MFS ep 1

Continuity: how to grow a human my Frankenstein summer with Dr. Phillip ball episode one, playing God.

Dr Philip Ball: I'm Phillip ball. And I have a second brain that spare brain never worked very well. And now that it's been dissected for the microscope, it doesn't work at all. It was about the size of a dried pea. And it was like a poor approximation to the brain that grew in my fetal self many years ago. Still. It wasn't many brain made from my own cells by neuroscientists in London, a couple of years ago, they made it from a piece of my arm.

If you think this sounds like science fiction, I don't blame you, but maybe it reminds you more of fantastical stories, not about the. But from the past,

Passage reader: remember, I am not recording division of a madman. Does not more certainly shine in their heavens then that, which I now have from is true. Some miracle might've produced it yet. The stages of discovery were distinct and probable after days and nights of him incredible labor and fatigue. I succeeded in discovering the cause of generation and life.

No more. I became myself capable of bestowing animation upon lifeless matter.

Dr Philip Ball: Yes. We often still turn to Mary Shelley's Frankenstein to try to make sense of new developments and how to make, or to grow humans. Recently, I wrote a book called how to grow a human in which I described my mini brain and explained how it was made and what it was for.

Biological technologies like these are now making it possible to imagine getting human body parts, not from the mortuary, like Victor Frankenstein, but by growing them from scratch. Meanwhile advances in artificial intelligence might leave us wondering whether rather than growing a soft and squishy brain, we can create thinking devices using computer techniques.

In both cases, we might not be limited to whatever we can salvage or what nature provides. We might be able to design improved versions, no one imagines actually assembling such body parts into a human body or something like that. All the same Mary Shelley's warning about the consequences of not

thinking through our technological advances or not taking responsibility for where they might lead seems more relevant now than ever.

Passage reader: When I found so astonishing, a powered placed within my hands, I hesitated a long time concerning the manner in which I should employ it. Although I possess the capacity of bestowing animation. To prepare a frame for the reception of it, with all its intricacies of fibers, muscles, and veins still remained a work of inconceivable, difficulty and labor.

I doubted at first, whether I should attempt the creation of a being like myself or one of simpler organization.

Dr Philip Ball: Last year, I went to Boston, Massachusetts to find out about the latest developments at the interface between biotechnology, AI, and cognitive science, to find out what the future might hold both for the human body and the thinking machine and how the boundaries between the two might become blurred.

Since then the world has changed. The global COVID-19 pandemic caused by the coronavirus has revealed the fragility of human life and society. We all survive it as we have survived pandemics in the past, but only at an awful cost in lives. And having been reminded that our bodies are frighteningly vulnerable and that we're deeply reliant on advances in science and medicine.

Some of the prospects I heard about last year from the use of AI for speeding up medical research, to the idea of re-engineering the human genome to make it resistant to viral attack are eerily relevant to this crisis. Underpinning it all is the fundamental question. How improvable is the human body?

How much can it be made more robust, more reliable, better able to read. And to function in society. The question I had last year, can we change the human now? Seems like a slightly different one might we need to do so to live in the world we've created.

Boston has possibly the densest concentration of biomedical science in the world, both Harvard university and the Massachusetts Institute of technology MIT located there as well as at least two other big universities. The place is a buzz with biotech, startups, and everyone seems to be working on or using.

If there's one place, a modern day, Victor Frankenstein would want a hangout to figure out how to make a human it's here over the next six episodes. I'll be

talking to world leaders in all these fields of science, medicine, and technology about the confluence of biomedicine, neuroscience, computer science, genetics, and more, and what it will mean for us and for society.

These days, we're encouraged to believe that there's a recipe for a human being tucked away in every cell in our body. It's the human genome often said to be the instruction book for assembling each of us. Well, it's more complicated. We can now read the DNA sequence, the molecular code of our genomes quickly and cheaply.

