Exploiting Our Genes to Fight Disease (Science During a Pandemic #1), with Max Fourman
Not Another Science Podcast
July 1st, 2020

General Introduction

Intro music

[Tom Edwick] 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 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

Today's episode is part 1 of a 4 part miniseries on coronavirus, in which we're exploring what it's like to do science during a pandemic.

The covid-19 pandemic has turned the world on its head. What started out as a small outbreak of cases of pneumonia in China towards the end of 2019 has exploded into a global disease crisis that has seen 54% of the world's population - that's 4.2 billion people - go into lockdown. Researchers and students from The University of Edinburgh rallied to respond to the crisis, using their skills and their knowledge to take the fight to coronavirus. In this miniseries, we're going to highlight this incredible work, explore what it is like doing

science during a pandemic, and discuss the knock-on effects this could have on science going forwards.

As we're in lockdown, all the interviews were conducted over Zoom, so excuse any funky audio…

Does anyone else wish they'd bought shares in Zoom by the way?

Intro music fades out

Main

Okay, so imagine for a moment: you've got two people, and they've both tested positive for SARS-CoV2, the virus responsible for COVID-19. Both are young, healthy, with no underlying conditions. One of them gets extremely mild symptoms and doesn't even realise they've got the virus, but the other person becomes critically ill and has to be rushed to intensive care. This is more than just a hypothetical situation - young, healthy individuals can have drastically different responses to the virus, and some have even died from it[1]. So it begs the question, why are some people more severely affected by disease than others?

> **[Max Fourman]** So, my name's Max Fourman. I'm a fourth year medical student at the University of Edinburgh.

To find out why some people are more severely affected by disease than others, I spoke to Max. He's part of the Baillie lab, which is based in the Roslin Institute here at the University of Edinburgh.

> **[Max]** And I'm connected to Dr Baillie's lab because I did my research project for my third year supervised by Kenny.

The lab is run by Dr Kenneth Baillie[2], a consultant in the intensive care unit at the Royal Infirmary in Edinburgh, and a specialist in the genetics of infectious diseases and critical

[1] https://www.telegraph.co.uk/health-fitness/body/why-young-healthy-people-dying-coronavirus/
[2] https://baillielab.net/

illness. The lab focuses on understanding the genetic factors that drive different responses to infections, and these factors can be really important[3]. In a 2013 study from the US National Institute of Allergy and Infectious Diseases[4] they found that a single DNA mutation was responsible for predisposing patients to chronic infection from the Epstein-Barr virus, which is responsible for a disease called mononucleosis, or as it's more commonly known, 'mono'[5].

But how do you know which genes are making some people more sick than others? Well, the lab uses a technique called genomics - which is the sequencing, mapping, and study of people's genomes - to look for the genes or that are important in different responses to infection.

> **[Max]** We all have a genome that is 3.2 billion base pairs long, and each of those points can vary with one of four nucleotides. And between me and you, there'll be millions of differences in our genome. And now we can read out the genome and we can see what the differences are between people. And if you do that over enough people, and you have a group who let's say have a disease and don't have a disease, or if you have a group, all of whom have a disease, and some of them get sicker than others, you can make comparisons and you can try and look for parts of the genome that seem more important for determining those differences.

So, by looking through the genome we can look for those areas that are important. But then, we also want to be able to take this knowledge and translate it into other fields, like medicine, or clinical applications. The wider field that the lab works in is called translational genomics, and they do just that.

> **[Max]** The idea of translational genomics is that, if we can understand some of the differences in people's genetics or their genomics, about why some people get more sick than others, then that might point us in the

[3] https://genomicc.org/
[4]https://science.sciencemag.org/content/341/6142/186.long
[5] https://www.cdc.gov/epstein-barr/about-ebv.html

> right directions of where we can develop more effective therapies. And I suppose that the translational part is that the lab includes everything from people whose expertise is coding and in the computer science side of it, through to traditional wet lab techniques, and through to in vivo animal models. And there's a drive now towards live animal models, so taking what's learnt from the computational simulations and then the cell work, and then working on animals, so in particular genetically modified pigs. 'Cause one of the limitations of a lot of the animal work that then tries to get moved into humans is that it gets done on small animals like mice that are not really representative for how humans behave when they get critically ill.

