Addressing Medical Challenges – the Research Process

Voiceover: [00:00:02] This podcast is brought to you by the University of Aberdeen.

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[00:00:47] European Researchers Night is a Europe wide public festival, which brings researchers closer to the public. All events run as part of Explorathon 2021 can be found on the website at www.explorathon.co.uk and the programme is funded by the European Union's Horizon 2020 Research and Innovation Programme under grant agreement 101036101. After listening today, please let us know any comments or feedback by tagging us on Twitter using the hashtag Explorathon21.

[00:01:29] Preclinical and clinical trials and an essential part of the process in developing new drugs and treatments for diseases and conditions. This panel session discusses the stages that researchers must follow in order to bring new drugs and treatments to market. I'm joined by Dr. Sadaf Ashraf, a research fellow in the Arthritis and Regenerative Medicine Laboratory. Dr. Gael Morrow is an honorary research fellow in haematology and cardiovascular medicine, Dr. Elizabeth Hay, a research fellow and the Arthritis and Regenerative Medicine Laboratory.

[00:02:09] So first of all, Sadaf, can you give me a brief introduction to your research interests?

Sadaf Ashraf: [00:02:16] Yeah so the focus of my research is on enhancing our understanding of arthritis, pain and improving its treatment. Joint pain is associated with arthritis, is a substantial unmet medical need worldwide and the leading cause of disability in ageing population. Yet how this pain occurs remains poorly understood. Interestingly, some individuals still experience joint pain, even after taking medications and following joint replacement surgery, highlighting the need to better understand how arthritis associated joint damage and pain occurs so that new treatments can be made available, especially for those in whom current ones are failing. And that's what Research in in at the moment.

[00:03:00] Gael, can you tell me about your research interests?

Gael Morrow: I'm a postdoc researcher in haematology, which is the study of blood. My research focuses on the biochemical processes involved and breaking down a blood clot and how this differs in patients with bleeding disorders such as haemophilia or those with a major traumatic injury. I mainly study how a transfusion of different blood products stops the bleeding after an injury. And this is important because bleeding caused by an injury is the leading cause of death in persons under forty four and it is preventable.

And Elizabeth, can you give us an overview of your work?

Elizabeth Hay: [00:03:44] I'm a research fellow in the Arthritis and Regenerative Medicine Lab. One form of arthritis that we study is osteoarthritis, where cartilage in the joint breaks down, causing pain and stiffness in the affected joints. Osteoarthritis has a high prevalence in the UK affecting around nine million people. But what causes it is not well understood. My

research focuses on the genomic regulation of stem cells in our joint tissue. These are the cells which can give rise to new joint tissue and gaining an understanding of the way to better understand what causes osteoarthritis. And this may help in developing new therapies to treat osteoarthritis and maintain healthy joints.

Voiceover: [00:04:28] So obviously a core part of your work is trying to develop new treatments and therapies to treat the conditions that you're investigating. Could you talk through the process you have to follow in order to get these treatments from discovery to actual use? Gael

Gael Morrow: [00:04:45]
So first of all, we have to test the treatment or therapy and what we call an in-vitro system. So invitro is Latin for a glass and essentially means we can carry it out in a test tube. So in my field, we tend to take blood samples from healthy volunteers and process it to clean the blood plasma, a yellow liquid which makes up 50 percent of a person's blood volume. The important point here is it's a very simplified and purified system and allows us to study the treatment in a very basic experiment. We can then move on to incorporating blood cells and then things like blood flow. So our experiment will be performed under conditions which mimic the blood flow of an artery or a vein.

[00:05:34] We can also use samples taken from a specific group of patients to help understand our research question. If the clinical trial is successful, then the drug can be licenced for use in the area that the trial was testing. If we want to use the drug and another area, a definite trial must take place.

Voiceover: [00:05:52] Elizabeth, maybe you can tell us a bit more. so in general, initially,

Elizabeth Hay: [00:05:55] So in general, initially research needs to be done in the lab to understand the causes of a disease on its progression. So this may lead to the identification of a biological target. So, for example, this could be a protein involved in the pathology of a disease.

