MFS transcript 2

Continuity: How To Grow A Human: my Frankenstein Summer with Dr. Phillip Ball episode two, finding the parts.

Announcement: Harvard avenue. The destination of this train is Boston college

Dr Philip Ball: in the 25 years or so there I've been coming to Boston. One thing that never seems to change is it subway system called the T I'd be a bit sad of it. Did this noisy smelly network. There's a certain charm. It's also. Vital to the health of the city, like a system of blood vessels at branches everywhere to bring people to where they need to go.

Living organisms and bodies are a pretty good analogy for cities and vice versa. There are places where energy gets produced and networks to distribute that to the phone lines and fiber optic cables are live the nerves. There's waste disposal, places where the thinking gets done and Boston common is like the lungs are there, outsiders like me, mostly benign keen to adapt to their new surrounding.

But just occasionally these visitors are far from friendly and rarely but disturbingly, they can be lethal for the community. As the Corona virus has reminded us all too clearly.

In the last episode, I spoke with professor George Church at the medical school, his ambitious goal of making humans more resistant to disease and infections like COVID-19. By rewriting the human genome, all our gene bearing DNA. George told me that he's also in the business of making organs specifically is growing brain organoids, which are like crude, miniature brains, cultured in a dish from special cells that have been reprogrammed to become neurons and other brain cells.

That's a topic close to my heart because I've had the process done to me by researchers in life. In my book, how to grow a human. I describe how they made me a mini-brain from skin cells taken from my arm, very rudimentary versions of other organs like livers, kidneys, and pancreas is, can be made this way.

In Mary Shelley's novel Frankenstein, the protagonist assembled his creature from old human body parts collected from the grave or the morgue

Passage reader: and the moon gaze on my midnight labors while with an relaxed and breathless eagerness. I pursued nature to our hiding places. Who shall conceive the Horace of my secret toil as I dabbled amongst the unhallowed damps of the grave or tortured the living animal to animate the lifeless clay. I collected bones from the journal houses and disturbed with profane fingers, the tremendous secrets of the human frame, the dissecting room, and the slaughterhouse furnished.

Many of my. And often did my human nature turn with loathing to my occupation whilst still urged on by my eagerness, which perpetually increased. I bought my work near to a conclusion,

Dr Philip Ball: but a modern Frankenstein might not need to harvest body parts this way. The technologies are already being developed to grow.

Growing human tissues outside the body in vitro that's to say has actually been going on for the best part of a century, but making them form complete functioning organs is another one. And we're not quite there yet. It's part of the discipline called tissue engineering. And I visited one of the true pioneers in that field.

Robert Langer of the Massachusetts Institute of technology.

I've known Bob for many years. It's often said that if that was only a Nobel prize awarded for where biology, chemistry, and engineering meet, he definitely have one by now. Entering his office. It's easy to see why you can hardly see the walls for all the awards and certificates covering them. But Bob remains a modest man who is passionately committed to making life better for people.

Who need new tissues and organs, but you've been working for a long time on tissue engineering or biomedicine. And the field has transformed so much, partly because we have these new capabilities for transforming our own cells. Um, and so I was really interested to know how that's, if that's changed your position on what we can now do in terms of regroup.

Organs, we can now regrow them in principle from the patients who we are seeking to give a replacement to. Is that something that's affected the way you're working with with tissues?

Robert Langer: I would say yes. I mean, I think that there's two things we try to do, right. To try to make new tissues and organs. And I think that provide,

you know, one of the issues is, is cell source, you know, and particularly if you can get the source from the patient themselves.

That's great. And then I think the second thing is, you know, what we've been talking about? Like Oregon's on a chip, you know, we're involved in, in several aspects of that. Cause it really uses all the same principles we developed early on for, you know, electronic to have a three-dimensional kind of system rather than a two dimensional one.

Cause it really mimics what happens more in real life. You know that the ability to engineer cells in the right way. I mean, I think that helps you tremendously. So, so yes,

Dr Philip Ball: I say some more about this concept of organs on a chair, because it sounds fantastical. What, what does it consist of and how do you use,

Robert Langer: uh, I'll pick the ones that were more directly involved in, but really it could be anything.

I mean, And some of it stems right out of the work that we've done in the lab for creating tissues and organs. But just to give a couple of examples, uh, one of my students, Melissa rederick, and, and Gordana Wozniak, who was a visiting scientist with us, you know, a number of years ago, published papers on how you could grow a heart heart cells.

