Near and IUPHAR: Repurposing Drugs For Covid-19 (Science During A Pandemic #3), with Prof. Jamie Davies
Not Another Science Podcast
July 29th, 2020

Pre-episode disclaimer

[Tom Edwick] Hey guys! Hope you're all doing well. I'm literally sitting in my cupboard as I record this, in a bid to kind of reduce the noise and echo and bounce off the walls in my room. Got like a duvet draped over the two doors, it's kind of like a little fortress, it's pretty cool. But it's not massively comfortable, so I hope it makes a difference.
Oh, and another quick note, I am recording this in my flat, and I have two very noisy flatmates, so if you hear any funky noises going on in the background, blame it on them. Cheers.

General Introduction

Intro music

[Tom] Hello and welcome to *Not Another Science Podcast?!*, I'm your host, Tom Edwick.

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 University of Edinburgh.

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. You can also drop us an email at eusci.podcast@gmail.com

Specific Introduction

[Tom] Today we bring to you the third part of our four part miniseries on coronavirus, in which we're exploring what it's like to do science during a pandemic, and diving into the

incredible response from scientists and students from the University of Edinburgh. We're speaking to Jamie Davies, who is a professor of Experimental Anatomy. His lab researches how complex organs form from simple beginnings, with a hope that one day we will be able to construct organs ready-made for transplant.

Professor Davies, with the help of his team, also runs two large databases, one of which has been really useful in fighting COVID-19. Back in April, we had a great chat over Zoom about the work that he does, about the databases he runs, and about how science might change as a result of the pandemic. Today we're focusing on coronavirus, but we'll be publishing the rest of our conversation in a later episode, so keep your ears peeled... That's not even a saying is it? Sounds a bit gross to be honest, and I wish I'd never said it.

Anyway, before we dive in, if you missed the last episode, you should go and check it out. We spoke to Jess Cox from Augment Bionics, who told us about their 3D printing operation, mass producing personal protective equipment for the NHS. It's a super interesting episode,and the work they're doing is so cool. And if that's not enough to pique your interest, we've got highschool drama, red wine controversies, and sci-fi film pitches to Ridley Scott, so you'd be daft to miss it. To find all other episodes and show notes, head to our website at eusci.org.uk, or subscribe on your platform of choice.

Main

[Tom] Hello!
[Jamie Davies] Hello!
[Tom] Can you hear me?
[Jamie] I can hear you, thank you. Can you hear me?
[Tom] Yeah, absolutely.

This is Professor Jamie Davies.

[Tom] So first things first. Welcome to the podcast. Would you like to introduce yourself, tell us a little

but about who you are, what you do, and the main research focus of your lab?

[Jamie] Well my name is Jamie Davies, and my position is Professor of Experimental Anatomy, which probably makes me sound like a contortionist. It comes from some of the work that we do in the group which is around working out how to program cells to build new anatomies. So some of that is about building for example, trying to build replacement organs. Kidneys are the ones we work on most because of course people with kidney disease may need a transplant, there is a shortage of transplantable organs, and also there are immune problems about getting matches. So the dream of being able to take a patient's stem cells and to build them kidneys from their own cells, would be very nice. So that's one side of it.

And then the other side is something we call synthetic biology, I mean the field called synthetic biology, which is to program cells that don't know how to build a particular thing so that they do. So we're effectively reprogramming development. I do that because I think it's the best way of finding out "Do we understand development?". If we understand it, we should be able to build new things with our understanding. To me the most interesting moments are when we get it wrong, when the thing doesn't work and then we realise "Oh, okay, so it's not like that at all", we need to go back and ask a better question.

And then on the other side of the lab, for almost accidental reasons, we run a very large drug database, the main one for IUPHAR…

That's the International Union of Pharmacology[1].

[Jamie] And that's a WHO-created organisation and the database that we run from the lab contains the information on all prescribed drugs, but also a lot of research compounds and about their targets and things[2],

[1] To be precise, it's the International Union of Basic and Clinical Pharmacology (https://iuphar.org/).
[2] https://www.guidetopharmacology.org/

[3]. And that's something — it was started by a colleague of mine, the late Tony Harmar, many years ago. And we carry on with that, and that keeps growing.