[00:06:21] For example, animal models can be designed where a gene is removed or knocked out, um, as we would say, uh, to help researchers identify the role of that gene. So then drugs can be designed against that biological target and these will be tested in in many different tests in the lab, for example, to determine whether it binds to the target and also at this stage, unwanted effects would be monitored. So, for example, whether the drug that's being tested has any other targets which could cause safety issues, could be identified at early stages.

[00:07:05] And the dosage of the drug, how it's absorbed, isn't excreted, would be tested and potential drug candidates would then proceed to preclinical testing. This would determine the toxicity or the potential serious adverse effects of the drug before testing in humans. As Gail said, successful candidate drugs would then proceed to clinical trials where they would be tested in humans to assess whether they work and whether they are safe.

Voiceover: [00:07:36] And Sadaf, you obviously work in a similar field to Elizabeth. What do you see as the key stages between the initial research to get into being a licenced treatment?

Sadaf Ashraf [00:07:48] Exactly like what Gael and Elizabeth were saying before, with any medical condition. I think identifying first the target molecule that you're interested in and which will be most beneficial in clinics is the key point. Once you've narrowed down that particular

target model, then you have to go through stages of, like Gael was saying, you first you think beta models, and then you go into a larger model, then into clinical trials.

[00:08:17] For example, I'm trying to understand the role of pain mediators in arthritis and pain mediators are signals released by cells in the joint in response to injury and then work by binding to specialised proteins on the surface of other cells, much like a lock and key. So in arthritis, the levels of these pain mediators increase, changing the behaviour of the surrounding cells, thereby enhancing pain and joint damage. But we still don't know how these pain mediators work, and there are many pain mediators. And like Gael said a lot of times at these targets that work really well in preclinical models, and when you take them into the clinical trials, they don't have the optimum effect that you see.

[00:09:03] And one of the key things that need to be done is trying these target molecules in different models, different disease models. So not just one disease model, but those models that better mimic the human condition. And also, like Elizabeth mentioned before, the whole process of taking a drug from laboratory research into clinical trials and for human use takes years. You can take up to 15 to 20 years, for example, even with the clinical trials, you need like a phase one, phase two and a phase three clinical trials. So you increase the number of volunteers in each step. And even the preclinical models or laboratory based testing can take around 10 years to do.

[00:09:57] The whole process is extremely long in that sense.

Voiceover: [00:10:02] Yes. So you've touched on it's been a long process. I would imagine it's also administratively challenging process. Elizabeth, can you tell us about what you need to do in terms of permissions in order to conduct the clinical trials that you do?

Elizabeth Hay: [00:10:22] Yeah, so the process of medical research and drug discovery is highly regulated. The ethics of many research projects need to be reviewed and approved prior to research taking place, for example, in studies requiring human volunteers, um, and licences, which would be issued by UK Home Office, are required to undertake animal research. And there are strict training requirements in order to do animal research as well.

[00:10:52] Researchers are also constantly considering the three Rs for animal research so that replacement reduction and refinement. So they so they consider using methods to replace animals in research and to minimise the numbers of animals used and they can do this by designing robust, reproducible experiments and analysing the data appropriately. So animal welfare is always at the forefront of research and ultimately a high standard of animal welfare leads to high quality research.

Sadaf Ashraf [00:11:28] Definitely, we need to ensure that the right paperwork and ethics are in place to do the work. For example, for the cell based assay's, especially if you look at these cells, like Gael said from human donors or from the tissues or blood, we need to ensure that these procedures are regulated and consent from the donors is obtained as per the Human Tissue Act to ensure that all the ethics and legislation that are set up by the government are being followed and also the individuals collecting those human tissues. They need to be properly trained and qualified as well as the institution. And the research department also needs to have the appropriate project licence in place.

Voiceover: [00:12:09] Gael, do you have anything to add?

Gael Morrow: Yeah. So my research focuses more on samples from humans.

[00:12:15] So it's also there's a lot of intensive ethical applications for human studies as well. And even once that is approved, there's a lot of work when you're recruiting the volunteers and making sure you're providing them with the right information and enough information about the study. So, you know, we are perhaps a week before you want to take a blood sample from a healthy volunteer. You have to send through an information sheet on the study and give them time to read it. And then also time to ask the researcher any questions and decide whether they want to take part or not.

[00:12:53] They then have to provide written and verbal consent. Even more difficult is taking samples from patients so people who are admitted to hospital may always not always be conscious. Or if they are conscious, they might be very sick and not able to provide written or verbal consent to take part in a research study or clinical trial. So there's also a lot of work goes into that.