The big advantage of the translational genomics approach is that it makes it easier to look for drugs and therapies that could work when treating patients. Often severe illness and death from infections are not a direct result of the invading pathogen, but from an overreaction by our own immune system. Basically, our immune systems are trying to kill us.

The human immune system is the result of an ongoing evolutionary arms race with bacteria, fungi, and viruses[6]. It has to be constantly adapting and updating to respond to new threats, and as a consequence is just ludicrously complex. With translational genomics, the hope is that we can sidestep this complexity and hone in on the exact part of the immune system to target with drugs. And work like this is really important, as there are still conditions that result from infections that we don' t fully understand. Max told me about sepsis, which is a common cause of death in critically ill infected patients. Unfortunately, the traditional methods of drug discovery haven't brought us any closer to a potential treatment.

> **[Max]** And sepsis is a condition where the body's immune response becomes dysregulated and starts

6 https://newseu.cgtn.com/news/2020-06-14/RAZOR-Can-genes-tell-us-who-is-susceptible-to-COVID-19--RjOUZ4F0Na/index.html

> damaging the body itself. You get this in response to different types of infections. And it's very apparent that some people get very very sick with sepsis and other don't, and for the last 40 or 50 years the research method has been to try lots and lots of individual compounds that, for whatever reason have some biological plausibility that they might cause a difference, and none of those have generated therapies that are used at the moment. And so, I suppose the idea is that, maybe rather than just keeping going with the way that we have been which hasn't been working, then try a new approach which, like you say, narrows the search space and allows a more targeted way of determining what might be a good molecule to try.

So with their work on translational genomics, infectious disease, and critical illness, Dr Baillie's lab was ideally placed to respond to the coronavirus outbreak.

In 2016, Dr Baillie launched GenOMICC[7] - which stands for the Genetics Of Mortality In Critical Care. It is a collaborative, open-source research study that aims to understand the genetic factors that affect critical illness outcomes. In particular, the question we posed at the start: why do some people get more sick than others?

> **[Max]** GenOMICC was a study that's been set up to try and gather the genomes of patients who get critically ill, and a particular subset of patients. So young patients, who are otherwise well and yet still end up in critical care, critically unwell, and the idea being that there must be something different about the genome in those patients which causes them to become so unwell.

The study was set up in such a way that it could react quickly to investigate emerging infectious diseases. So, when COVID-19 hit, focus shifted almost immediately.

[7] https://www.theedinburghreporter.co.uk/2020/05/covid-19-is-the-answer-in-our-genes/

> **[Max]** GenOMICC was also set up with a kind of clause for emerging infections — so that's new infections that we don't know anything about — and so it was very kind of dynamic and quick to be able to become a way of studying the genomics of the host response to Covid, and that's exactly what happened. And the aim is to get a genome for every sick patient for Covid in the country, basically, who end up in a critical care bed. Obviously, subject to them agreeing to be in the study or their loved ones agreeing to have them in the study.

The first cases were recruited in March, and there has been a huge increase in the number of sites and beds involved since the project was given priority status by the National Institute for Health Research.

