Teamwork makes the (scientific) dream work, with Drs Ed Hutchinson and Sara Clohisey (S01E05)
Not Another Science Podcast
October 28th, 2020

Introduction

[Tom Edwick] Welcome to Not Another Science Podcast. I'm Tom.

[Helena Cornu] And I'm Helena.

Intro music plays.

[Helena] Before we start, we have a sponsor on the show. This podcast is sponsored by Greiner BioOne, supplying laboratory, diagnostic and medical products to research institutions, higher education the NHS and others across the UK. For details of the full product range, visit www.gbo.com.

I am very excited about this week's guests. Do you want to tell our lovely listeners a bit more about them?

[Tom] Yeah, so on today's episode, we have two of the loveliest people that I've ever spoken to. Dr. Ed Hutchinson, he works at the Center for Virus Research at the University of Glasgow — he runs a lab there — and Dr. Sarah Clohisey. She actually works in the Bailie lab, which has been featured on the podcast before, at the University of Edinburgh. And yeah, they were basically part of this really cool study. Not only was the science behind the research really cool, but the story of how it all came together is really interesting, 'cause you know it was a bumpy road. It wasn't a straightforward path.

I went and counted how many authors were involved in this paper and it was 54 different people. I don't know how you coordinate something like that.

[Helena] Oh, imagine the email chains. I just… Goodness.

[Tom] I have a hard enough time trying to organise a Zoom conference…

[Helena] This podcast is hard enough to organise, and that's three of us!

[Tom] Oh my God, yeah.

So basically the study is looking at how viruses do their thing, basically how they go into a cell and hijack the cell's machinery to make copies of the virus. And basically what viruses do — and this is a process called cap-snatching — they take a little bit of host DNA and put it on their own DNA[1]. And so it kind of goes under the radar in the cell. It doesn't get detected by anything else. And then this DNA makes its way over to the ribosomes — these are the big cellular machines that make proteins and molecules and stuff that the cell needs — and it exploits that to make copies of itself, which is wild.

[Helena] It's as if the virus steals a hard hat, gets into the factory and then poof! Can participate in the production line, incognito.

[Tom] Yeah, on the down-low.

[Helena] On the down-low. I think what's cool about this as well is that he… The reason that they managed to collaborate was 'cause he tweeted about it on Twitter, and it kind of gives me hope that when I mention, you know, people that I really admire in my tweets, maybe one day they will reach out to collaborate, you know?

[Tom] Just always tagging them in the hopes.

[Helena] You never know!

[Tom] Yeah so this is a story of collaboration, teamwork, generosity, kindness in science, which is maybe different to the typical sort of cutthroat world of research that I definitely thought was the case. And yeah, Ed and Sara, are like the two of nicest people ever, just really nice.

Main

Transition music.

[Tom] Our story begins with Ed Hutchinson, working on cells infected with influenza virus.

> **[Dr. Ed Hutchinson]** All viruses… They really have two unifying features. One is that they produce infectious particles, but the other is that they parasitise their

[1] It's actually RNA.

> hosts at the molecular level and they take over the ribosomes of the host, and use those to make proteins. They don't encode ribosomes of their own, so all viruses have to feed ribosomes messages which ribosomes can use.

[Tom] As we mentioned in the introduction, viruses need to dress up their DNA so it can move undetected in the cell. Influenza is a member of a family of viruses that disguise their DNA in a process called cap snatching, essentially stealing a bit of host DNA and attaching it to their own. The ribosomes, which are the factories that make proteins and other molecules for the cell, can't tell this camouflaged DNA apart from the host's. As a result, they start making viral proteins and unwittingly creating new copies of the virus.

As a postdoc in Oxford, Ed was researching influenza by using a technique called mass spectrometry, which allows you to see all the molecules and proteins that are getting made within a cell during the course of infection.

> **[Ed]** At the time I was working in Ervin Fodor's group at the University of Oxford, and Ervin had been encouraging me to develop my own projects around using mass spectrometry to look at influenza virus proteins. And the first thing to explain a bit about is the way this technique works. So for this sort of analysis you take a sample, you purify proteins out of it, you use enzymes to break those proteins into short chunks called peptides, and then you use a technique called mass spectrometry to work out what those peptides were.

[Tom] With this method, he discovered some strange proteins that didn't appear to come from either the virus or the host. Or more accurately, it seemed like they came from both.

