

Hello again, Ars Technica readers. This is the third and final installment of a three-part interview with George Church – who is one of the most influential people in the worlds of synthetic biology and genomics. If you haven't yet heard part one or two, there are links to them on the page where this player's embedded, and I strongly suggest that you go back and listen to those installments before this one.

And with that - back to my conversation with George Church.

Rob Reid: So Cool as it might be to engineer a multi-billion letter mammalian genome from scratch, we couldn't possibly do that design process today. So as a practical matter, we're less limited by strand length than by our understanding of what the genes would do and how they'd interact with one another in the environment. With that in mind, what do you expect, largely or purely synthetic DNA to enable, say, 10 years from now that we're not currently capable of? Whether it's for a lack of understanding of the metabolic pathways or an inability to stitch things together in as error-free and efficient of a way as we'd like?

George Church: Well, 10 years is a pretty long time in this exponential field that we're in. My prediction is that we won't be purists. I think we will be pragmatists, just as we are today. If we're given a choice between making three billion base pairs of human DNA that's purely synthetic and making a set of three billion contiguous bases, we'd say, "Well, let's make three million changes, but do that in a thousand different contexts, and they all have an impact." So now I can make 1,000 different genomes, each of which has been changed quite radically, and then we'll also use that synthetic capability of building test circuits. We're not just building a thing. We're building all the machinery to test it. I think what we're going to be very good at 10 years from now is making lots of prototypes. But these will be more radically engineered because we'll be better at design. So I think we'll be at the point maybe 10 years from now where making billions of genomes – that are radically altered and still have new functions – will be taken for granted.

Rob Reid: I'd like to move to a subject that has significant connective tissue with xenotransplantation, literally and figuratively I guess, which is synthetic meats. For the benefit of listeners who aren't familiar with this, these are meats that are grown entirely in the lab, no animal involved. So this is quite unlike the pigs growing transplantable organs ,in that there'd be no conscious entity living, dying, or suffering in the creation of this meat.

George, what's the status of synthetic meats today, and what breakthroughs do we need to get to lab-grown meats that can both pass a blind taste test and ship at consumer price points?

George Church: What's holding us back is the recipes for making the media to grow the cells. Those recipes typically involve fetal calf serum. Fetal calf serum, just by the name, you can tell that sounds expensive. A fetus, first of all, is a rare, small thing. And getting serum from that fetus?

Rob Reid: It sounds like a real process.

George Church: It is. And the replacements for it, where you'll purify the proteins, are even more expensive. But there's no reason why you can't make cells that don't need that stuff, because all those things are signaling molecules that tell the outside cell: "Grow, grow, grow." You can just tell the cell directly to grow, internally. Or you should be able to make that media for cheap. In principle, everything that's made biologically in the world is extraordinarily complex and free. You can go out into the wild, and as far as the eye can see – dozens of kilometers – you see forest and farmlands, which is benefiting from the sun and the air and the soil. And it's pretty close to free.

By the time they're delivered to consumer, a lot of biologicals run on the order of dollars a kilogram. That's what everything should be. Everything made biologically should be dollars a kilogram.

Rob Reid: But for now, at least, fetal calf serum is a necessary ingredient, it's expensive as hell, and we don't know how to synthesize it?

George Church: There are now cell lines that are serum-free.

Rob Reid: Meat cells that can grow without the expensive serum?

George Church: Exactly. That's a big step. And then it becomes a matter of scaling up. I've been excited about bringing down prices, radically. We've already talked about bringing down sequencing and synthesis by more than three million fold. I'd like to see manufacturing of things in general to be brought down to the dollars a kilogram. The more we think about manufacturing as either biological or biologically inspired, the more we can think that's a reasonable goal. Meat is just one thing, but we should be able to make organs for dollars a kilogram, right? Because organ is just meat. It happens to be meat that hasn't been killed yet, but in principle, you could grow it the same way. I'm very excited about ... This is the next price revolution, if we can bring down the cost of meat by thousands fold. I mean, we're not even asking for three million fold this time. We're just asking for thousands fold. We're already down in the couple thousand dollars a pound range.

Rob Reid: Currently, thousands of dollars per pound for synthetic meat that's what? Good enough for most pallets?

