From the simple to the complex: building organs with Prof. Jamie Davies, part 1 (S01E03)
Not Another Science Podcast
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Introduction

Intro music starts.

[Tom Edwick] Welcome back to Not Another Science Podcast. I'm your host, Tom Edwick.

This week we're back with Jamie Davies, who is professor of experimental anatomy at the University of Edinburgh. In the third episode of our coronavirus mini series, I spoke to Jamie about the database he and his lab created, which was a curated list of known drugs and drug targets that should be prioritized in the fight against COVID-19. We also covered how the pandemic has changed the way research is done and what effects this could have on science going forward. It's a great episode, so go and listen if you haven't already.

In this episode we bring you more of our conversation, where we dive into the mysterious work of an experimental anatomist, discuss the value in taking things slowly, and talk about the quest to grow organs in the lab.

Enjoy.

Intro music ends.

Main

[Tom] So a lot of what you do is looking at how you get from the simple to complex. What does the best research that we have today tell us about how organs develop from just a single cell?

[Prof. Jamie Davies] Well, it's very difficult to put that in a nutshell. It's… What's clear is, for most organs, there is a huge amount of self organization that goes on. So even if you take organs apart — not when they're fully formed, but the cells that are about to form the organ in the embryo, typically a few 100 cells maybe up to a few thousand — even if you take them apart and shuffle them

about and put them back together, they will still be able to produce the tissues of the organ.

And what's been very clear, in the last 20 or 30 years, is that the cells are communicating with each other intensely, so there are sort of feedback loops of: "Well I'm going to do this, you my neighbour, please do that." And the neighbour will reply saying: "Yes, well I'll do that, but then you do this please." And there's a kind of… There's a very strong conversation happening in the language of signalling molecules between cells, and I think one of the ways that we are now moving is — almost having identified what a lot of the signals are, in the sort of you know, grand old days of grinding biochemistry, or genetic knockout — is now starting to think: "Well, OK, having identified all of these individual ones, let's step back and try to analyze the conversation,and understand as a whole how these conversations take place to generate order from relative disorder." And I think that's part of where all of this is going.

You know, as you said, my interest is how you get complexity out of simplicity. But of course, the sort of experiments that we've been using to pursue that question, like taking progenitor cells apart and away from each other and putting them together, that led very naturally to the idea: "Can we take progenitor cells (stem cells, in other words) that want to make an organ, and put them together and make a new human organ." And what we find, if you just do something as naive as that, you get the micro structures of the tissues forming beautifully, but you don't have the macroscopic anatomy.

So for example, the kidney. The kidney is a whole load of plumbing, and essentially there's a big tree of tubes and then lots of fancy tubes arranged around that tree. And the whole blood system also arranges around that tree. So it's really important that that single tree forms properly. If you just do the kind of experiment I said — take the progenitor cells, throw them together in the tube — what they'll make is lots and lots of little trees that are disconnected, each of which will happen with everything right around it.

So we've discovered, in the last few years, we need to break the symmetry of the system in some way. So it isn't that all parts of it are the same, but for example, if we have the tree forming cells in one unique place or all together at the beginning, they will form a single tree and then everything else will arrange itself properly

around that tree. Or if we have an asymmetrical signalling environment mimicking what happens in the embryo, we can make one branch of that tree, the trunk, effectively becoming the ureter, which is a tube that leads away from the kidney, while the rest become the kidney.

And that was a case of realizing: "Well, that doesn't happen when we just do this in culture. Let's go back to the embryo, find out why, ask new questions of the embryo, find out, oh, there's a signalling molecule coming from one side of the developing kidney. Let's go back to culture. Let's put a fake source of that signalling molecule there, and then suddenly, bam! We get a ureter."

So there's this kind of interplay between embryology, trying to do some engineering, running against a brick wall in the engineering, going back to the embryo with a new question that you didn't really have before, making a new discovery in the embryo, getting past that brick wall, and running into the next one. An iterative process of… Well, I mean, all scientists will recognize the 'banging your head into a brick wall'.