And, and it actually mimics what happened. Pretty well, you know, they basically have a hard on a chip. The heart actually beats like irregular heart. You can even do an EKG on it or things like that, but you can use it for toxicity testing, you know, and they're working with a number of big drug companies on both toxicity testing, but also drugs.

You know, so that you don't use an animal again, it's ultimately you will have to do it, but you can do much more higher throughput when you have it on a ship than an animal or a person. Certainly

Dr Philip Ball: this image of something like an artificial beating heart on a Silicon chip sounds fantastical, but it's actually a natural development of one of the first products of the field of tissue.

In the early 20th century, when researchers grew embryonic heart cells from a chicken, into a piece of tissue in a dish that twitched with animation, what else

Robert Langer: can we make? So that's one example. A second example is a witch, a geo traverse, and Thomas Von Ehrlich had been doing, uh, in our lab is a gastrointestinal track on a chip and they.

What we're trying to do is predict, uh, or absorption in other words of a drug. So we've been able to create, uh, tissues on a chip that, uh, intestine on chip. And so far, it's like got 63 drugs correlating with what they do in humans. But of course, the big reason why we want to use this as is, it provides a way to.

Screen, literally thousands and thousands of formulations. So let's say you wanted to have, um, a nucleic acid delivered or something like that, or a peptide that's really hard, but if you could get the bioavailability up by screening and finding what type of excipients or what types of formulations might work, that would be a really big deal.

And you might be able to take something from a, a drug that might have promise, but could never be taken orally to one that could be taken. Th that would be terrific. And, you know, it could lead to new therapies for patients and, and, and, and the reason it's so important to orally is like, you know, if you look at patient compliance is just a disaster in the us alone, over $300 billion of healthcare costs occur.

And maybe over a hundred, I think over a hundred thousand deaths due to heart disease alone, just because people don't take their drugs. And if you had ways to make. Do you know, better. And of course orals the easiest way to do it. That could save a lot of

Dr Philip Ball: lives. So this could be the difference, for example, between something you just pop in your mouth and an injection that you have to

Robert Langer: that's right.

And which people won't do, you know, it's like, we're, we've also worked on things. For example, just to get the, an idea on the injections. And this is even for older women, sometimes there's a drug parathyroid hormone. You're supposed to inject it every day. I think. Compliance rate is 23%, you know, people just drop out.

So yeah, it could be a huge deal. And these are just two examples. What you mentioned, you know, we've had a number of conversations about making a brain on a shop and we haven't done that much out, but I think it would be true. Because there's air everything from things that you've mentioned, like Alzheimer's disease, where you could study it better.

We're also working with Anne gray bell on new medical devices to put in the brain, but it would be so great if we could have something, you know, where you're going, you could do high throughput things and also look at blood brain barrier transport, which to me is a huge

Dr Philip Ball: issue. So that would be a way to enable drugs to get more readily

Robert Langer: into again, again, I think one of the biggest problems, and I think this is a problem with Alzheimer's.

I met hardly that I'm any expert in that, but it seems to me like getting drugs at a significant bioavailability into the brain is very, very difficult. And of course there's different strategies that people have tried ourselves included. But if you had some something on a chip that works again, you could screen through, you know, hundreds, if not thousands.

Formulations or pro drugs or other kinds of things and, and hopefully find something that might make a real difference. So, and then you could test the leads and animal models and ultimately humans. Again, that's not an area where we've contributed to yet. You know, just the basic ideas of tissue engineering itself.

But I think it's really important. And I think almost any tissue arguing, you know, saying you just don't work on liver on a chip. So it was Linda Griffith here, Don Inbar, who I collaborated with. He started a company that is looking at a variety of tissues on a chip. And so I think there's just, it's just an important area that.

And a lot of things and might reduce animal testing and might speed up drug discovery and drug toxicity testing.

Dr Philip Ball: Um, and when you talk about organs on a chip, to what extent are they really like organs these, or are they more than a clump of cells? Do they have any of the shape? The morphology of, well,

Robert Langer: I think that's a great question.

I would say. Yeah, they do. You know, so if you do the harder. There's things like soccer, MERS, and other strong ultra structural components that you see, and you can actually see the cells beating in unison, you, and like I say, you can even take an EKG of it. And actually the gastrointestinal track on a chip, most of the structures, you can see the Villa and other things.

So, so yeah, I would say.

Dr Philip Ball: Okay. And to be clear about what you mean by a chip, we're talking here about a microfluidic chip as I write so little channels that are allowing fluids to come to and fro

Robert Langer: from the, well, that's a fair question, you know, that's usually what I mean, but it doesn't have to be that way.

