that we have from precision medicine initiative and others. And then probably the gene drives will be something that will be best done in a nonprofit mode as well so we can spread resistance to malaria through mosquito populations.

Terrence McNally:

We've both mentioned CRISPR. Can you explain, so a listener can understand it, what that actually is, what you found that worked and then how it worked.

George Church:

We and others have been working on various ways of doing genome engineering or genome editing where you can change small or large parts of the genome as designed in the computer. Almost all of them involve enzymes from micro organisms. Some are called recombinases, so they're called nucleases. They're all site-specific, which means they either use a protein component or in the case of CRISPR an RNA component to search through all 6 billion human-based pairs or different number for other plants and animals and microbes, search through those six billion to find the one match and then either cleave or recombine at that particular location.

It's kind of like a human walking up randomly to every door of every person on the planet, maybe 6 billion different doors randomly until they find the right one. Sometimes repeating oneself on doors that don't work. Anyway, so once it finds it, you can then replace it with a particular piece of DNA you want or delete the DNA that you've targeted. And this can be either passed along from cell to cell or from generation to generation or in some cases spread through entire populations of rapidly growing organisms.

Terrence McNally:

And as you said, there have been various methods. This one, CRISPR, this discovery is the thing that really brought the price and the speed down, right?

George Church:

Right. CRISPR is probably distinguished in its flexibility and hence ability to make it more precise than the previous ones as well as low cost and ease of use. It used to be very challenging to make any genome editing tool customized for a particular task. Even one or two would be challenging and expensive. Now we make hundreds of thousands of them to make whole libraries of CRISPR targeting basically every part of every gene of a genome.

Terrence McNally:

Yeah. Could you tell us, you mentioned gene drives, could you tell us something about some of the work that's been done with gene drives in yeast and in mosquitoes?

George Church:

Gene drives can be used for dealing with managing invasive species like rats and carbon plants. It can also be used for disease vectors such as the mosquitoes that bear malaria ending a fever, ticks and fleas and so on. But before we wanted to deploy this new technology that CRISPR combined with gene drives, we wanted to make sure we had some safety mechanisms in place. These include physical isolation, ecological so that there's no breeding population outside of the lab, just outside lab, and then thirdly molecular biological isolation where we can separate

the components of the gene drive so that even if one part gets out it can't affect the surrounding population.

George Church:

We tested that in almost all of those safety components in yeast and have just published the results of that showing that all these safety mechanisms that we had proposed on paper seemed to work in a variety of different wild yeast strains but physically contained in the lab. Now we're moving on to Anopheles, which is one of the major carriers of malaria.

Terrence McNally:

You talked about the amazing speed with which the prices decreased, the possibilities have expanded. You actually say, in talking about the promise of biology, and I think when we say biology, we're saying using biological organisms to do lots of things that we would have never thought. You contrast it with electronics and point out that biology is far outpacing Moore's law. Can you talk about that?

George Church:

Biology is outpacing Moore's law by factors of five or so per year. It's doing that by essentially catching up with the miniaturization revolution of Moore's law. It will probably continue beyond where conventional silicon fabrication can go, which is limited by the resolution of the printing process right now, while biology is intrinsically capable of printing atomically precise components at scale, at sort of multi-meter scale.

You think of a tree as atomically precise when you look at it in detail but is gigantic, and biology can do that at very low costs and can replicate. So there's a number of advantages, the main one being that we're already working at atomically precise scale, which is well beyond where Moore's law would eventually like to go. Essentially biology is a nanotechnology that works already and is very appropriately matched for medical and agricultural interfaces as well.

Terrence McNally:

And when we're talking about biology, what we're talking about is our ability to harness biology, right?

George Church:

That's right. We're talking about synthetic biology and its exponential improvement in our capabilities to program it.

Terrence McNally:

Can you talk a bit about the qualities and risks associated with synthetic biology versus natural biology? Some will say that society as a whole has gotten pretty bad at assessing risk. And you can cite the Wall Street subprime derivative's crash, the

war in Iraq. Both were seemingly based on best case scenarios. How do you assess risk?