When it comes to controlling an outbreak, like the current COVID-19 pandemic, there are three things we can do[4]. The first is public health interventions, such as the current lockdown. Secondly, and probably the most effective, is vaccination. This allows us to confer immunity to the population without people having to actually catch the disease. Unfortunately, vaccine development takes a long time, and it will be a while until we reach a stage where we can roll out a successful vaccine. The quickest vaccine ever developed was for mumps, which took four years. With coronavirus, there has been talk of pushing through a vaccine in 12-18 months.

In the meantime, it is important that we can effectively treat patients who are severely affected by COVID-19. This brings us to our third option: drugs. If we can find drugs and therapies that help treat coronavirus, then we can reduce the number of people severely affected by the disease. The trouble is, drug development is a notoriously slow process, so instead, a lot of treatment strategies have emerged to potentially repurpose drugs that we already know about. Like any other organism, viruses exist in a family of related species, and we can use this knowledge and knowledge of the structure and genomics of SARS-CoV-2 to see if we can employ drugs that work on related viruses. It is also important to see if currently used drugs are actually doing more harm than good. So to keep track of these rapidly emerging developments, Professor Davies and his team set up an entirely new section of the *Guide to PHARMACOLOGY* database dedicated solely to COVID-19.

[Tom] So yeah, I wanted to talk about the new section of the Guide to PHARMACOLOGY database that you set up in the wake of Covid-19. What were you aiming for, for this new section?
[Jamie] What we were aiming for — I suppose it was… Well, the simple is just: to have a living, very very rapidly updated summary of everything that seems to be

[3] https://en.wikipedia.org/wiki/Guide_to_Pharmacology
[4] http://golgi.ana.ed.ac.uk/Davieslab/blog/2020-03-COVID.pdf

known with reasonable certainty about the pharmacology of Covid-19. So right at the beginning, that typically meant concentrating on the drug targets. So viral proteins, for example that drugs might target their function, or the targets where — it was already becoming clear that the immune response of the human was part of the story — targets that might change the immune response. Some of the targets were… You know, part of it is: can we find drugs that can be useful? And some of the questions were: are there drugs that patients might be on now, that make them particularly vulnerable? Because that's another question. It's a less asked one, but a very important one. And we worried about — as it turned out, not with justification — but we knew that the main way that the virus infects cells is its spike protein interacts with a molecule called ACE2 on cells, particularly of the cardiovascular system, and a few other places as well. And we knew that a class of blood pressure-reducing drugs called ACE inhibitors caused there to be more ACE2 expression in the body. So we and other people had an immediate worry about: do ACE inhibitors make you more vulnerable? Actually, some data coming out from Wuhan suggests, in a relatively small post-hoc clinical trial (so that's looking backwards), it suggests the opposite: that the people who are on the ACE inhibitors were actually somewhat protected. Now obviously, people are not put on ACE inhibitors willy-nilly, those are people who have cardiac conditions, so it's not a full randomised clinical trial, but at least it's enough to say no, they were not at enhanced risk. So there were a few worries like that right at the beginning. And then the rest of it was finding drugs that might interact with this virus. So there are other antiviral drugs that affect viral proteases for example, part of the viral life cycle. There's a drug which has been in the news a lot, chloroquine, which affects, when the drugs[5] enter cells, they go into a pathway of closed bags of membrane in the cell (vesicles), and in that pathway

[5] I think Jamie meant viruses.

> they uncoat and become activated and chloroquine messes up the way that pathway works. It's a dangerous drug, it has very bad cardiovascular effects. And we were following that intensely because particularly, a few people have tried it in humans. There's one person in France who's become an evangelist for it although — I'm trying to work out how to put this tactfully — the data are by no means fully persuasive. So there were things like that. And essentially, just being given the task by IUPHAR and WHO of trying to find a reasonably prioritised list of which drugs which already exist, so they can already be used in humans, ought to be tried.

In the short term, repurposing existing drugs could be incredibly useful, but Professor Davies stressed the need for continued development of new drugs as well.