> **[Max]** GenOMICC has been massively scaled up in the last kind of month or two, and a lot of that has been more logistical challenges, which aren't necessarily the kind of super sexy side of science. One good example, I've been helping, is building the sample boxes. So each sample gets posted from a critical care unit, in a little biohazard box, and those boxes arrive flat-packed, and we have to fold them. So a whole team of people who'd otherwise be busy in the lab — so the lab has a few PhD's a postdocs, and a couple of scientists who are employed full time — and we've all been kind of taking shifts building boxes and posting boxes out to ICUs, and then there's also been a huge logistical challenge in terms of just setting up sites. Obviously there's a whole ethical process it has to go through, and approvals and local procedures and things. And this was all run by one woman called Fiona who's been doing amazingly, and we've now got a few people, me included, who are helping her man the inbox and respond to queries [...]. So quite a lot of it has just been helping the logistical side as much, if anything.

Thanks to the incredibly hard work of Max and the other lab members, the project has steadily recruited more and more

patients. In the UK, as of recording just over 3000 patients have been recruited, across 205 intensive care units.

> **[Max]** I think the samples are starting to come back now, so you can keep up to date, if you're interested, at the GenOMICC Twitter feed. But I've seen recently the sample get posted back to a lab at the Western General Hospital, in Edinburgh, and they're starting to do the genetic analysis of those, and once the data becomes available then people will start to analyse the data, and see if there's anything there.

Ultimately, the project is aiming to get 100,000 samples, and this may sound like a lot, but the key in genomic studies like this is just volume. As Max mentioned before, the human genome is around 3 billion base pairs long, and between any two people there are millions of differences. Looking for the ones that are important is like looking for a needle in the proverbial genomic haystack. Big sample sizes give us more confidence that a gene we've found plays an important role in making someone more sick than someone else.

> **[Max]** The long term aim of any of this kind of research really is to find out, you know, what are the differences, and how can we make the people who, you know — let's say there's a hundred people who get critically ill, who get Covid let's say, and, I'm sure you're aware that, even in our age group, there is a small proportion who still get very unwell. And why do those people get so unwell, with these diseases, and is there any way that we can alter their biology so that it looks more like the people who fight it off? And that might be that their immune system gets too excited in the face of the disease, and it needs to be dampened down, or it might be that it's not responding aggressively enough, and it needs to be kicked into gear, and those are the kind of answers that perhaps this kind of research can find.

In the quest for these answers, GenOMICC is part of a host of other studies that together aim to further our understanding of COVID, determine which treatment options work best, and for

who they work best. The studies have all been designed to be deployed quickly and in a coordinated manner in response to a disease outbreak. This is thanks to a group called ISARIC, which stands for the International Severe Acute Respiratory and emerging Infection Consortium. They have come up with a standardised method for any clinic to collect samples from patients, and this allows us to rapidly study and understand emerging infectious diseases as they happen.

Within ISARIC is a group called 4C, which just stands for the Coronavirus Clinical Characterisation Consortium. They're a UK based group of doctors and scientists that are focussing on coronavirus in particular.

> **[Max]** This is a worldwide consortium that's been set up to study emerging infections and respiratory pathogens. And basically the idea is to have a protocol that can be activated really quickly. So, setting up and designing these kinds of studies takes a long time, and a lot of organisation. And if there's a reasonable amount of similarity in what you're studying — so let's say you're studying emerging respiratory infections — you can already know the kind of things that you're gonna wanna know, and you can design the study in advance, and then when a new disease appears, the study can just very quickly be altered to fit that. So that's essentially what ISARIC 4C is.

Also, if there's anything we've learned today, it's that scientists *love* a catchy acronym. Do you think we could get #NASP trending for this podcast? No, me neither…

Anyway, another great thing about these studies is that because the data is collected in the same way, it can be pooled into one large source.

> **[Max]** I think the other thing that's really great about it is that, obviously something like this comes along and everyone wants to understand it and everyone starts to study it, but actually, if everyone collects data in slightly different ways it doesn't really

work, because you can't compare the datasets. Whereas if you have one standard — the clinical characterisation protocol — one set of data which is agreed by a set of experts, who say these are the kind of things that we need to know about respiratory pathogens and what happens to patients when they get them. And actually that's another thing I've been helping with is, there's a number of medical students who are just doing the data entry. And it's very basic kind of work, taking information from the patient record system (the NHS patient record system), and entering it into the online database for ISARIC. But, by doing that you see the incredible amount of detail that goes in, and it's everything from when did they first start having symptoms, which of these huge list of symptoms did the patient have before they got it, how did they progress, what kind of treatments did they [receive] in hospital, and how were they afterwards, how did they recover from the illness and what happened afterwards.