George Church:

Certainly some of the financial and military risks that we've taken seem unjustified with hindsight. Similarly for chemical, nuclear and biological mistakes that have been... technological ones have been made in the past. I think that's why it's good to have discussions well in advance. As soon as you see the technology coming, even if it never arrives, the conversation about its positive and negative potential consequences is extraordinarily valuable and you need to keep reassessing it, not just after you've made a decision, you can start looking at it again.

I think anything that has the ability to spread, so that includes ideas, education, the worldwide web, viruses, mosquitoes and so forth. Those appropriately demand a higher scrutiny. It doesn't necessarily mean that they take longer to arrive in the marketplace. Maybe they require a larger number of eyes and brains on the topic and a more careful set of tests that are done under well-controlled physical, ecological and biological containment.

Terrence McNally:

And I've heard you say that for you, engineering and building safety is your obsession. How does that drive the questions you ask and influence your work?

George Church:

Our lab is fairly unusual both in academia and in industry, among other things focusing on cost and safety costs so that you can get deployment in a more egalitarian way and safety so that by the time it's deployed it's been rigorously tested and then continually retest as you get to scale. At first it doesn't seem like it could be sufficiently exciting to get grants and graduate students involved, but if it's transformative enough and thoughtful and it has philosophical as well as practical implications, you can justify several labs working on those aspects of costs and safety.

Terrence McNally:

And so, what are some of the ways we talked about it in terms of the yeast where you supplemented the physical isolation, if you will, with metabolic isolation and genetic isolation and so on. What are some of the other ways that safety as an initial question influences what you're doing?

George Church:

In the case of yeast, we're de-risking gene drives, which were intentionally to be delivered into the wild to eliminate malaria, essentially delivered into the wild for spread as in the case of malarial mosquitoes. There's another set that are intentionally put in the wild but not for spread like crops or animals. And then there's a set that is never supposed to go into the wild that's usually physically contained in fermenters or something like that, typically micro organisms.

And for each of these you have a slightly different strategy. For the ones that shouldn't escape, you might want to have something where there's protection for the laboratory to keeping viruses from coming into the laboratory and contaminating sometimes many millions of liters of expensive culture and that might make the culture virus resistant. But virus resistance, resistance to all viruses, although it sounds desirable, it could give a laboratory strain one of the few ways that it can survive in the wild.

George Church:

Most laboratory strains like let's say chickens that would be good meat products would not necessarily fly well and wouldn't survive in the wild. Now, the same thing applies from micro organisms unless they're multi-virus resistance. In that case, you want to have other forms of safety built in that genetically isolates it so it can't exchange DNA as many organisms do and it's metabolically isolated and that it's completely dependent on a chemical that is made in the laboratory, is not available in the wild, we call it bio containment.

Terrence McNally:

What are your opinions on whether there's a need to perform work with synthetic biology, some of the work we've been talking about, under scrutiny and transparency and formalized risk-based practices and procedures. What's your thought about that in your own lab and in the field broadly?

George Church:

Yeah. I'm basically in favor of additional scrutiny. I think regulations in general that have been thoughtfully developed with many groups on all sides giving feedback are not onerous. You can get your work done and make sure that multiple groups have, because it's transparent, multiple groups could look at it from the outside and try to imagine ways you could go wrong in ways that perhaps the scientists doing the experiment because they're so engaged, focused and upbeat, optimistic, they may not see all the possible downsides. They may even push back a little bit when you bring it up.

We try to do this internally in our own lab of thinking of how everything could go wrong, but it's still helpful to have the transparency and the shared databases and so forth so that people and machines can look through them for potentially new risks that should be discussed and possibly paused in some rare occasions.

Terrence McNally:

And that's going to take us to the letters that I referred to in the opening, the letter in nature and the letter in science. So, we talked about CRISPR and how that in some ways is a game changer because of the way it brings the price and actually I think it makes it possible for labs of somewhat less sophistication to get into this activity. So, what happened in Napa, and I don't mean the specific negotiations or the politics that went on between people, but what was the vision? What was the concern? What was the goal?

George Church:

I was involved in the science paper that reflected that meeting. There has been a recurring concern about manipulation of the human germline, meaning something would leave a permanent impact on a family or on the entire human race. That goes back to the early days of test tube babies in the early 1970s. They're common at DNA debate, now synthetic biology and CRISPR in particular being so easy possibly applicable to human embryos or other germline experiments.