> **[Jamie]** The other side of it is for the development of new drugs. So, drugs that are not already licensed for humans.

Professor Davies recently co-authored a paper charting a roadmap for the future research and development of COVID-19 drugs and therapies.[6] The purpose of the paper is to inform clinical drug trials by presenting what we know so far, in an effort to guide which approaches to treatment might work best. In a blog discussing the paper, Professor Davies stressed that although there has been a lot of talk of vaccines in the press, there are really important reasons to continue pharmacological research.[7] The first is simply that there is no vaccine yet, but there are some drugs now. The second is that getting a vaccine isn't necessarily a certainty.

> **[Jamie]** Of course, we all hope there will be a vaccine to this, we know that's going to be about a year away. We all hoped there would be a vaccine to HIV; there

[6] Alexander, SPH, Armstrong, JF, Davenport, AP, et al. A rational roadmap for SARS-CoV-2/COVID-19 pharmacotherapeutic research and development: IUPHAR Review 29. *Br J Pharmacol*. 2020; 1– 25. https://doi.org/10.1111/bph.15094; https://bpspubs.onlinelibrary.wiley.com/doi/full/10.1111/bph.15094

[7] "Map-making in a hurry", Jamie A. Davies, April 2020. http://golgi.ana.ed.ac.uk/Davieslab/blog/2020-04-Roadmap.pdf

> never has been. It’s not a given. At the moment, politicians are speaking as if it’s certain there will be a vaccine. Of course, we very much hope there will be but it’s dangerous to think it’s a given. The huge improvement in the control of HIV has been done by designing drugs. And the sad thing about HIV is it’s not eliminated in most cases, {drugs} have to be taken for a long time. If we can design drugs to control how badly the SARS-CoV-2 virus (the thing that causes Covid-19) affects people, the drugs wouldn’t have to be tolerated for life probably because the infection would go away again. Then that could be the quickest thing to do but also, so if the vaccine doesn’t come along, that actually might be all we have. And there is that risk. It’s a risk not being talked about very much. So keeping the pharmacological effort going and moving to drugs. At the moment, test compounds that are already sort of in databases with a lot of data but are not yet fully registered drugs are the way to go, but then there’s also another tranche of well, can we develop entirely new compounds which would be even better?

Another important reason to continue pharmacological research into COVID-19 is that vaccines are only useful against one specific virus, whereas drugs can be useful against whole families of viruses. SARS-CoV-2 is not the first coronavirus that we’ve had to reckon with, as you might have guessed by the name, SARS-CoV-***2***. The SARS epidemic of 2002 and 2003 was caused by SARS-CoV-1, but frustratingly pharmacological research into the virus dried up in the months that followed.

> **[Jamie]** You get this horrible feeling of deja-vu reading papers now. Because there was a lot of work on that virus, and that virus is 79% identical to SARS-CoV-2. And had that carried on pushing forward, we probably would have had the drugs by now, we’d have had them for a decade. The frustration is that when the disease more or less went away, then the effort into developing drugs all went away. Because obviously — I’m not being an apologist for drug companies — but

> they're not going to develop something they can't sell.

So when writing the script for this episode I came across some news which proved Professor Davies' point exactly. A recent early-stage clinical trial has found that a drug called SNG001 — catchy, I know - which was originally developed to treat viral infections in asthmatics but never made it to market has been repurposed to treat COVID-19. The study of 101 people found that patients were 79% less likely to develop a severe form of the disease. Richard Marsden, the chief executive of Synairgen, the company that developed the drug had this to say, and I quote: "Imagine if we had done this work five years earlier, this drug could have been stockpiled by governments… When coronavirus emerged in Wuhan we could have given this to all healthcare workers and anyone exposed on cruise ships or elsewhere."[8]

The hope of researchers like Professor Davies and Richard Marsden is that this pandemic can spur some positive changes in how we do science.