What they had found was that these proteins were actually a weird Frankenstein molecule made from host/virus hybrid DNA, created by the virus cap-snatching host genes and attaching them to its own. To the ribosomes, these combined DNA sequences basically just look like one big gene, and the resulting proteins were a combination of host genes and virus genes spliced together.

> **[Ed]** That was completely unexpected and we had no initial explanation for what was going to happen there, and I think because this story is going to touch on people being generous in science as well, it's something which Ervin

would have been entirely entitled to say: “This is great. We're going to continue working on that. We’ll let you know how it goes.” But in practice what he did was to say: “Take that away with you. Use it as preliminary data to get a lab funded.” And in fact, when we finally wrote the paper, he didn't even choose to be an author on the paper, he was just keen to see the story fly in a new lab. So he was extremely generous in supporting that being set up.

[Tom] Once Ed’s lab in the Center for Virus Research was set up, he began looking for backup to help piece together this complex story. Colleagues from the University of Glasgow pitched in and talking to other researchers at conferences led to the re-purposing of unpublished data.

[Dr Sara Clohisey] Last year, I was invited to speak at the Glasgow Virology Workshop, where I got talking to Ed. And we were talking about how cap-snatched sequences were awesome. And then we started working together on this, although what we contributed was a very small part of this fantastic and long, amazing, story.

[Ed] Although the basic idea, at least in molecular virology terms, is quite simple, there were a number of really quite difficult technical hurdles which needed to be tackled in order to figure out what was going on. So the work Sara was describing was absolutely key to figuring out what was going on, as well as being a fantastic story in its own right. When I heard Sara talking about the work she was doing, it was clear that if she was willing, she would be able to help us.

So this was people being generous with their time, but through the usual channels of scientists working together. So colleagues down the corridor, people you bump into at conferences, friends who, in my case I'd trained with, and had gone off to work elsewhere, and I’d stayed in touch with. So a group of people came together and by the end we had a fairly large collaboration.

What happened next was… Was unusual though, because at that point Maria Amorim, my friend in Portugal, who’d been helping us with mouse stuff, said: “Yeah, I've been to a… I’ve been to a seminar, which sounds really like this study, and they have just submitted it and have you seen

their preprint?" Which I hadn't. And so I looked it up on Biorχiv[2], and there was a description of a study which was different in the specifics from ours at every single point, but in general terms followed exactly the same path and reached exactly the same conclusions.

And that wasn't a great {moment} I have to say. I felt like I'd been kicked in the gut, you know? [laughs] I had just got out of a fairly stressful training session in the university library and I was recovering with a cup of tea and checking my emails, and it's probably fortunate I was sat in the library at the time because you have to watch your behaviour whilst you're there. But I did what you would do under those circumstances, so I thought: "Okay, you know, we have to make the best of this." I rang up the postdoc in my group, Liz Sloan, who was working on this, to immediately let her know what was going on. I went and moaned at some considerable length to the director of the CVR, and between the three of us we agreed that, you know, what we were going to do was obvious: we were just going to publish what we had, and as our director Massimo[3] put it: "At least, in any case, you'll have a paper."

We did two things then, which were… I wasn't totally sure about, I suppose. One was: when we put out our preprint, we included a discussion of the other study, even though it was still in pre-print form. Although I find preprints very valuable, I'd never actually discussed an un-peer-reviewed study in something I'd written before. And the other thing was that I wrote about it on Twitter. And I was a grumpy late adopter of Twitter, so that was quite a new thing for me at the time.

And both of those paid off. The reviews which came back, which were, you know, appropriately critical, but very constructive, included very positive comments on the fact that we had discussed this complimentary, competing study as it would normally have been seen. But then the author of that competing study, who I didn't know at all, got in touch — so this is someone called Ivan Marazzi from the Icahn School of Medicine at Mount Sinai — and he said: "Look, it's up to you. This is your paper, of course." But

[2] Pronounced "Bio Archive", it's an open access preprint server for biology, where researchers can publish non-peer reviewed versions of their papers for free.
[3] Prof. Massimo Palmarini

he said: "I'm getting fed up of fighting with people over papers. Our results could support each other very well. Do you want to combine the work and we'll make sure that the first authors stay first authors and last authors stay last authors, so everyone is still credited for their work, and we'll have a stronger story for it." And their study, like ours, was in major revision at that point as well.