[Tom] That's basically, that's science in a nutshell really, isn't it?

[Jamie] Yeah, yeah.

[Tom] So I suppose it's a challenge because you're creating tissues, they're not inside the body, and so they don't have the natural sources of these signals telling them where to go and what to do. So has that posed a big challenge for you in your research?

[Jamie] Well, you know it's both the challenge and the outcome. Yes, it's the challenge, but that challenge is what made us ask questions that then got us to understand the embryo better. At the moment, our big challenge is that we could only grow these things to be fairly small because they don't have a blood supply. One PhD student in my group is working very hard to get, not just blood vessels into these, but to have blood flowing through those vessels. Julia Tarnick is her name, and she's built this wonderful arrangement of pumps into microcontrollers and tubes, and she's learned a lot of microsurgical stuff so that she can start to connect the mechanical to the biological. And yes, it's an amazing setup. And actually some of the engineering behind it was made by her father. He's an engineer and she was talking to him about her project, and he's produced some wonderful custom-made materials for her.

[Tom] Oh, that's amazing! Do you find yourself collaborating with different labs in different fields entirely, a lot of the time?

[Jamie] Yes, yes, absolutely. So there's a collaboration I'm in at the moment, an EU collaboration where we have me as a mammalian biologist, a botanist who works on light sensitive proteins from plants, an expert in cybernetics and control theory, and a physicist who is a modeler. And we're trying to put all of this together so that we can use light to control the behaviour of cells that are making organs.

[Tom] Yeah, I imagine that there can be a lot of different perspectives coming together, and you don't necessarily all think in the same way perhaps, and have different ways of tackling the same problem which come… You might get some really interesting outcomes from that.

[Jamie] Yes, yes absolutely. I mean sometimes communication can be a little bit difficult, especially when two fields use the same word to mean something different. But again, that's the fun of it, and everybody, you know in these collaborations everybody's patient. We all realise that we have to drop our in-lab slang and start to speak to each other — with a huge respect for each other's intelligence — but speak to each other like first year undergraduates in terms of the vocabulary, and always be near a black board or white board, or just the tablecloth.

[Tom] So you did your PhD on neural development. Is that kind of developmental biology something that you've always been interested in? Did you pick up an interest for it during your undergraduate degree?

[Jamie] Yeah, I suppose my longstanding scientific interest is how you go from simple to complex. And before, when I was at school, before I was going to university, I'd sort of assumed I'd turn out to be a radio astronomer looking at the formation of galaxies. But where I went to university, you don't study a single science, you study Natural Sciences which is a mixture of things. That's the first time I'd really met developmental biology, and sort of thought: "How did I miss something so {important}, as an example of going from the {simplicity} of an egg to the complexity of a person?" I mean, it's just one of those reminders that {...}. But yes, I got hooked very, very quickly.

[Tom] Can you tell me a little bit about that project and what the main research focus was?

[Jamie] Yeah, sure. So when a nerve fiber grows, its very leading end is called a growth cone and it's an exploratory structure that sort of feels around the tissues around it and makes decisions about which way to go. And everything that we were taught as undergraduates, at that time — which was the early to mid 80s — was about attractive cues.

And I'd thought as an undergrad: actually, this can't work. Because if you're trying to get things down a narrow path, if you make the path of attractants really narrow, that's brilliant for accuracy, but how do things find the path? Because it's too small. If you make it really wide so they can find it, how do they avoid blundering around along the wide path having no idea where they're going? Whereas if you did it the other way, if you had… If instead you defined walls each side which were repulsive, then things would go straight down the middle between the walls and any blundering around would quickly be self correcting, because they'd blunder towards a wall and run away from it again. So it struck me that that actually repulsion has to be part of the story.

I was bothering people about this and a wonderful man called Roger Keynes — who's still a professor in Cambridge — said that he had a system where they thought they were seeing repulsion. And this was… Down your spinal cord…

I'm sorry, I must stop talking with my hands on an audio.

Down your spinal cord, nerves come out from it, and they come out on each side of your body. You get one nerve per vertebra. They come out between the vertebrae.