George Church: It's molecularly identical.

Rob Reid: Molecularly identical? Wow.

George Church: Vegans already had a solution for this, just eating vegan burgers, and there's some pretty good ones. There's a transition where a lot of people have their favorite recipes, and it has to taste exactly like beef or chicken or snake, whatever your favorite meat is.

Rob Reid: Ridiculous as it feels to say, "Only," in this context, the fact that you only have to drop down three orders of magnitude in price feels pretty doable in this crazy world of synthetic biology. And it probably goes further than that to eventually being way cheaper. Also, building on what you said about engineered organs not only being abundant but resistant to cancer and senescence and pathogens, there's really no reason why synthetic meat couldn't be engineered to be much healthier and tastier than the real thing. When you combine that with the ethical dimension of no animal suffering, I could see the market for real meat eventually becoming like – I don't know, the market for vinyl records. You know, expensive, artisanal, and retro, and some people swear they can tell the difference, but most people would rather have the thing that's cheaper and better, right?

George Church: Right. Almost all the reasons that you want to be vegan could be addressed, including the zoonotic diseases. This is sometimes called clean meat, not just virtuous, non-cruelty meat. But clean, in that when you streak out on a Petri plate, your best meat from your favorite grocery store, it's just covered with bacteria. But this, you streak it out and there's nothing. That's a plus. You can make it low cholesterol. You can make it so that it's not hurting the environment as much. Beef, right now, uses up about 20 times as much of the environment as the equivalent vegan resources do.

Rob Reid: Remind me which synthetic meat company you're involved in.

George Church: Memphis Meats.

Rob Reid: Knowing what you know about where they are now and the trajectory of the science in general, do you think we're within five to 10 years of synthetic burgers that are as good and as cheap as cow burgers?

George Church: I think we're very close. I would be reluctant to say it's a lot more than five years because it doesn't require the kind of breakthroughs we need in some of the other things that we've been talking about. Like the

BRAIN Initiative, where we want to be able to read every neuron in the brain, there's some serious technology development there that we can't spell out. When we talk about reversal of aging, we think we have a short list of genes, but working out all the interactions among all those genes and getting good delivery to all the cells in the body – there are going to be some wins before that, but really getting that solved, that's unpredictable.

- Rob Reid: Wrapping up our wild and woolly topics connected to animals, if you'll forgive the pun, what's the latest with de-extinction and the woolly mammoth project?
- George Church: We're hoping that this year, 2018, will finally be the year where we publish a lot of peer-reviewed articles that are relevant. The things that we've got are computational analysis of 23 elephant and mammoth genomes. That's a lot of genomes.
- Rob Reid: For folks who aren't familiar with the De-extinction Project, you've been able to recover fully-intact woolly mammoth DNA.
- George Church: Yeah.
- Rob Reid: And woolly mammoths died out 30,000 years ago?
- George Church: Some of them did. The most recent die off was around 3,000 or 4,000 years ago on Wrangel Island. But a lot of the genomes we're working with are older than 30,000. That's a revolution all by itself, and that's past tense. That's not wishful thinking. The sequencing technology we talked about earlier has been used to sequence lots of extinct species, including mammoth.
- Rob Reid: And Tasmanian tigers and passenger pigeons and Neanderthal humans. And in the case of the woolly mammoth genome, you precisely know how it differs from the genomes of existing animals like Asian elephants and African elephants, correct?
- George Church: That's right. Our project is very pragmatic, as all of our projects are. The goal isn't to necessarily de-extinct a species, but to develop a method by which we can invigorate current species. We're using extinct DNA. So we're essentially de-extincting genes rather than species. And this can help many species other than elephants. Because a lot of them are endangered because they went through a population bottleneck. They're missing diversity. Even if you go around the world, there's limited diversity, but if you go back in time, there's all kinds of diversity that you can get.

Secondly, we can help modern endangered species because the environments are different. For example, for elephants, we'd like to extend their range into the cold, because this vast arctic region, which is underpopulated with herbivores – we depleted it of herbivores that were valuable to the environment.

Rob Reid: What herbivores used to be up there, other than the woolly mammoths?