> **[Jamie]** One of the things I really hope comes out of this model — not just for antivirals, but also for antibiotics — is that the role of the state in protecting people, in health, part of it is saying to drug developers, whether academic or companies: "Look, we want antibiotics of this kind, we want antivirals that will deal with this whole class of viruses, whatever it is. We know there's no disease right now that needs them. We will pay you this much for this stock and this guarantee that you can produce again, so that you can quickly fire up a factory." You're commercial, by all means a competition will pay the winning company this, the second company that, and the rest of you, sorry bad luck. We can make it fully commercial, we're not about nationalising the drug industry, but to be able to do that, so that we don't have this thing that we're going through now of

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8 https://www.theguardian.com/world/2020/jul/24/major-breakthrough-in-covid-19-drug-makes-uk-professors-millionaires

reading papers thinking: "I've practically read this before in 2003, and if only."

[Tom] One thing that has struck me is the pace of how quickly scientific research has had to move, in these times, because it's quite unprecedented really.

[Jamie] Yes, and it's very interesting. One of the foundations of the way that normal academic research happens, not just in science but in everything else, is peer-review. Typically, you do your work in the lab, and you make whatever discovery you think you've made, and you write it up in a paper, and you send the paper off to a journal, and then they will send it to at least two independent reviewers who are in your field, and they will take a look at it and either say: "Oh, that's great!", or more typically say: "Well that's kind of okay, but you need a better control for that experiment, and that graph isn't plotted properly, and you've used the wrong statistics", and so forth. And that acts as a kind of… Well it's no barrier against fraud because if somebody just lies then they lie, that won't be detectable, but it's a barrier against inadvertent mistakes, that mean that something would, without peer review, be published and give a misleading scientific result. Peer-review takes months, typically. Even journals that say they do it quickly take a month. So in the response to this crisis, everything is being put onto the web, even when it's been submitted to a journal, people are releasing, even journals, are releasing the pre-peer reviewed version because it's so important. And it's really interesting to see science moving so quickly, using this sort of stuff. And it's sort of interesting and dangerous, because there's a great deal of rubbish and snake oil out there. Leaving aside the absolute snake oil that's infected that's infected the internet with miracle cures, even things that look a lot like scientific papers, from places that jolly well ought to be producing scientific papers, there are some hair-raising things out there. And one of the roles of bodies like WHO and IUPHAR is to sort of screen this. So what's happening is that we have a pre-screening of a lot of these papers on sites like our database, so

that experts can do a very fast peer-review. It's not what they do for the journals, but they're spotting obvious charlatanism at any rate, and really howling mistakes. And I suppose that's part of the role of these databases: to think "Well, this information can clearly go in" — with a warning it's pre-peer review. Then there's another set which gets attached with really big warnings, about "there are concerns", and then there's other stuff which frankly, we're not going to put in until something more sensible comes along. And sometimes the data are unsafe not because anybody's being stupid, but because — especially clinical trials — the trial is so small.

[Tom] Yeah, I've heard a lot that the experiments that are taking place — the trials — they have promising results but there's just not enough data to actually make any sort of valid conclusions from that, reliable conclusions.

[Jamie] A week or so ago, I was in a teleconference with CNPHARS, who are the leaders of the Chinese Pharmacological Society, and they gave some wonderful presentations about what they'd been doing, particularly in Wuhan — trials. The sense of the conversation was about them handing the work over to Europe, for the very happy reason that they're running out of patients. The disease is under control so much they're saying: "Well actually, we don't have hospitals full of patients to do these trials on any more. There are now so few people getting sick, we can't do any more work on this, whereas you guys have now got the huge problem, so please, you take it on." It was actually very heartening to feel… It's really nice to feel that things are turning around in some parts of the world. We had a conversation with people who are doing vaccine development, and they were saying, they're in an absolute break-neck hurry, in the UK. Because, obviously you can't give people the virus to test a vaccine, but what you can do is take a bunch of health workers, randomise them, give some of them the vaccine, some of them not. They're all going to be pretty exposed because of the job they're doing, and then ask how many of them actually went down, and

how many — "down" as in "got symptoms" — and how many of them then developed serious symptoms, which is a way of testing vaccines. But you can only do that kind of test if there are plenty of people being exposed to Covid-19. So once we get on top of the epidemic and are closing down, then actually it becomes harder to test the vaccines that we need desperately in order to be able to lift all of the restrictions. So science is actually having to move absurdly fast, and there are really interesting discussions about what corners can you cut, and what can you absolutely not cut. And it's childish to say "You can't cut anything", because clearly, things have to be done very quickly.