There's a degree of risk in that 'cause neither Ivan nor I knew each other at all, but we felt it was a risk worth taking. So we combined the studies, which is a very short sentence to say, and was three months of incredibly hard work. [laughs] They were both {quite large studies} and it required a lot of unpicking, and a lot of putting back together again. And they were written in completely different ways, 'cause Ivan and I write in completely different ways, but we ended up with something where I think the science was certainly richer, and I think also complemented itself at key points in the papers, but also probably where the final product, I'd like to think, probably balanced out the the better tendencies of both of our approaches to writing papers. So it was a long and challenging process to do, but it ended up with a paper which thankfully the journal liked and which we were able to then publish with all 54 coauthors in the end, credited for their work.[4]

[Tom] Sara, I wondered if you could talk a little bit about what it was like just being one of those authors and being part of such a big project. Were there certain challenges involved that you haven't faced before or?

[Sara] There was challenges involved. One of the challenges that I had personally was… You become, when you're working on something with somebody else, you become very involved in how they've approached a problem. So when the two papers were being combined, personally I just found it… Although everything now is just so beautifully laid out, my head couldn't get around how they were going to integrate everything together, and make it, not not necessarily understandable, but succinct. So that for me,

[4] Hybrid Gene Origination Creates Human-Virus Chimeric Proteins during Infection (2020) Cell 181(7), p1502-1517.E23 https://www.cell.com/cell/fulltext/S0092-8674(20)30630-9

when the final paper was written, it was amazing to read through it and just see how excellent a job they had done. And just integrating everything together and making sure that everyone's work was represented, that no part of the work fell by the wayside, or was forgotten about. So following that was challenging at the time, but to be honest, Ed and Ivan did a fantastic job of almost shielding the rest of us from that, and really taking it upon themselves to carry the heavy burden of integrating everything and working together. But apart from that, Ed is a very communicative person in general, so kept us involved at every step of the way, which again is something that you don't always get when papers are being written. You usually find out you're being integrated at this point, and then at the end you get a final manuscript and you're like: "Whoa, what happened in the middle?" But Ed kept {us} involved continuously, which was fantastic.

[Ed] I'm glad you felt that was the case, but I will say as well that the involvement of people — and actually particularly Sara — was crucial, because a number of the datasets, in order to integrate them in the way she was saying, needed to be really completely rejigged. I think you were the recipient of a number of frantic emails from me saying: "Can you do it this way instead? And I know you've been doing it that way for months, but could you do it this way instead?" And you were extremely obliging at doing that at short notice.

[Sara] Well, one of the things that I was planning on saying during this podcast was: I think it's… You have mentioned it, but I'm not sure you quite mentioned how much of an amazing thing it is, is how many datasets that already existed you integrated into this. That is phenomenal because I think there is a general theme in science of 'You have to do everything yourself' and I think your collaborative nature and communicative ways have meant that you've been able to integrate all of these datasets together, and you haven't had to start from scratch, have been able to see what's there and work on it, which is exactly what science should be.

[Ed] And I think that was definitely a challenge we ran into, actually. It's interesting you pointed that out because… Yeah, there was still this sense that,

particularly if you're writing a high profile paper, your data needs to be new and it has to have been generated for the first time and not been seen by anyone else. But we were fortunate in many ways that useful datasets existed, but also it wasn't simply a case of: “Let's pick up a dataset which someone else has already produced and analysed and take credit for in its form.” So, a number of people who took data — which was used in other papers, so Sara's data had been used in a very nice paper she’d published in the Journal of Virology this year, for example — those data that were completely reworked and re-analysed and a lot of work went into doing that. So it… Although the raw data has now featured in more than one paper, for each of those they're providing new information and new parts of scientific stories in a new setting.

I think as we move towards a time where data openness is increasingly required of us, that's something — a real opportunity actually — for us to to start making use of the growing number of large datasets which are out there. It's also, of course, something which is possible to work on remotely during lockdown, so it's one of the reasons my group has not been completely twiddling our thumbs over the last few months, is that we have been able to… Actually in that case, largely working on data we've accumulated ourselves which we are now re-analysing in different ways, but most of the new results we have recently have been had from re-analysing data when we haven't been able to get back into the lab.

[Tom] It feels to me that, from people that I've spoken to, the world of research can sometimes feel a little bit cutthroat, and like you're competing with everyone else to try and get your thing published before them. So I guess it must have just been quite refreshing to work on a project where you and Ivan had just decided to just throw that out of the way.