And what Roger and his colleagues had found is that the tissues each side of the spinal cord seemed to be responsible for stopping the nerves coming out where they shouldn't. So if you take those tissues away, the nerve can come out anywhere.

They'd done a little bit of staining with lectins, which are proteins that attach to carbohydrates, just because those are a kind of broad spectrum, if you don't know what you're doing, and especially really in the early days of molecular biology being applied to mammals, those kind of probes you could you can… 'Don't know what you're doing' in the sense that you don't know what the molecules are. Then a broad spectrum kind of thing to see if you can find

any patterns… Just going through somebody's lectin in catalog and buying lots, {...}.

And they found one lectin which stained embryos in stripes, only staining the cells that seemed to tell the neurons to go away. And he and a colleague of his, Geoff Cook, from the Pharmacology Department, who is an expert in carbohydrates (the things that lectins bind to), offered a PhD project to me if I wanted to go and pursue this. So I jumped at it.

And working for two supervisors was actually great because Geoff was a really fine chemist, and as long as I could make him think: "Well, Jamie is a rubbish chemist, but he seems OK as an anatomist," and make Roger think: "Well Jamie is obviously a rubbish anatomist…" you could kind of survive them.

{They were} both wonderful supervisors, and I had the great luck… So my job was to fish out whatever molecule this was that was binding to the lectin, and it could have been anything. But I had the enormous luck that that did turn out to be the thing that was repelling the growth cones, which is the third turn of luck. So I got as far as identifying it as a protein with a particular molecular weight, and then that was the end of the PhD. And it was fine, you know we got a Neuron paper out of that.[1] In those days we weren't expected to do as much to get a paper or a PhD, as people are now.

Only this year have Geoff and Roger finally discovered what that molecule actually is. {It's} a surface bound enzyme that causes a nitrous oxide signaling response in growth cones.[2] It took something like 30 years to find out what the molecule actually was. Nobody was expecting it to be an enzyme. It's just kind of… When muons were first discovered in nuclear physics, one of the physicists who read the news just sort of said: "Who ordered that!?"

[Tom] Yeah, it's quite a nice journey from your initial discovery all the way to finding out what the actual…

[Jamie] Yes, really, really nice. I mean really nice that Roger and Geoff are still working together and still did that together, because obviously quite a few years have

[1] Davies, JA, Cook, GM, Stern CD, and Keynes, RJ. (1990) Isolation from chick somites of a glycoprotein fraction that causes collapse of dorsal root ganglion growth cones. *Neuron* 4:11–20.
[2] Cook, GMW, Sousa, C, Schaeffer, J, et al. (2020) Regulation of nerve growth and patterning by cell surface protein disulphide isomerase. *eLife 2020;9:e54612.*
For more information, you can also read Jamie's blog post about it:
http://golgi.ana.ed.ac.uk/Davieslab/blog/2019-11-WhoOrderedThat.pdf.

passed and at least one of them isn't really a spring chicken anymore. Well, none of us are, goodness knows.

I think the other message of this… They… Obviously they've been doing other things, but they stuck at a problem for 30 years, and they were allowed by their university to stick at a problem for 30 years, without publishing a Cell paper every year or any of that kind of thing. And you know, often in science people are expected to solve things quickly, and to be producing paper after paper after paper. I think this is a nice illustration of just the value of sticking at something and being allowed the time to stick at something until you get the answer.

[Tom] Do you think certain things are lost when you're just on that publication train, trying to get out paper after paper? Do you think that pressure has an impact?

[Jamie] What's lost, it's the choice of the work to do. Peter Medawar,[3] the Nobel winning immunologist, once described… He defined science as the art of the soluble.[4] And he made the point that, in choosing a scientific problem, you have to choose something which is probably soluble: there's no point in devoting your life to something which you can never solve. But also don't devote your life to solving an endless succession of trivial things, which, yes, they are soluble, but really, was it worth all of that? And I think the problem about the publish, publish, publish, get a grant, get a grant, get a grant pressure is that it can push people towards either the trivial, or towards things that everybody is trying to do, so it's a mad race, and it actually doesn't matter whether an extra person jumps on the bandwagon or not, that's going to get solved.