[Tom] Yeah. And I guess it's really important to have all this information just open-access, essentially, to everyone so whoever needs access to that can see it.

[Max] Yeah, and that is a big part of both ISARIC and GenOMICC, is that collaborators are welcome and that data should be shared openly, and I think that's really important, and my understanding is that that's a big part of how the lab works and how [...] which I think is really good.

It's clear that collaboration has been a huge part of the response to the crisis, and Max told me that labs across the country had been diverting their resources to COVID.

[Max] Each lab is kind of contributing in the way that they best can, and you know, Kenny's been studying critical illness and emerging infections for a while now, so you know, the lab was kind of made for this in a way, and a lot of other labs won't be so focused on this exact corner of science, but there's some great

examples of labs still finding really creative ways to help and doing things. And that might be anything from the new set up at the Western where the Institute of Genetic and Molecular Medicine (I think — that's the IGMM — I think that's what it stands for), but they've set up a coronavirus testing thing because they've already got labs with the equipment to do PCR and to do the kind of tests which are needed. So you know, that's one great example. Or another one, I've heard that in the Informatics building, people are building face visors and masks for NHS staff. So I think there's amazing ways that people can help.

Speaking of masks and visors, make sure you come back for episode 2 to hear all about a business start-up led by students here at the University, that has been making personal protective equipment for the NHS.

But as Max says, there's so many ways you can help, and you don't need a fully stocked lab or a 3D printer to contribute.

[Max] Personally, I'm not doing anything particularly advanced at the moment. Most of the way I'm helping is just doing quite simple either logistics, or helping posting things, or helping organise things. And I have a little bit of knowledge about how the lab works because I've been there for a year, but I'm not doing anything particularly special so I think I would put the message out there that if, assuming your podcast has listeners who are studying science at the uni and things like that, you know if you wanna help, for sure there's ways to help. And they're not all gonna be super cool things but they will be useful. And there's a lot of useful things you can do if you're kinda keen and you just want to get involved and help.

Outro

Outro music starts

[Tom] Thank you so much for listening to our first ever episode, we really hope you enjoyed it. 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.

Massive thanks to Max Fourman for his time and his knowledge, and giving us an insight to the important work done by Dr Baillie and his lab. You can stay updated with progress of the GenOMICC study and learn more about the other studies at their website, genomicc.org.

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[8], and the outro music is an edited version of Funk Game Loop[9], both by Kevin Macleod, links in the show notes.

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

Outro music ends.

[Tom] *deep sigh* Keep it science? Really?
[Helena Cornu] Yeah? Is science an adjective?
[Tom] I have no idea. All the cool sign offs are taken already, you know? Neil Degrasse Tyson's - "Keep looking up" - sounds amazing, you know? It's punchy, it's short, and like he's an astrophysicist so it just works.
[Helena] Mmhmmm…

[8]https://incompetech.filmmusic.io/song/3788-funkorama
License: http://creativecommons.org/licenses/by/4.0/
[9]https://incompetech.filmmusic.io/song/3787-funk-game-loop
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[Tom] But y'know here we're trying to capture the whole of science, and I think that's kinda hard.
[Helena] Okay, but "keep it science?"
[Tom] Well, I think our listeners hopefully can cut us some slack. It's only episode one. The only way is up.

> **[Neil Degrasse Tyson]** And as always I bid you, to keep looking up.

Transcribed by Helena Cornu and Tom Edwick. Comments or enquiries about this or other transcripts can be addressed to eusci.podcast@gmail.com