[00:13:20] A lot of the time we're able to take a research sample or sample for part of a trial while we're taking routine blood samples. And then when the patient then recovers and feels better, they can decide whether they want to take part in the study. If they don't want to take part, the sample is destroyed and we're not allowed to use it. But if we do, we can then process it in the lab for experiments.

[00:13:45] So, yes, that's something that's always, always very difficult and obviously very important to obtain the samples for research and for the clinical trials. But it's it's not easy by any means.

Sadaf Ashraf: [00:14:00] Just to add to that. There's one thing that's really important and that takes a long time as well is getting approval from the FDA. So the Food and Drug Administration. So once all of these drug targets have been identified, we need to sort of get other scientists involved, like the chemist, for example, who can make those drugs and then they need to be approved by the FDA before they can be used in humans.

[00:14:26] So all of these considerations need to be sort of taken on board before a drug can go from lab based research into clinics and stuff.

Voiceover: And Sadaf, is lab based research necessary prior to treatments being taken into clinical trials, what would be the implications if you didn't conduct preclinical trials?

Sadaf Ashraf: [00:14:49] No, definitely. I think the preclinical work is the initial step in taking a drug target into humans, because all of these preclinical research are where we identify the right drug target. You able to understand the exact mechanism of action if there are any side effects related to that particular drug target. And we need to test these drugs in various models and those models that are most closer to humans and they mimic the human condition the best possible way.

[00:15:28] And I think that's where we need to use more than one model. So we need to use models which are cell based assays as well as using maybe 3D assays where you are growing an artificial organ outside of the human body. And now there are a lot of initiatives that Gael works on as well as stem cells that Liz works on. Is that you are getting the human cells and then using them to understand the mechanisms of action.

[00:15:58] So all of these need to be regulated and satisfied before the FDA can give you approval for that particular drug to be used in humans. So, yeah, it's extremely important, but there are challenges involved with it.

Voiceover: [00:16:15] And so moving on, how can we increase the understanding and acceptance of your concepts into delivery and research? Why is it that drugs don't work? Some drugs that work really well in preclinical models don't do that well when they go into clinical trials, Elizabeth?

Elizabeth Hay: [00:16:33] So I think collaboration between academia and industry is often required for getting a concept or a treatment to the clinic um, pharmaceutical companies, the resources to do more high throughput research and get treatments to clinic.

[00:16:53] So a recent example of this would be the Oxford AstraZeneca collaboration for the covid-19 vaccine. In terms of why drugs that work well in preclinical models don't do so well in clinical trials, that often maybe a lack of effectiveness of the drug in humans and problems with safety profiles of the treatments in clinical trials. And these would not have been predicted from the preclinical studies. So often this is likely to be because animal models may not be fully representative of a human disease or how the human body works.

Voiceover: [00:17:39] And Gael, do you have any thoughts? Yeah. I agree with what Liz was saying about the collaboration between industry and academia, it's important, I think as well, the collaboration between clinicians and scientists is also important in all medical fields. There are many examples where clinicians and scientists work completely independently, but in my experience and opinion, it works better to have a team mixed for medical clinicians and scientists because it brings about stronger data sets and you work together to bring about change for patients and improve the treatments.

[00:18:21] And I guess just as Liz said, that in-vitro models can't always fully replicate the physiological conditions in the human body. So I guess that's why quite often they fail to work in humans after being so successful.

Voiceover: [00:18:38] And Safaf?

Sadaf Ashraf: You know, I think that's right. And one way to maybe avoid that or to minimise the sort of lack of translational validity that we have is by looking at the phase of the disease as well, because sometimes treatments that work better in early disease, if you detect the disease early on, or they might work better in the later sort of therapeutic window. So having the right animal models where we are testing the drugs in the right time frame, I think is also important. And like Gael and Liz mentioned is that collaborative effort within academia as well and within different diseases like, for example, inflammation is like a core component of arthritis, but it is also a part of cardiovascular disease and other diseases as well.

[00:19:31] So like I said before, I think targeting drugs and testing them in different disease models is another way of reducing this sort of lack of validity between preclinical and clinical research.