And unfortunately, a lot of the stuff that reaches the journals that people really like publishing in are the things that are huge races, because journals like accepting papers that will get cited a lot, and obviously very hot fields do lots of citations. Whereas a lot of the stuff that really really matters isn't like that at all. You know, an example is CRISPR. CRISPR DNA editing is a massive massive thing now, but the original paper around CRISPR was published in a relatively obscure place, and was barely cited for eight years. And I think they're absolute heroes to have done that work carefully, when it

[3] https://en.wikipedia.org/wiki/Peter_Medawar
[4] *The Art of the Soluble*, Methuen & Co., London/ Barnes and Noble, New York, 1967

didn't look trendy and it wasn't being cited, but look what it's done now.

[Tom] So you mentioned before that you've chosen to focus on the mammalian kidney. What was your reasoning behind that?

[Jamie] But I left the number system for two reasons. One was… OK, I know I got very lucky. I probably wasn't going to again, and I was really scared of its complexity. The other reason is that — this is a very personal thing, so it won't be the same for others — the way that that research about neural repulsion was probably going to go, towards clinical things, towards helping spines and things regenerate, which is very, very important, was pretty soon going to force me into doing work in living animals, and I didn't want to do that. So I wanted to work on animal development without actually doing experiments on living models.

And I'd come across a book in the anatomy library in Cambridge called Organogenesis of the kidney, and one of the things that shone through from that book from the very beginning is you can take kidney rudiments out of freshly culled embryos, and which had not been messed about with, and they'd just been killed instantly, and you can grow them in culture. So you can see them, you can mess about with them, but there's no animal suffering in the middle of all of this. Whereas of course, the problem about mammalian development is there's the mother. You can't… There's no way of experimenting on embryos inside the mother without it really being fairly ghastly for the mother.

So that's the reason I chose the kidney and I'd written… When I was looking for a postdoctoral job, I'd written to… Well, Geoff actually recommended an amazing scientist called David Garrod, who was working down in Southampton. And he worked on the interactions between cells, and he got interested in the kidney as somewhere he could study his favourite interactions. And I was very lucky that he… I went down there to talk to him and he offered me a postdoc position to work on the kidney. And the first thing he did was send me off to Helsinki to learn all of the techniques. And I've stuck with the kidney ever since, because it's horrendously complicated. If you want to study building some complex things, it is, but also there's a clinical need to make some progress with it, so it's possible to get funded for it, and it's possible sometimes to have that feeling of: "Maybe what I'm doing

is possibly doing a bit of good." And a lot of the people who work, postdocs and things, are motivated strongly by the need to do good. I'm more scientist than medic at heart. It'd be nice to do something useful, but knowing is what really fires me up in the morning. A lot of my colleagues in the lab are very fired up by doing good, and good for them.

[Tom] And I think you mentioned somewhere that the kidney, a lot of the ways in which it develops is similar to the way other organs develop in the human body as well or mammalian body.[5] And so you can kind of scale up and apply it to different organs.

[Jamie] Yeah, I think the technique, certainly. I mean for a lot of organs this idea of: "make a tree shaped set of tubes, and then clag stuff around it," that is a very standard way of making an organ that gets rid of something, secretes something or breathes, because that's a way of getting a lot of a stuff in a small space. But also the general techniques, just understanding things like what cells can organize for themselves and the important role of breaking the symmetry of systems to get large scale anatomy. I think those are going to be principles that extend across almost anything. It's making us understand the embryo in a slightly different way, and when you start to look with that idea in your mind then you see it everywhere.

[Tom] Can you see a future where there's absolutely no animal testing? Do you think that's a possibility?

[Jamie] I doubt it, for two reasons. One of them, which is probably the easier one to explain, but I'll have a go at both. One of them is just: there is too much that we don't know. Just testing as in testing drugs and things, maybe one day, but it is… It may be easy to test whether a drug will damage the heart or the kidney. It will be harder for relatively high brain functions. I mean, we're used to the fact that we really can't test everything that human brains can do because we don't have other animals that can do all that we can.