I think the concerns tend to entangle vague unknown unknowns with very concrete safety and efficacy issues. I feel that once the safety and efficacy issues are addressed as they have to be for all new medical technologies, nothing is really exempt including CRISPR. Once those are settled, then you get a situation like you have with in vitro fertilization, which was very anxiety inducing in the 70s before there was an example of a test tube baby.

Once the safety and efficacy issues were addressed in 1978 with the first baby born and then soon thereafter many others, then the argument dissipated and was put off basically until CRISPR came along. But it's still the same basic argument, which is, is it safe to alter the natural process of reproduction and exactly what are we worried about? I think the main thing we're worried about is inducing in a young baby that can't give consent, possibility of getting cancers because of off target effects of CRISPR.

Terrence McNally:

And by off target you mean that you do it to do one activity within a gene and it ends up affecting others that you didn't predict?

George Church:

Or maybe you predicted them, but it happens at a rate that's unacceptable. That off target rate can be reduced, and they're half dozen different ways of reducing that rate by empirical searches, by dosage of the CRISPR machinery, by requiring two CRISPRs to be near one another and precise. Anyway, there's many ways of improving that and we're kind of walking through them and they'll probably be tested mostly in humans' somatic tissues, meaning adults or childhood tissues or the germline of animals for agricultural reasons.

And then once both of those off targets have been proven to be acceptable, that is to say they don't cause cancers, then the conversation will focus much more sharply on what are examples of medical treatments that can only be achieved by CRISPR and the germline that cannot be achieved by any other medical intervention.

Terrence McNally:

In an article in the Daily Beast, New DNA Tech: Creating Unicorns and Curing Cancer for Real? David Ewing Duncan makes this statement about Napa and the science and the nature letters, "The US and the world should waste no time in

getting creative with developing new processes for ensuring that CRISPR-Cas9 and other powerful molecular technologies are allowed to move forward if safe and restricted or shut down if they are not." Is that basically where you stand?

George Church:

Yes. I mean that's where I stand on all new medical technologies, is you need to leave an avenue open for safety testing in something that is not impactful on real patients or populations and you also need to promote things that are looking safe and effective and either shut down or move to a safer zone things that look like they're having problems with safety.

Terrence McNally:

Now, we've sort of threaded through this safety and kind of behind the safety concerns is fear. How do you deal with the public sphere of the unknown?

George Church:

I think the first step is to not be dismissive. I am, myself, I have fears that are pretty well aligned to the public and then transmit to them all the ways that we go through de-risking a technology before it gets deployed into the wild world. Many people could benefit from seeing in more detail of the steps that are involved in research and final approval for clinical trials and how carefully and how small those steps are and all the checks and balances. So that's part of it. And a part of it is also talking about alternatives. This is risky, but the alternative is even riskier. Kind of walking through all the options we have in front of us.

Terrence McNally:

In one interview when you were asked how you were able to shift your focus because you're involved in so many different things that to most of us it looks like that would take all my focus and yet you bounce from one to the other, your answer was, "It's all one project." What is that project? And looking back from, you pick the year: 2030, 2040, 2050, what does that project look like?

George Church:

Well, the project is integration of technologies, assessment of needs and safety and to some extent looking at the possible futures. So, if we look back from the future and a project is the future, hopefully we'll see some on target predictions and deliveries. So, if you imagine multiple possible futures and as many of the negative and positives as you can and engage a lot of other people to participate in this and constantly adjust course as you go forward, hopefully the future is basically always now.

Terrence McNally:

I like that. Thanks a lot George.

George Church:

Oh, it was a pleasure.

Terrence McNally:

So again, you've been listening to Disruptive, synthetic biology. I'm Terrence McNally. My guests have been Pam Silver and George Church. To learn more, go to Wyss.harvard.edu. You can sign up at the Wyss site on iTunes or SoundCloud to have podcasts delivered to you. My thanks to Seth Kroll and Mary Tolikas of the Wyss Institute, to JC Swiatek Production and to you, our listeners. I look forward to being with you again soon. And finally, thank you to Pam Silver and George Church. Keep up the good work.