George Church: Caribou, elk, bison, small horses, and so forth. They're being repopulated, but they are much less than they used to be. Possibly because the keystone species, the mammoth, was responsible for keeping the ratio of grass to trees high. That has all kinds of consequences, because even the biggest non-elephant herbivores can't knock down the trees, and the forest area's impenetrable. You can't even fit between the trees. Also, they don't photosynthesize well, so they're not capturing carbon well.

Rob Reid: The trees?

George Church: The trees, and the snow comes in and kind of makes this big, fluffy tree/snow blanket. Then what happens is, in the summer, the temperatures get up close to 20 degrees Centigrade. And then the snow on the trees protect it from the minus 40 degree wind in the winter, so it doesn't cool down well. And we want it to cool down because there's more carbon trapped in the arctic than in all the rainforests in the world put together, plus all the carbon in the atmosphere.

Rob Reid: You mean in the permafrost, right? How much carbon is trapped in there?

George Church: The permafrost has 1,400 gigatons, which is like two and a half times all the tropical rainforests. Letting that melt would be a disaster. What we really want to do is put more carbon in there so the grass can do that. They can keep fixing carbon. So we want to favor the grass, both because we can keep the current permafrost frozen, but also the grass in the summertime will add carbon to that.

Rob Reid: Let me play back the sequence just to make sure I'm understanding it. The forest has become impenetrable up there because we don't have these big ol' mammoths knocking over trees anymore. And the high tree layer insulates the ground, trapping the summer heat, which drastically raises the risk of the permafrost thawing?

George Church: Right.

Rob Reid: And all these trees crowd out the grass, so we don't have elk and other ruminants devouring grass, which would suck much more CO2 from the air than these trees. Now I see why you want giant tree-wrecking mammals up there, whether it's woolly mammoths or elephants that have some mammoth-like properties that'll let them live much further north. So it sounds like there's a lot of follow-on effects if you can pull this off.

George Church: This would be good for the elephants and good for the environment and good for humans. The challenge is that the closest species to the mammoth is the Asian elephant, and the Asian elephant's endangered. We could go with the African elephant, it's close enough. Probably all three of them are interbreedable. There's some evidence that you can interbreed those – actually a lot of evidence that there were hybrids. but even the African elephants, we really don't want to interfere with their normal reproduction. We want African elephants and Asian elephants to be making baby elephants. Figuring out what genes were selected for in the short distance between elephants and mammoths was a very short genetic evolutionary distance. We've got a short list. It's about 44 genetic changes.

Rob Reid: That's it?

George Church: That's the list that it looks like if you look at their genomes. We can change those easily with CRISPR. We're already doing it in pigs. We can do it in elephant cells. But then we want to grow those into embryos and fetuses without interfering with normal reproduction of elephants. And so we're taking another ambitious project, which is to try to get mammalian development to work entirely in vitro in the lab.

Rob Reid: Entirely in the labs? So, not with surrogate mothers?

George Church: Yes, that's right. That's the goal.

Rob Reid: I hadn't realized that. Why not use surrogate mothers, given that you have these closely adjacent species?

George Church: Well, they're endangered species. And even cloning in pigs, which is a pretty well-established agricultural cloning species, doesn't have that high success rate. If you get a success rate of around 10%, you're doing well. And probably for elephants it'll be even lower, at least to start. Also when you get a litter of pigs, you're talking about a dozen piglets. And fast, too. We're talking about three months gestation. And mice is like 20 days. Elephants? It's 22 months. And they have one child. And then they'll nurse it for a while, and it'll be quite a while before they have their next child. So you can really put a dent into them by lowering their fecundity to 10%.

Rob Reid: Yeah. If there aren't many Asian elephants to begin with, and we use the few that we've got to try to create mammoths, and there's a low hit rate ... we could really whack the Asian elephant population. How many are there?

George Church: I estimate there's probably on the order of 17,000 that are in prime reproductive years and are female. Now, there's hundreds of thousand of African elephants. But it's still limited. And there's another reason to it, is if we want to scale this – if we want to have 80,000 more or less at once ...

Rob Reid: Woolly mammoths?