[Tom] And I guess, before this was all happening, there wasn't necessarily the willpower or even the necessity to cut those corners. Sometimes I feel you need something like this to stimulate changes that can be made for the better.

[Jamie] Some of them are not really for the better. There's a lot wrong with peer review at the moment, but it's still better than the alternative of not having it. And anybody who does a random web search will be rapidly convinced about how bad things can be if there are no barriers. But I suppose it's just a case of accepting. It's a little bit like emergency medicine, in a field hospital: you don't have what you have in Edinburgh Royal Infirmary, but you get by with what you have because there's an emergency. And that's the spirit of it. All scientists, all the time, we deal with uncertainty. But I think it just accentuates the fact that people are having to make rapid decisions on uncertain, noisy data.

[Tom] I think there's been so much with this pandemic that we've realised we don't have to do it the way that it's always been done: people teaching from home, stuff like that, and a lot of jobs that have been able to be moved onto the job platforms. Do you hope that science will, do you think it will change as a response to this pandemic?

[Jamie] One thing I'm really hoping for is that there's an awful lot less jetting around the world. People are holding not just little conferences with 6

or 7 people, but are holding real conferences electronically. And far too much of scientific life — I {...} long distance travel, but that's just me being grumpy and belligerent — but far too much scientific life is spent waiting around at airports. And for climate reasons, for time reasons, for efficiency reasons, it's silly. I mean of course sometimes there is a need for a face to face meeting, but with there being fewer of them, they'll probably be higher quality. There is a conference circuit that develops, where everyone speaks the same talks at each other in LA, and in Washington, in Moscow, and in Rome, and you kind of think: "Look, you all know by heart what you're all saying to each other!" Maybe a different set of grad students being brought. So I hope that will change. I think the ability of academia and industry to work together in a hurry, that's been amazing. And one of the things that I've been really impressed with is that in this emergency, people from different companies are not caring about what company they are from. Everybody, just, you know: there's a fire burning and people are picking up hoses. And they're really not caring about whose name is on the hose, they're just getting on with it. That, obviously, that won't carry on completely, but I hope people will remember that way of working. And another thing I suppose, we have a short window for this probably. Right now, it feels as if the public, over quite a lot of the developed world, have decided that people who know something aren't such a bad idea. That could reverse very quickly. It may be that it doesn't take long at all before a great storm of fake news says that we never needed to shut down, we never needed to do that, we never needed to do that, and all of these experts are to blame and we should never listen to them again. So we probably have a short-ish window to try to build on trust. And I think the more transparency and the more engaging we can do, the better. And people like Neil Ferguson I think have been — you know, from Imperial — have been amazing, to be really really clear at engaging people about the uncertainty.

Professor Neil Ferguson led the study from Imperial College London, which modelled transmission of SARS-CoV-2 and predicted the number of people that could die under different government strategies. This study is ultimately what led the UK government to move away from its 'herd immunity' strategy, which involved allowing some spread of the virus in a bid to promote natural immunity in the population. However, Professor Ferguson's study demonstrated that this option could lead to 250,000 people dying, and forced the government to set stricter lockdown rules.
Unfortunately, there has been some controversy surrounding Professor Ferguson, when it was discovered he himself had broken lockdown rules, arguably undermining the very advice he had helped the government create. But the point still stands - good things happen when we listen to scientists.

> **[Tom]** Yeah, that surprised me: they did the research, the paper came out, and then it had such a direct and tangible impact on the strategy that the government chose to use. It would be so refreshing to just see that in the future I think.
> **[Jamie]** Yes, and this constant engagement about the uncertainties. I think that's what's been so impressive — from the scientists. The politicians tend to just say: "We're taking scientific advice, this is the best thing to do." Whereas the scientists are tending to say: "Well, everything's pretty uncertain. This is what our modelling is saying. This is the best thing to do because it's the best we've got, but we don't **know** know, we just think because." And I like that {...} approach.