And it's been done more or less precisely for thousands of people, but not only do we not yet fully understand the language it's written in. We're discovering that the genome isn't really a blueprint after. Nonetheless, we do know that we can alter the kind of organism that emerges from a genome by rewriting it by gene editing,

I went to Harvard medical school to speak to one of the most skillful and ambitious gene editors on the planet. Professor George Church, George has suggested the plan of writing. In fact, rewriting the entire human gene. From scratch based on its natural sequence, but with changes made to improve our health in particular, we might be able to solve some of the problems of aging.

George Church: Some of the complex diseases will get redefined as diseases, aging. Quite a few of them are diseases of aging. And if you can solve. Then it doesn't really matter that person, the person varies whether they die of heart disease or cancer or nerve disease or diseases or, or osteoarthritis, these are all diseases of aging.

And if you can get at the underlying cause he's aging, then you'll get all of them at

once.

Dr Philip Ball: What would solving aging mean to

you?

George Church: Solving is a bigger word. Uh, it's coming up with pragmatic therapies that reverse aging as defined, not. Not just by molecular biomarkers, but by physiological ones, like strength, reaction, time, cognitive memory tasks, healing of damage, all of these things work much better in young people than an

old, most of the diseases we die of in industrialized nations will not kill 20 year olds.

So 90% of us will die of diseases that are only found an old people are mostly found in old people. And there's no fundamental law of physics. We can't live past a hundred bowhead whales lift to 200. So there's no fundamental physics. Osos you can't live past 200. Right?

Dr Philip Ball: I remember we corresponded some way back about you.

You were thinking it's not unfeasible. And also it could be useful to think about right. The entire human genome. Yeah. Yeah. Um,

George Church: where do you want to make changes? You don't want to make a copy. And so once you say that you want to make changes easily, which changes, and nobody has ever defined, even as a goal, even as a stretch goal, something evolve more than 4% changes and for human since so much of the genome doesn't do much.

I'm not saying it doesn't do anything. It's just at our current state of ignorance. It doesn't do something super medical. Then it's probably less than 4%.

Dr Philip Ball: What George is telling me here is that at least in theory, by rewriting the human genome, we might be able to grow a person who is immune to viruses and other diseases.

And who ages more slowly. That's an extraordinarily ambitious goal. And before the COVID-19 pandemic, you might've been inclined to see it as a rather overblown approach to. Given what we now know about the reservoir of deadly viruses that exist in wild animals, however, and how they hold the potential to wreck the economy and killed vast numbers of people at any moment, perhaps we shouldn't dismiss it out of hand, but do we really know enough to try this or know if it's possible at all?

Do we understand. Well enough, what if you're, if you're editing on that scale, you're inevitably going to be changing more than just the thing that you're looking for it. I mean, D does that make it

George Church: well, there's two kinds of off target there's off target genetically. Where you touched something, some DNA, DNA, you didn't mean

to touch there's off target consistence biology sense where he did everything you thought you were going to do.

Exactly. But it has unintended ramifications as you, as you percolate out. That's exactly what I mean. That's happened. For example, the one of the first monoclonal trials, monoclonal antibodies, you thought you were doing X, um, but it had systemic effects that almost killed the first four humans. Uh, even though it didn't have an effect.

Many times the dose in animals. That's why we do clinical trials. That's why we do preclinical trials and in animals and organize is, uh, so that we can minimize that

Dr Philip Ball: far less ambitious plan is already being explored to rewrite individual genes, for example, to correct harmful mutations so that we can cure diseases with a genetic basis.

That's called gene therapy and scientists have been working on it for years. One of the challenges here is that many genetic diseases. Don't just stem from mutations of a single gene, but might involve many of them. They're poly genomic. So, so you think that, um, that gene therapy at least might work for.

Diseases. Oh yeah.

George Church: Well, the other thing is, I think some of my colleagues kind of like mystify these things, uh, but there's so many things, so many complex things we don't understand that we never list engineer. I mean, a perfect example is vaccines. We were doing smallpox vaccines back in the 15 hundreds and to.