But there are things, you know… Vision would be an example. Does something have an effect on vision? Or well… That's going to be really hard to test in a dish, so I think there will always be some things like that.

[5] http://sbmsintranet.bms.ed.ac.uk/sources/Briefings/davies.pdf

I think the other problem: people often concentrate on trying to look at the headline numbers of how many animals are used. The thing is, using animals is really expensive and is a bottleneck in the discovery of new medicines. When we move a great deal of it to non-animal testing, it doesn't actually mean fewer animals are used. It means far more medicines get tested with the same number of animals because each medicine is mostly tested nowhere near animals and only the few that look as if they might make it to humans get to the animals. So there will be more that can actually get to that path. So what… I suppose the pathway that we're taking is to have much more gain per animal used.

Now, obviously for a moral absolutist, then no animal use is acceptable full stop, and there are people like that, and there are people who have, who are totally convicted and they don't use things that are tested on animals, not even medicines. And I respect that. For people who are more relativists then at least getting as much as you can for as little damage is a way to go.

[Tom] Awesome! So I think we should move on to talk a little bit about the synthetic biology stuff that your lab does. For someone who doesn't really have any idea about synthetic biology, what would you say to them to describe what it is? In a nutshell, if you can.

[Jamie] In a nutshell, it's just genetic engineering, but done with attitude. So where genetic engineering is typically just changing one gene in a cell or an organism, with synthetic biology we're tending to make entire systems of genes so that we're introducing a new behaviour into the cells.

And sometimes — this isn't our work — but sometimes, for example, that's introducing a new metabolic pathway to make a valuable compound. That could be a drug, that could be the kind of enzyme which is used in low temperature washing liquids that we're all used to now, it can be an enzyme for remediation, bioremediation, or for turning wood into a fuel. At our end of things we are changing cell behaviours not biochemically, but what cells do in terms of communicating with each other and in terms of making patterns and in terms of making shapes. Because again, we're interested in how tissues are made and we're interested in programming cells to make designer tissues. Again, for me that is often done to find out: have we really understood how tissues form?

For a lot of my colleagues working with me in the lab, the reason is because they want to build a tissue to solve a particular medical problem. And again, it's fine. In a way, the motivation doesn't matter, we're all trying to get the job done.

[Tom] Is the end goal to move away from using things that have naturally evolved and just creating completely new molecules, proteins, tissues that act in a different way to what we've seen evolve in nature?

[Jamie] That's part of it, yes. I mean some of it, which is just for application. For tissues, you can imagine some reasons you might want to do that. Life support machines that live outside the body, or even ones that you could imagine living inside, at the moment, they're almost completely mechanical, but there are aspects of living organs that are missing. And putting tissues inside the machines would be a way of bringing back some of that function. But just putting a lump of liver or a lump of kidney inside a machine is not going to work. What we really want to do is to generate something which is intrinsically really happy in the machine — ideally they couldn't live anywhere else, for safety reasons — but still does the biochemical or the physiological thing that a normal tissue would.

That's one reason for it. Another reason: surgeons will recognise that a typical body suffers damage, then they need a part just to reconstruct the normal part of the body. But if somebody is born with an atypical body, then repairing that may need a custom part, because what you're trying to fix isn't the way that most humans are anyway. And at the moment plastic surgery is used to do that, but of course typically plastic surgery is a long succession of operations and a long succession of changes. It would be very nice, just effectively to be able to order this part. I'm being slightly fanciful, but those are the sorts of ideas behind all of this, as well as just 'doing to understand'.

[Tom] Yeah of course. And do you think it's still quite far off like having designer organs and for transplant and stuff like that?

[Jamie] Yes, that is definitely far off. But there are things you know… Well, I suppose the most accessible things such as skin transplant, cornea, that kind of thing, that are very 2 dimensional, that's a little bit more imaginable in the near future.