I mean, you know, I think anything that enables you to do high throughput screening, and I don't know that that's the only way with microfluidics to do high-throughput screening, but as. One of the better ways of doing it. I kind of think of a tissue on a chip or an organ on a chip is something that's three-dimensional that goes back to our general principles of J Vacanti.

And I wrote on tissue engineering a long time ago, where you have something that's three-dimensional as compared to just a two dimensional system, you know? So you have the kind of right surface divine structure and. Mimics to a certain extent, the structure and function of the tissue or organ, and then how you apply it.

I mean, you could apply it different ways. I don't think it has to be microfluidics, but that's certainly a very good way to do

it.

Dr Philip Ball: These organs on a chip then a mostly made for fundamental research. For example, for drug tests. But what about making organs and tissues

that we can actually stitch or implant into the body say to replace ones that go wrong.

You've also worked a lot on making actual tissues that are going to be used in surgery that absolutely planted in the body. So where are you with

Robert Langer: that at the moment? Yeah, so, so there's several different ones that we've been working on. You know, so some of it's basic work on new materials and cells and bioreactors, but in terms of specific tissues that have stemmed from our work, you know, skin now is made both, it's been approved by FDA for, for both patients who are burned out burned and, uh, patients have diabetic skin or.

There's clinical trials ongoing for blood vessels. Uh, uh, again, one of my postdocs who Laura, Nicholas, and she's now a professor at Yale and she started a company Uma site, which has done really. And they published a paper and lasted about two years ago on these blood vessels. And they were working very well.

That's a phase two trial. Now they've just finished a phase three trial, which will be submitted to the FDA a I think fairly soon, you know? And so I'm hopeful and you know, that that could lead to a whole new way of, of, of creating blood vessels. Another thing that we did is create new spinal cards for patients who are paralyzed and that's in clinical trials.

And another one that we've done is, uh, artificial pink. The big issue on the artificial pancreas is a little bit different strategy. You know, most of these strategies we've tried, we've had these polymer scaffolds and three-dimension, and we've, uh, you know, try to mimic the structure with the artificial pancreas.

There, we've used a dis idea of encapsulating the eyelid cells in a semi-permeable membrane. And then you get the Porsche just right. And insulin can diffuse through and glucose can diffuse through, but antibodies can't get through because they're bigger and immune cells can't get through. And that's an interesting strategy that goes back a number of years.

But about 12 years ago, the juvenile diabetes foundation called me up. And they said, you know what happens every time? And probably about 20 companies started and billions of dollars spent is that they get encapsulated, you know, with

fibrous tissues and blocks off the pores. So they said, could we solve that problem?

So Dan Anderson, who was one of my postdocs now he's got tenure here at MIT as a faculty member. And I, we put. Again, some high throughput synthesis approaches, and, you know, we made quite a bit of progress, you know, finding materials that wouldn't cause fibrosis, at least in nonhuman primates, showing that you could treat diabetes and figuring out the best locations and things like that.

So those are all examples of, um, of sort of the scaffold approach. We've also developed some other approaches that are, I think, you know, sometimes we've been able to use a material by itself if we get them in. That has the right tissue property. So we've been working with Steve at mass general. Who's a voice surgeon to try to make new vocal chords and that, and Julie Andrews actually from, has been involved in helping us with that.

Yeah.

Dr Philip Ball: I was amazed by this, the idea that damaged vocal cords by not be replaced, but regrow. This is a different, and in some ways, even more challenging idea to find ways of allowing the human body to regenerate itself. But we know it's possible. Some animals such as I'm Fabians and fish can regrow limbs or other tissues that get lost or damaged.

The best we can mostly do is to heal our wounds and broken bones. And even that might produce scar tissue rather than normal skin and other tissues. But Robert told me that it's not too much to hope that true regeneration could eventually become feasible for us to, by making use of the versatile cells called stem cells.

Robert Langer: Uh, Jeff Karp, who was another one of my postdocs, we came up with this way of finding that certain molecules could help unlock certain pathways. And you could have a stem cell, which is like sort of a progenitor kind of cell. In other words, it hasn't, it's not like an embryonic stem cell. It's, it's more advanced.

But it could then turn into, you know, more sophisticated cells. That's probably the wrong way to say it. And we, and Jeff and I published a paper, actually, one of the nature journals about six years ago, showing that you could cause a

proliferation of, of, of the cells. Um, we used an intestinal cell model, but there are also precursor cells and other parts of the body.