Way before we knew anything about virology or immunology, we didn't have the core concepts of our religion immunology. By the time the smallpox was already on the run, uh, by the time we had made it completely extinct, we had some inkling, but I would say even today, there's big gaps in our knowledge of virology and immunology.

But that didn't stop us. And I think that happens again and again, in engineering in general and bioengineering in particular biology, biological systems are so incredibly complex and most of our drugs are single target drugs,

Dr Philip Ball: supposedly succeed, and being able to edit genes and even entire genomes to make humans, immune or resistant to some diseases.

That's not likely to be. So who benefits might we end up with a genetically stratified society of haves and have not, as in the movie Gattica can we bring

George Church: down the price to make it equitably distributed, which is one of the ethical issues. Can we make it safe and effective? What would be the definition of safe and effective, right?

Because we've got definitions for many therapies, including this one, FDA does a great job. We should be, we should celebrate how good the FDA is. We could even give them more resources if we want, but to say that there's something qualitatively wrong. I think as an exaggeration, what's interesting is people are declaring.

This little thing that my colleagues and I invented CRISPR as some revolution, I don't think it's a revolution. I mean, I'm, I'm glad for the kudo.

Dr Philip Ball: CRISPR is a method of editing DNA invented over the past few years that is transforming the science because it seems to be more accurate than earlier.

Techniques uses a combination of molecules that can target precisely the section of DNA you want to. At least that's the idea, but

George Church: what we call editing is like, you know, vandalism's kind of random on target a little bit off target. If an editor of English text did what CRISPR does, they would be fired.

And I was like, oh, I'm gonna rip the sheet of paper out and crumble up another piece. And that's that I'm done editing. Right. Good. And so. So, so why,

Dr Philip Ball: why, why, why has CRISPR got this

George Church: reputation that you, you, I think it's because we have a genuine revolution going on and people can't tell it was for the trees.

They can't, they can't see the revolution. And so they just like grab onto some one on buzzword. So the revolution is reading and writing DNA, reading, writing, and editing in general, reading, writing of improved 10 million full both

in cost and quality. So. When we started the genome project, we were, a lot of people were proposing doing a fraction of the genome and doing it at 1% error rate.

Uh, now we're very close to complete genome and we have, we can have errors as low as 100.

Dr Philip Ball: At the end of 2018, a Chinese scientist reported that he had used CRISPR gene editing to alter the genomes of human embryos used for IVF, which developed into two baby girls with edits in one particular gene that he believed would protect them from infection by the aids virus, HIV.

This makes them what is popularly called design a baby. Most of the genetics community, believe that the technology is nowhere near, ready for such a step. And the announcement was widely greeted with horror, with calls for a moratorium on human genome editing for reproductive purposes. So do you think there should be more talk about.

Germline editing with CRISPR or some other means where that might be useful rather than a moratorium. That just means we're not going to talk.

George Church: Uh, we've been talking about designer babies since before in vitro fertilization, before the 1978, uh, Louis Brown birth, um, talking is, is generally acceptable. Uh it's uh, it's just a blanket ban where we don't describe what would be.

Evidence that it's, that we're ready. Right. So if we're going to say we're not ready and that the FDA can't decide when we're ready, then we need to say what, who can decide. And under what circumstances will, we've done lots of animal trials. We've done even human trials and embryos that were not implanted.

Um, there ways of doing it without embryos at all, where you could do it through clonal engineering of spermatagonia stem cells. But if you do a clone. You have intrinsically a billion times lower risk. And if you analyze the clone before you put it in the germ line, you can get that down. Another factor of six orders of magnitude because of the accuracy of sequencing.

Dr Philip Ball: Look to me as though you, you took a more permissive view than a lot of people about the crisp from this. And

George Church: it doesn't mean in cautious. I urge probably more caution than most people do. I just feel like. Uh, we need a more balanced discussion with less posturing. We already have a ban on any new pharmaceutical, including germline editing until it's proven, safe and effective through a series of animal human cell trials and then human trials.