George Church: Woolly mammoths. Or, let us say, cold-resistant elephants that satisfy the woolly mammoth range. If you want 80,000 at once ...

Rob Reid: That's a lot of 22-month gestation cycles.

George Church: Yeah. There aren't enough mothers that you have access to, even if all the relevant governments said this was a good thing. So this is a better way of scaling.

Rob Reid: You grow these prenatal critters entirely in the lab and not in a womb. Would you somehow get them to gestate in, I don't know, something like an egg?

George Church: We're not necessarily talking about eggs, but it's something like that. It's full development outside of the body with adequate blood supply and nutrients.

Rob Reid: So, full prenatal development outside of a womb. Like completely in vitro. Has any scientific team ever managed to do that for an animal that doesn't come from an egg?

George Church: No. There's a lot of reproductive technology. Human preemies now survive from almost about halfway through the gestation. That's coming in from the end. Going forward, there are some mammals that grow essentially free-floating. They're not hooked up to an umbilical cord. So you're eating a few days from that end. So we're trying to meet in the middle. We're working out, in mice, which have only 20 days gestation ... and, again, you can get lots of mouse embryos. That's pretty easy to do. And we're getting better at turning stem cells into embryo-like structures. And we're getting better at turning embryos into support structures that are vascularized. We're making vascularized decidua using the same kind of technology we used for making human organ and organoid-like things in the lab. This is just another organ. It's like making cardiac tissue or making brain tissue or making decidua, which

embryos can implant into. Then, once that's working well for mice, we'll try moving it to larger animals.

Rob Reid: When do you imagine the first woolly mammoth will be born?

George Church: Again, we're not aiming for woolly mammoth. We're aiming practically for 80,000 cold-weather elephants, and that's ambitious enough.

Rob Reid: That's plenty ambitious. When do you think that might be?

George Church: The first success could be within a decade. We have to work out all the stuff in mice. Then we have to scale it up. And then, at a minimum, there's 22 months for the gestation. It's going to take a while. That 22 months is a big problem with getting feedback and doing a cycle of innovation. But that's why we're doing it so much in mice. 20 days is a reasonable period of time

Rob Reid: I'd like to close by talking about human longevity. More and more labs are starting to dedicate themselves to combating aging now. What do you think the landscape of human longevity will look like in 10, 15, 20 years, and what vectors are we pursuing right now that could have a real impact on how long people live?

George Church: There's two major strategies. One is aiming at extending longevity, and the other is aging reversal. The problem with longevity extension is if you're not careful, you extend some of the weaker years of your life. Nobody really wants that. Aging reversal, on the other hand, sounds a little more speculative, but there are several cases of it in mice. You can get aging reversal with bloodborne components, essentially a transfusion from a young to an old. You can get it from the ends of the chromosomes, telomeres. And then there's a way that you can return old adult cells to embryonic stage, and if you do that in limited doses in an intact mouse, you get some evidence of aging reversal. So those are three examples. And then there's vast literature on longevity as well in many model organisms, flies and worms and mice. We're taking that literature, and we're asking, "Which of those could we turn into gene therapies to try aging reversal in a gene therapy form in mice?" You can summarize the different ways of aging in about nine different categories, and you might have to fix all nine of those things simultaneously.

Rob Reid: That sounds a lot like Aubrey de Grey's approach.

George Church: Well, his is more focused on damage, and mine is more focused on epigenetics. I'm sure there's damage, but the fact is that young cells respond to damage better, fix damage better. And so I'm just trying to convince old cells that they're young cells, and then let them handle the damage.

Rob Reid: In other words, if an old cell becomes young, it's innately configured to fight damage.

George Church: So Aubrey's is a very complementary approach – I'm one of his advisors to his group. But it's a complementary thing. If we need additional damage control, they will do it. So we're basing it on all the examples of either longevity or aging reversal, and we're reformulating it as aging reversal gene therapy, turning gene therapy into an aging reversal drug. We've got about 40 now in the pipeline, which we have tested on pre-aged mice. These are aging reversal gene therapies that have been chosen to be compatible with where we are right now for gene therapy. Which is we can't treat every cell in the body, so we have to pick a subset of genes, where we don't have to treat every cell in the body. That's what we want right now, because most people who are worried about aging are not the unborn.