[Ed] It was really nice to be in that situation. I mean, not least 'cause of course we benefited personally from it, but also 'cause it is nice when people choose to work together. I think one thing I will say on that though, is that there is this prevalent idea that science is necessarily a really cutthroat place, and if you ask anyone, they’ll say: “Oh, you know, I've got this series

of anecdotes which people told me over drinks and conferences of people doing terrible, terrible things." And, you know, people do sometimes do things which range from the secretive to the downright unethical, because there are these pressures to get there first on them. But then if you ask people: "How do your colleagues behave?" they usually say: "Oh no, my colleagues are great. Yeah, the people I work with all the time are really nice, and you know they're really keen on open science and data integrity, and people being credited. But you know scientists, oh no no, scientists are terrible." I think that the problem is that the stories of people being… I don't know how child-friendly your podcasts are actually! But the stories of scientists behaving in less than desirable ways, let's say, are compelling stories. And they're stories which, in a sort of malicious way, is quite fun to share, but that feeds into this idea that science has to be a cutthroat place.

And that's one of the reasons why I'm really pleased you've chosen to talk to us about this, 'cause I don't think this is an intrinsically unusual story. It's perhaps unusual that it happened on a fairly large scale, but scientists collaborate all the time, scientists share data all the time, and scientists, for the most part, are keen to see each other acknowledged all the time. And it just doesn't always make for a particularly memorable story, so it's nice to actually have a chance to try and balance out the narrative a bit, and tell a story of what I think is actually a story of scientists behaving pretty normally but just not in the way which we often talk about.

[Sara] I think that Ed is right, that collaboration and stuff is very common, and people generally are quite open, but I think that with stories like the one that's being presented at the moment becoming more common, and especially through things like Twitter and podcasts and more kind of informal presentations, things are changing. And I think that earlier career researchers (which I get to claim to be even though I don't think there's that many years between myself and Ed!), we get to see this amazing change, that… Or well, I suppose you're saying that it's not a change, aren't you, Ed? But you're saying that it's just… We get to see that this is more represented and so it's more encouraging for us to be able to enter

conferences and talk openly about our work, or speak openly about our work and not be scared, I think is one of the biggest things. I think that video conferencing and similar things might make networking more difficult. One of the advantages of going to the Glasgow Virology Workshop and literally just sitting next to Ed with a cup of tea was that we could just chat. And we spoke about the methods that I'd used and how we could apply them, and we were able to have a nice informal chat about that, where nobody felt under any pressure. But with a video call it might feel a bit more formal, and you're less likely to just run into someone over tea or coffee.

[Tom] I mean social media in this case has been a really useful tool for you to connect with other people, and I guess in the large part that was how you ended up getting put in touch with Ivan.

[Ed] So ironically, Ivan is actually not on social media himself, or if he is, he's hiding very effectively, but I… Do you know, I don't even know what the correct terminology is, I'm not great at this myself. I tagged? I think? One of his… Sara, you probably know.

[Sara] It's tagged, yeah.

[Ed] [laughs] I tagged one of the other authors on the paper, and I think that's how word eventually got to him. And that is a real challenge, actually. I think preprints offer a huge opportunity for scientists to compare ideas. Actually I say scientists, I do mean biologists, 'cause physicists have been doing this for years and think it's hilarious that we think this is new. But there's such a great volume of it, I mean even before the firehose of papers which started coming out with coronavirus, there's such a huge amount of preprints that you need some sort of social glue for holding chats about ideas together and for holding discussions between people together, and that needs to be something which can accumulate over time as well. And up to this point, this has worked through physical meetings.

So Sara pointed out that we met through the Glasgow Virology Workshop. I think the reason it was as easy to have a chat as we did, other than that she's very

approachable, is that we move in similar professional circles, so we had met repeatedly at many conferences in the years running up to that, so I wasn't just completely springing out of woodwork when I said: "That was a great talk! Let's talk about your work." At least, I hope that wasn't how it came across.

[Tom and Sara laugh]

[Ed] But simply listening to recorded talks through Zoom, although it can convey information as Sara says, doesn't build up those connections, doesn't facilitate that informal chatting and building up of relationships. So I think it… There are real opportunities for doing that in a way which doesn't involve huge amounts of national and international travel, and I'm quite excited about the possibilities there, but yeah, it has to be something a bit more sophisticated than simply watching pre-recorded talks.

[Tom] Coming back to the research itself, in your opinion, what do you think are the big implications of this sort of research?

[Ed] One of these… The striking features about it is that viral genomes are extremely small. I don't know if you have ever been to the Wellcome Trust Museum in Euston Road in London, but they have a very nice display there where they have the entire human genome printed out.[5] And it's a bookcase worth of printout. And if you print out the influenza genome on the same scale, it's a single sheet of A4. So we're talking a very, very small genome there, and it's startling how much complexity is packed into that small genetic space.