I think what really we should be focusing on in these cases. Uh, more tournament involves like voluntary will of the people that are already doing the right thing is you want something somethings involuntary and has a surveillance component. So we have very high surveillance, not just fun, germline editing, sematic, adult editing, synthetic biology in

Dr Philip Ball: general, a few more definitions here.

The germline cells are the ones that make eggs and sperm. So any genomic editing on them gets passed to future generations. Somatic cells, uh, once in the rest of the body, if you edit them in one person, their offspring won't inherit the change for the so-called CRISPR babies in China, the genetic changes are ones that affect the germline.

It's really changes to the germline that provoke the controversies in genome editing, because these changes are going to affect any future generations to, should we take that risk?

George Church: The problem with picking like one particular thing that demonize. Is it kind of false reassurances? Oh, as long as we pay attention to this thing, as long as the whole world pays attention to this one little thing, we're going to be safe.

When in fact there's all sorts of things erupting right next to it that you're not paying attention to like gene drives and, and, uh, somatic engineering of your brain hybrid devices, brain, computer interfaces that, that you can say, well, that's not my department. You know, maybe somebody else has taken care of them.

Maybe they are, but maybe. Uh, a lot of people are being distracted by a germline editing. There's certain things you don't need to ban because there's just not that popular. I think it's quite possible. Germline will be one of those. It's like jet packs, you know, maybe the band jet packs, they're just not that popular.

Dr Philip Ball: so genome editing and rewriting might be one way of making new kinds of people. Especially if we conduct it at the embryo stage, but there are clearly still huge questions about that approach. Both scientifically and ethically. George though is also exploring the techniques, used to grow my mini brain.

Brain organized. These involve some reprogramming to not have genomes, but of cells. The trick is to convince cells of the body like skin cells to revert to a state like a stem cell, which is the kind of cell in an early embryo that can grow into any tissue in the body. You can do that by injecting a handful of the right genes into.

Once you have a stem cell, you can guide it to become some other kind of cell, like the neurons in a brain they'll then start to organize themselves into a brain-like structure, a body part, indeed. Perhaps the crucial body part, like those used by Frankenstein, but grown in a day.

But these neurons aren't terribly good at making a real brain on their own. And George has been trying to make brain organoids look more like the real thing

you say, your, your, um, the organoids are, are improving. D do you mean you're your you're finding way? Providing this, the signals that the neurons and other cells need to become more brain-like and an organoid

George Church: is that. So it's improving in at least three ways. And one is, uh, we're getting all the cell types in the right ratios.

And, and usually when you get the right ratios in the right places, roughly as well. Um, so, so some of the cell types were not well-represented in the original organized. But particularly one that was missing was in the theological cells and the capillaries that remove waste and bring in. The oxygen and other foods that vasculature kept the organoid small.

So if you had something more than half a millimeter, uh, it would become necrotic in

Dr Philip Ball: the middle necrotic here simply means that the cells die.

George Church: And so now with vasculature, you know, we're starting to make either baskets or a suit of assets, or we're starting to make organs that have organoids that have billions of cells and, and soon there'll be.

Normal size or bigger. I mean, in principle, in a synthetic, Oregon, Oregon ID, you can make it any size you want. So you can take a hippocampus, which is normally, you know, the size of tip of your finger.

Dr Philip Ball: The hippocampus is a part of the brain that processes, memory,

George Church: and make it the size of the brain. That's the, that's the options that you have with.

With organoids. So we're increasingly building brains out that are atomically precise. Um,

Dr Philip Ball: I've got to go ask more about that straight away. What, what does that mean? Building grades that are atomically

George Church: precise? So, so, so almost all of biology is atomically precise. I mean, it has some imprecision in it, but it is capable of building at very high accuracy, large numbers of copies, um, and reconfiguring, uh, real time.