As we neared the end of our conversation, Professor Davies wanted to remind people that behind all the numbers and statistics are real human beings who have had to deal with this disease, and many who have lost friends and relatives to COVID-19. The truth that has been highlighted by this pandemic is that when we ignore scientists, lives are lost. We need to trust the scientists and the experts, and provide the necessary funding and opportunities so that the next time something like this comes around, we're ready.

[Jamie] We see that the death statistics… Some of us, I mean there are people are know who've had this disease, there are people I know whose relatives have died from this disease, which suddenly turns the curves not into curves but into something with real people. And that's when you particularly feel the tragedy of not using the science and not pushing on. And I hope that one of the things that changes with the world, when we come out of this, is that we will prepare. Like preparing for effects of climate change, as well as mitigating them, preparing for the effects of fire, bushland fires, as well as mitigating, that we will prepare for epidemics as well as mitigating ones that we have. We will try to have things in place.

Outro

Outro music starts

A huge thanks to Professor Davies for coming on the show. We have another episode coming soon with the rest of our conversation, where he tells us about how our bodies make complex organs from simple beginnings, how to grow organs in the lab, about shockingly rude reviewers on journal articles, and more. He also writes a blog, called *Waiting for the cells to grow*[9], where he talks about life, science, and everything in between. It was a fantastic resource for this episode, and you should go and check it out. You can find the blog and learn more about his work at the Davies lab website[10], links as usual will be in the show notes.

The coronavirus miniseries is an opportunity to get your feedback: what you liked, what you didn't like, and what we could do differently, so please don't hesitate to get in touch. The podcast is brought to you by the Edinburgh University Science Magazine. You can find the show notes and the latest issue of the magazine at eusci.org.uk, that's E-U-S-C-I .org.uk. Next time in our final episode of the

[9] http://golgi.ana.ed.ac.uk/Davieslab/wftctg.html
[10] http://golgi.ana.ed.ac.uk/Davieslab/

coronavirus miniseries, we talk to Dr Samantha Lycett, a computational biologist using virus genomes to track the transmission and spread of SARS-CoV-2.

This podcast is edited by my partner in crime, Helena Cornu. The awesome podcast cover art was designed by our EUSci co-editor-in-chief, Apple Chew. The intro music is an edited version of Funkorama[11], and the outro music is an edited version of Funk Game Loop[12], both by Kevin Macleod.

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

Outro music ends.

[Helena Cornu] *sigh* Jamie's awesome.

[Tom] Oh yeah, you've met him, haven't you?

[Helena] Yeah! He and his partner teach swing dance at the Edinburgh University Swing Dance Society, and they are some of the loveliest people you'll ever meet. I love that they call themselves the Swing Doctors[13] — that's their teaching name — because they both have PhDs. And if that's not enough to sway you, I recently found out that Jamie owns a ship which is older than the Royal Yacht Britannia, and is only registered as a ship accidentally, because she's actually a 72 year-old canal boat[14] called, I kid you not, the Saucy Mrs Flobster[15,16].

[Tom] Forget Boaty McBoatface, we should definitely start a petition to rename the Sir David Attenborough. What a legend!

[Helena] Right!?

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[11] https://incompetech.filmmusic.io/song/3788-funkorama
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[12] https://incompetech.filmmusic.io/song/3787-funk-game-loop
License: http://creativecommons.org/licenses/by/4.0/
[13] http://golgi.ana.ed.ac.uk/Swing/home.html
[14] She's 76, my mistake. — HC
[15] https://www.ed.ac.uk/biomedical-sciences/about/staff-spotlight/prof-jamie-davies
[16] https://www.nationalhistoricships.org.uk/register/1422/saucy-mrs-flobster

Edited extract from Sing, sing sing (with a swing), performed by Benny Goodman. Written by Louis Prima in 1936.[17]

[17] https://en.wikipedia.org/wiki/Sing,_Sing,_Sing_(With_a_Swing)