One in particular is the year for hairstyles. So what's been really exciting. Is that, um, we actually showed that you can give certain molecules and cause the stem cells to proliferate literally a thousand to 2000 fold and organize it's actually. But, but what's really exciting. And some of this has just come out.

In fact, it's not really been published, but, uh, but there's been some announcements. So I helped start this company called frequency therapeutics and they've done clinical trials now on about, um, you know, 20 patients. Again, when you do these early trials, safety is the big thing, but what's really exciting is you give injections of these molecules through the eardrum and it causes proliferation of the cells and they turn into hair cells.

And what's amazing on the clinical trial is not only is it safe, but, but what you see as a certain number of people are able to, to hear better. And, you know, there's, I think two ways of thinking about hearing. You know, like people have things like, uh, hearing aids or cochlear implants, and they raised the level of, um, you know, they make things louder for a person.

But if you are, for example, in a restaurant everything's louder, right. So it doesn't help you very much. So what this does is since it hair cells are really the key thing, you know, for helping people. And an in animals, what happens is hair cells can regenerate, but that's never happened in humans. So if somebody goes deaf, there is no way I, I, as far as I know, it's been a 0% of the time out of millions and millions of people that anybody's ever been able to restore the hair cells and to restore hearing.

So what has happened here is in a certain percentage of cases, you can, you can, and you get the hair cells restoring and, and, and the way you test that as they do WordPress, So the cochlear implant test, you know, there's the noise elevation doesn't affect the word recognition. This does. So here you get quite significant improvement in word neck recognition.

So that's in clinical trials. And what was just announced yesterday, again, this is from a business thing is a Astellas, which has a big Japanese company just gave frequency $80 million down-payment $650 million total for European and Asian rights to. But I'm very excited about it. Cause it could be a whole new treatment.

It's also a whole new strategy for possibly regenerating tissue. So it won't work on other everything, but it's, it's kind of recreating what happens and I think certain types of animals. And so those are some of the things that we've been working on. Wow. That

Dr Philip Ball: would be huge. I mean, the reason. Yeah, yeah, yeah.

Extraordinary. And w w what is actually, uh, how is that working now? So these small molecules are triggering the regroup of how cells, but from what are they from these stem cells that are specialized in the tissue type that are in there already,

Robert Langer: and they're in there, and they're dormant and they're dormant and the hair cells die over time, but you're absolutely right.

And, and, and, and it, it causes the multiplication of the, of the precursors. And then they can, because they're dormant, but now, now you can multiply them and they will turn into hair cells.

Dr Philip Ball: Right. Okay. And it looks as though they're being regenerated in the same way, as, as you say that are animals, fish couldn't do

Robert Langer: this.

I can't remember which ones, but definitely animals. Yeah. Right.

Dr Philip Ball: Yeah. I mean the same problem of course applies to, um, Um, which degenerate well,

Robert Langer: and we thought about that too. And, and so our hope is that this kind of strategy can be applied to a number of things. You're right. The I, the intestine, but I mean, we haven't done it.

I mean, but it's, I think that's possible.

Dr Philip Ball: Right. So just be in a way, a matter of finding the right molecules that will unlock the potential that these adult stem cells already have tissues

Robert Langer: that's right. Yeah. And so, so I think this kind of strategy could be very exciting, right?

Dr Philip Ball: I mean, you know, I called my book how to grow a human, but how to regrow human.

It's really

Robert Langer: one of the biggest, I think that's right. I think that's right. Thank you so much. Oh, that's my pleasure. Anything I can do in any way.

Dr Philip Ball: It's truly exciting to hear what advances in tissue engineering and making medically possible, not least for treating the problems that arise from aging, but making a huge. Well, of course, no one really thinks it's possible wise or desirable to make a complete human being by stitching together lab grown body parts.

We don't even know what it would mean to join them up and kickstart them into life like Boris Karloff, strapped to a table and energized by a lightning storm. The quest for researchers like Robert Langer and George Church is not to make new human life from scratch. But to improve the lives of those who already exist or who will come into being by the normal methods still let's imagine it here's a body stitched together and ready to go.

Passage reader: It was on a jury night of November that it be held. The accomplishment of my toils does already one in the morning, the rain pattern Disney against the. And my candle was nearly burnt out when, by the glimmer of the half extinguished light, I saw the double yellow eyes of the creature, open it, briefed hard and a convulsive motion, agitated its lemmings.

Dr Philip Ball: But what would it behave? Like? What would it think? How would it think? Could it really be sentience? It's the brain, just an organ. Like. Or might this seat of thought and consciousness need something extra. That's what I'll be asking in the next episode,

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