So part of your brain is constantly reconfiguring. Um, 86 trillion neurons, about a thousand times as many synopses, just constantly reconfiguring. Uh, that's not something you can do with hardware. Furthermore, the brain is about, um, 10,000 to a million times more energy efficient, um, and is just capable of doing tasks that we have.

Been able now, conversely, there are things that silicone can do that, that the brain can't do, but hybrid systems seem to be very promising to me. And we're just not focusing enough on the, uh, the bio part of that hybrid

Dr Philip Ball: with what aim,

George Church: why are we making computers? Okay. Right.

Dr Philip Ball: I was a bit taken aback by that.

It seems George imagines making these brains to act like little computer devices perhaps hooked up somehow to a Silicon based interface. Well, after all around brains can still do things that computers can't.

George Church: The other aim is, uh, uh, mental health. Mental health is one of the most tragic and expensive healthcare problems in the.

And effect, and it contributes to poverty because a lot of times, if you're impoverished, the normal distribution of, uh, mental health becomes shifted towards unhealthy very easily because you just don't have proper medical. Yeah. So is

Dr Philip Ball: the idea that the, the, the, the physiological reasons for a particular mental health problem might be addressed by some kind of hybrid device, some kind of implant?

Well,

George Church: We are hybrids already. I mean, right now the interface is mostly visual, but audio visual through typically through cell phones, those are getting, those will get better and better, uh, interfaces, you know, probably get sort of infrared input output would be one possibility. There will, there, there might be ways that you could, uh, Have cells that are distributed, um, the, uh, in your brain, um, through the blood.

So it would be semi invasive. You know, it's like very invasive. I think our electrodes where you, you Ram these big rods into your brain and the more you put in the more invasive it is, and it just doesn't scale. Well, But as an example of a cell that's distributed throughout the brain is the endothelial cells.

There's about one capillary per neuron in the brain is about 86 billion neurons in the brain is about someone number of capillaries and via the is you can distribute even smaller cells that. Do input and output to, uh, either neurons or synopsis. All of this, I think can be, uh, tested it with, uh, increasingly accurate Oregon brain organoids.

We're making right

Dr Philip Ball: as these many brains get bigger and better. They'll surely come a point where we have to ask what's going on in there. We know that these

neurons are active. They're signaling to each other by this eventually become something resembling real for. What would that even mean for a brain in a dish?

You remember Fritz? Yes, not Eagle, but Fritz in the 1933 Frankenstein movie, stealing a brain in a jar for his master and taking one that is labeled abnormal with terrible consequences for Frankenstein's crew. So how will we know what sort of brains we've grown?

George Church: Yeah. One of the ethical issues is when is a part of a brain, enough of a brain to worry about.

And when does that brain advanced the, not that part of a brain advanced enough to worry about one of the dilemmas that we will face? Yeah. If you have the brain read out to you, it's internal state, which I think is a safe thing in general, it's better to be transparent. I think computers should read out should have, as we get more and more advanced computers, they should be telling us how they're coming up with their solution.

The more we do black boxes as let's say, if we are right. Okay. So the brain tells you what it's thinking. And at some point you, you might want to through a Turing test, uh, you know, where it's basically saying. You know, I, I think therefore I am or something like that. But at that point, if it's gotten so far, that's doing a Turing test and you've inconvenienced in any way, given it pain, not necessarily pain, receptor pain, you can always remove this pain receptors that are pain pathways, but other kinds of existential pain, uh, on we, uh, you know, anxiety, all these things, you can try to eliminate all those pathways, but you have to be able to ask it in a way that it is.

It can honestly answer whether it's in any kind of form of pain, right? So we didn't want to do that. You have to be able to have a conversation similar to the one that we're having, but, but, but to get it to that point, you may have already given it quite a bit of pain to get to that point where you can have a conversation.

So that's a bit of a dilemma. I think probably, uh, our history is that we will probably go there in the same. We're doing the same thing with silicone-based computer is as we get closer and closer to than having a. Say the intelligence of, uh, uh, intellectually disabled person. Um, they are, it will be, have some form of pain.