And also there are other uses. And we've talked entirely scientifically and medically, but several sculptors have contacted me about this, because they're interested as artists in having self generating art, and sculptors don't have to work in enormous blocks of granite that they can't lift, they could work at the microscale, and it's interesting the way that creative people from all over the place, like artists, are starting to engage with all of this.

[Tom] Yeah, I think that's really interesting, actually. I was reading about vantablack, which is the incredibly dark pigment made from carbon nanotubes, and how…

[Jamie] Black you can get.

[Tom] Yeah, yeah exactly. And it started out as just, I think it was military research or something like that, but then artists got interested in it, and then there was a whole big fight over who owned the pigment, because can you own a pigment? It's really interesting when you have that interplay between…

[Jamie] And another pigment that's being produced that can be sold to anybody except for the one who… [6]

[Tom] Yeah.

[Jamie] A very complicated story, that.

[Tom] Yeah, so I think the interplay between science and art is really interesting sometimes.

So I was wondering what are the limits of synthetic biology, because I know that when you're making a protein from scratch or something like that, you can't necessarily predict how it's going to fold once it's inside the body.

[Jamie] Yeah, I think you… Whether it's proteins, or entire cell behaviours, you've exactly put your finger on it, we can't predict.

There is a peculiar kind of act of faith that a lot of synthetic biologists have, and they like to present the subject as if it's an electronic set. They refer to the host cell as the chassis, the way that radio builders of the interwar period would refer to the bit of aluminium onto which they attach their valves and things as a chassis.

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[6] See *Art Fight! The Pinkest Pink versus the Blackest Black:* https://www.wired.com/story/vantablack-anish-kapoor-stuart-semple/

And they talk about genetic modules that can be plugged together, rather the way that one might buy computer boards to plug into your PC. They really talk like this and they really write like this, and I think one of the reasons that there's been a lot of hype and the dreams of you know, five or six years ago, have not been realised by people who reckoned they could easily knock these things off in a year, because life isn't like that. The host cell is not a neutral piece of aluminium that will let holes be drilled in it. It will react physiologically.

And we don't understand biology very well in the first place. It's easy to do electronics. Electronics is so well understood that each component is understood and the way they interact is understood. Biology… We're right at the beginning of understanding how life works. However arrogant people want to be, I think there are far more not known, than is known. And I think it's… This way of just pretending that we know it all is frustrating and is slowing the field down, and just accepting we're blundering around in the dark, so let's have open minds and learn, and particularly, let's learn from our mistakes. Rather than just kicking the cat, and slamming the draw, and stopping the project, actually work out why something didn't work, what didn't we understand. That's much more promising, but rarer.

Outro

Outro music starts.

[Tom] Huge thanks again to Professor Jamie Davies, famed experimental anatomist, swing dancer, and owner of a boat called the Saucy Mrs. Flobster.[7] If you haven't fallen in love with this man yet, I don't know what's wrong with you.

Join us in the next episode to hear the rest of our conversation, about the perils of running a peer-reviewed journal and about how he inadvertently created the first biological database on the Internet, because of his poor memory.

This podcast is brought to you by the Edinburgh University Science magazine. In each episode we explore fascinating themes and ideas, talk to awesome researchers about their work, and find out about the science being done by our very own staff and students here at the

[7] See episode 3 of our coronavirus mini-series, *Near and IUPHAR: Repurposing Drugs for COVID-19, with Professor Jamie Davies*, from July 29th, 2020

University. If you'd like to get in touch with a question, suggestion, or if you want to be featured on the podcast, you can reach us on our Facebook page, Edinburgh University science media, or at our Twitter, @EUSci, that’s E-U-S-C-I. You can also drop us an email at eusci.podcast@gmail.com, and you can find the show notes in the latest issue of the magazine at eusci.org.uk.

This episode was edited by my partner in crime, Helena Cornu. The awesome podcast cover art was designed by EUSci chief editor Apple Chew. The intro music is an edited version of Funkorama and the outro music is an edited version of Funk Game Loop, both by Kevin MacLeod.

I've been your host Tom Edwick. Until next time, keep it science.

Outro music ends.