Rob Reid: Right.

George Church: And so our market is people who are old. So we're doing it on pre-aged mice that are like two years old, almost dead. The ones that work there, we're moving into dogs, pre-aged 10 to 12 years. And that's a market in and of itself. That's not only a good test bed to move up from mice to something that's more like humans – Dogs live in human environments, they get human attention. It's a nice pause point for the technology because we can get feedback from pet owners. They will actually do our scale-up preclinical animal trials for us, and they'll pay for it. So it's a win-win all the way around. That's the business model for the company that we're starting called Rejuvenate Bio. But we've already done a bunch of trials in mice, and we're doing some in dogs. Then we'll move onto humans.

Rob Reid: And the company's fully up and running?

George Church: Well, it's up and running in the sense that we're doing all these experiments.

Rob Reid: Have you seen anything eye-popping from the experiments yet?

George Church: We are publishing a paper where we did three pretty eye-popping experiments in various combinations.

Rob Reid: How long do you imagine it'll be before you start seeing major results in dogs?

George Church: I have to apologize for, "Everything seems five years away," because that's almost a cliché.

Rob Reid: It's fine with me. I want you to be right about all this stuff!

George Church: But I'll tell you why I'm less embarrassed than I would have been. I've seen a bunch of things that even the optimists felt were six decades away. Like affordable sequencing. When it was \$3 billion, six decades was pretty optimistic. It was assuming that we could get genomics on a Moore's law curve and then keep it on the curve for six decades. Instead, it took six years. When I say five years, I have a few examples in my pocket that are past tense. Sequencing and synthesis and CRISPR were even less than five years. The clinical trials for dogs is much shorter, and we're talking about aging reversal. That's another reason to do aging reversal rather than longevity. It's hard to get FDA approval, even for a veterinary drug, because if you say it's going to extend the dog's life by 10 years, that's a 10-year clinical trial. Whereas if you say, "In five weeks, it's going to make them stronger and more resistant to injury," then that's a five-week experiment.

Rob Reid: Well, I'm keeping you from the joy of entering Boston Friday rush-hour traffic in End of Days weather.

George Church: Well, I'll be walking.

Rob Reid: You'll be walking? Good. Well, thank you so much for affording me so much time. This has been a fantastic conversation.

George Church: Well, I've enjoyed it tremendously. Thank you. Hopefully we'll do it again someday.

Rob Reid: I would absolutely love that.

[So Ars listeners. To reiterate what I said to George toward the end of all that, I sure hope he's right about everything.](#)

particularly when it comes to timing. All those amazing things that might just be five to 10 years off. Because what an amazing world we might soon inhabit if he is right! Cheap, healthy, abundant meat created without animals suffering and with a tiny ecological footprint. An unlimited supply of healthy organs savings millions of lives and radically improving the lives of multitudes. And aging reversal. And more. When I list these things, it sounds a bit like a science fiction pipe dream. But how crazy would the capabilities of our telephones have sounded to a level-headed person living in the '90s? The improvements in our phones and everything else in tech have been driven by compounding exponential improvements in various components, above all microprocessors. Human minds just aren't equipped to think intuitively in exponential terms, because when the psyches of our ancestors were

shaped across thousands of generations on the savanna, nothing exponential was going on in their environment. At least not visibly.

We're now entering the influence of an even steeper set of exponential curves, those of life science – including the genetic sequencing and synthesis curves that George and I discussed. Not only are these curves steeper, but they're going to influence us in much more intimate ways and in ways that cut much more closely to our humanity than the cost of transistors and bandwidth.

So Ars Technica listeners - here we conclude the third and final installment of my interview with George Church. If you enjoyed this, you might like to browse my 30-ish other episodes, which can all be found at after-on.com. Or, type the words After On into your favorite podcast player.

You'll find a lot more conversations about genomics and synthetic biology. Multiple episodes connected to neuroscience and consciousness. Conversations about robotics, privacy and government hacking, cryptocurrency, astrophysics, drones, and a whole lot more.

I'll also be back here on Ars next week, with another episode from my archives. I hope you'll join me.