It won't be the pain that we experienced, but it will be some sort of, you know, awake. Self-awareness the next official risk. I don't think that's particularly. Difficult to program.

Dr Philip Ball: I I'm surprised to say that. I mean, is it, how clear is it that we're talking even qualitatively about the same thing when we're talking about Silicon computers?

You know, certainly if we think about machine learning at the moment, um, it's, it's looking for correlations in data. There's no

George Church: one. Field is if it particularly talked about field is particularly prominent and rapidly moving field, but there are other ones like, you know, for example, uh, uh, self-awareness there are small demonstrations, uh, Uh, a machine will look in the mirror and will notice, uh, you know, something on its face and brush it off.

There's another one where it w where it is, um, asked a question about its voice. Like, can you hear yourself? Or can you, you know, is this youth speaking? And it, and it can tell itself from some other, uh, robots or, or some other person. And it says, oh, that's me. That's, that's the one that's me. Right. And so, so both verbal and.

There's a self-awareness um, and you eventually get to the point where they're faking it, but they're faking in such a way that I can't tell if you're faking it right now. Right. You know, I don't, I don't know that you're not a robot that, that happens to look a lot, like a person who's pretending like you're conscious.

And when they get to that point, I think we have to kind of, uh, either come up with a better definition or get in and just say, okay, they're conscious. They're self-conscious. Once they get better at conversation, they don't have to be that good at conversation. There are plenty of humans that are terrible at conversation, not just, not just intellectually disabled, but you know, just neuro-diversity, uh, people who haven't learned very much.

And I think we're getting there. You know, I have pretty interesting conversations with Google and Alexa. Yeah. Okay.

Dr Philip Ball: Okay. Now I can see, but you don't, you don't presumably have the con have, have the feeling with, you know, Alexa that it's anything more

than simply a, a sort of recognition that this type of input generally stimulates this type of output.

And so if you like, Alexa is saying, what

George Church: is that? Saying is it wouldn't take much to take it to the next level. And I know there are these competitions every year, whether you can pass the Turing test, but if you broaden that and I think it is broadened from time to time to include a broader set of, you know, Not just your, can you pass a 20 tests where you act like a colleague, you know, computer science colleague, but, but, you know, can you act like a down syndrome person?

Can you act like a high functioning? Autistic, can you act like a, you know, somebody like Kim peek who just like memorizes books? Um, if you, if you can be any of those categories and you can't quite tell which I think. You end up with a fake that's as good as you know, it's hard to tell the difference from a person and it's not just about self-awareness.

So if you add the self-awareness module in there, I think that will help. Um, if you have an actual robot in the room, right. And a person representing a robot, you know, just so they're, they, they look the same, but that having that personalization person, likeness of freewill.

Dr Philip Ball: Free. Well, we don't yet know what brain organoids grown outside the body might be capable of, but it seemed that George at least didn't see any obvious limits, but a brain on its own.

Isn't a. And maybe however, complex and sophisticated it is. It could never function and perceive itself as an autonomous entity, a self without being encased in a body that enables it to sense and interact with the external world. We haven't got to Frankenstein's creature yet.

It

Passage reader: was with these feelings that it began the creation of a human being. As the minute, most of the parts formed a great hindrance to my speed. I resolved contrary to my first intention to make the being of a gigantic stature. That is to say about eight feet in height and proportionately, large. After having formed this determination, having spent some months in successfully collecting and arranging my materials, I began

Dr Philip Ball: in the next episode. I'll talk to bioengineer, Robert Langer of MIT, about how we might grow the rest of that body, how we can generate organs and limbs and perhaps regenerate our own where they get damaged or go wrong.

Continuity: How To Grow A Human: my Frankenstein Summer is written and presented by Dr. Philip Ball and directed and edited by Keith Engish. This show is brought to you by Aurra Studios. Listen to the full series on Apple podcasts or wherever you get your podcasts.