And the main… I think the main takeaway from this study is not really any specific function for a gene or any particular outcome — although we did point to one or two things in that direction — it's simply the fact that this is a new way where there's a huge amount of potential genetic diversity, which can be looked at not just in influenza, but in all viruses of this sort. So there's new places to look for ideas.

[5] https://en.wikipedia.org/wiki/Reference_genome#/media/File:Wellcome_genome_bookcase.png

That said, most of the work we did focused on influenza, so we can say some specific things about influenza there. One is that genes expressed in this way are visible to the immune system. What the actual implications of that are for controlling infection, we're not yet sure. It's something we're hoping to follow up on, but certainly T-cells can detect the presence of these cryptic genes produced through this mechanism, from infected cells. So that's one angle.

The other angle is what these variant genes actually do, but RNA viruses like flu, they mutate so quickly, and they're under such strong selective pressures that there is scope for them to rapidly develop function within {super} regions of their genome. So there seems to be genetic architecture of these viruses, whether it has been selected for originally or whether it's just inadvertent, which means that they have a lot of suitable material which they can start selecting for genetic functions, when the need arises. And although we don't yet know what those functions are, they do seem to be valuable in certain settings, so there's a lot more interesting work to do to figure out what's going on there. But I think the bigger thing this this study points to is that there is a lot of genetic variation which it will be interesting for scientists to look at, in influenza and in many other viruses as well.

[Sara] One of the things I wanted to say was, as a kind of cap-snatch-ophile, I used to make the joke that the integrated sequences from the host into the viral genome or the viral mRNA, rather, were the epitome of a host virus interaction. And honestly, this work has taken that idea to an entirely new level, that I… I don't know if everyone else gets excited about stuff like that, but I just think it's amazing.

[Tom] Cool, I mean, so I think that that's all the questions that I have about the research and the paper. I don't know if there's anything else you guys would like to to add or highlight before we switch off?

[Sara] I would like to say that if people are interested in seeing what a lab should be run like, obviously the

Bailie lab is amazing, but the Hutchinson lab has made resources available. For example, your pamphlet? You've made a document available to new members of your lab, which talks about everything from, you know, where the pipettes are to what to do if you're feeling down, which I think is a fantastic resource, and you made that publicly available on Twitter.[6]

[Ed] I'm really touched you brought that up. What I will say, just in the spirit of… Well firstly, thank you very much, but also in the spirit of pointing out that these are increasingly normal behaviours, I'll point out that that document, which we have found very helpful in welcoming people to the lab and and making it clear how we work together as a group and what they can expect of us and what we will expect of them, that was based on other similar documents and there are other very good examples out there. But thank you Sara for mentioning that.

Outro

Outro music starts.

[Tom] Massive thank you to Dr. Ed Hutchinson and Dr. Sara Clohisey. We had a really lovely chat and they're both just wonderful people. You can find them both on Twitter, and as usual we'll put all the links in the show notes.

[Helena] 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 more about the science being done by our very own staff and students here at the University.

[Tom] 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 and the latest issue of the magazine eusci.org.uk.

[Helena] Yes, check out the Sustainability issue. It's very good.

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[6] https://github.com/EdHutchFlu/HutchinsonLabManual

This episode was edited by me, Helena Cornu, and hosted by my partner in crime, Tom Edwick. We'd also like to welcome Alix Bailie, our new podcast manager, to the team.

The podcast logo was designed by EUSci chief editor, Apple Chew, and the awesome podcast episode art was designed by Heather Jones, our social media and marketing genius.

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.

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

Outro music ends.

Post-outro antics

[Tom] And one final question I have for you, Sara, is how many cats do you have?

[Sara] I have two cats, and I do fear that you were able to hear one of them, because my partner had to come in and kind of crawled along the floor to grab one who was trying to get up the back of my chair. But they are very, very, very spoiled and naughty, and they're a bit ridiculous to be honest. [laughs]

[Tom clears his throat]

[Ed] I have a very creaky chair, but I'll try to sit very silently.

[Tom] [laughs] Yeah, me too actually. When I was recording the first episode of the podcast, I was sitting down on this chair, and I sent it to my editor and she was like: "What's that weird clicking noise in the background?", and then we figured out it was this very old creaky chair.

[Ed] I'll just pretend I'm phoning in from a rickety sailing ship.

[Tom laughs]

[Helena] And after a few rounds of that, I managed to get Tom recording in a closet under a duvet and I no longer have to deal with that infernal chair!