Voiceover: [00:19:52] And so the research lab environment is changing in response to new technologies. How are the new technologies, such as artificial intelligence, impacting on clinical preclinical trials, Gael?

Gael Morrow: [00:20:01] Yet so artificial intelligence to identify an algorithm to stratify patients has been a huge part, a huge part of research in any field. So in my field, for example, researchers at my institute recently developed an algorithm to identify patients who attended the GP who may be positive for a deep vein thrombosis or blood clot in their leg or dvt and require an ultrasound that has been very accurate at predicting a positive blood clot so greater than 90 percent.

[00:20:37] So that means that the clinics are now more manageable and more time with the patients who need it. And there's also studies going on where patients who are likely to bleed are being protected by their routine blood tests and that minimises unnecessary blood transfusions. So there's a lot of preclinical studies using artificial intelligence to support and provide evidence for larger clinical trials.

Voiceover: [00:21:08] And Sadaf, what about in your area of research?

Sadaf Ashraf: [00:21:10] So I think new technologies such as artificial intelligence are enabling us to screen for subtle changes within the tissues, which we may have otherwise overlooked with the conventional tools that we routinely use in the laboratory that also enable us to maximise data output from our studies. As well, for example, a study published last year only by a team of American scientists have shown that machine learning or artificial intelligence was instrumental in detecting early signs of. So like Gael said using machine learning algorithms, the team were able to train a system to automatically differentiate between people who may progressed to arthritis and those who may not.

[00:22:04] So, like I mentioned before, treating arthritis early on and identifying that window of opportunity is critical, and through machine learning and artificial intelligence, we can achieve that goal. I have recently teamed up with NENO Spring and University of New York, as well as the University of Nottingham to use the digital spatial profiling, which maps changes in the whole tissue and is far superior than the conventional methods that we routinely use in the laboratory.

[00:22:35] So using this technique to better screen joint tissues for subtle changes that we may otherwise overlook and that can help identify patients and we can put them into subgroups for personalised medicine, which is going to be far superior than the current treatment that we have available.

Voiceover: [00:22:55] And Elizabeth, if you've got anything to add,

Elizabeth Hay: [00:22:57] So another technology which has the potential to impact clinical research is the reprogramming of stem cells. So the reprogrammed reprogramming of stem cells into any cell type has the potential to more accurately predict the effectiveness of a treatment in the earlier stages of research. So researchers could therefore have a specific type of human cells in a dish in the lab without the need for primary cells.

[00:23:26] So those would be cells that would be donated by patients and would therefore be in limited supply.

Voiceover: [00:23:32] So we're now running out of time for today's session. But is there anything you want to sum up or highlight part of a closing remark, Gael?

Gael Morrow: [00:23:41] Yeah. So I think we've mainly talked about the difficulties of getting treatments through clinical trials. But I think it's important to highlight, though, there's many success stories within all fields of medical research. And so specifically in haematology recently, gene therapy has been used to treat haemophilia patients. The gene therapy trials are still ongoing, but many patients are essentially cured. And the gene therapy is a perfect example of medicine that started in a test tube and the most basic scientific model and has translated into humans successfully. And this is how personalised medicine will progress in the future.

Voiceover: [00:24:21] And Elizabeth?

Elizabeth Morrow: Well, currently, patients with osteoarthritis receive treatment for the pain.

[00:24:28] And in advanced osteoarthritis, they may receive joint replacement, but there aren't any treatments that slow the progression of the disease at present. So I think we need to better understand the causes of the disease in order to develop treatments for it. And that's where research into stem cells in the joint comes in. So if we can understand how stem cells work in repairing damaged tissue in the joint, we can potentially identify target or drug targets to be able to stimulate this joint repair.

Voiceover: [00:25:10] Sadaf, Elizabeth Gael, thank you for joining me.

[00:25:14] Thank you. Thank you.

Voiceover: [00:25:21] We hope you find today's podcast interesting, but for now, thanks for joining us and keep an eye out for the other explorers on podcasts being launched throughout September. As I said at the beginning, we'd love to get your comments and feedback on today's podcast, so please use the hashtag Explorathon21 to tag us on Social Media.

[00:25:39] If you're interested in finding out more about the other events taking place as part of Explorathon 2021 then you can visit the website at www.explorathon.co.uk. Bye for now.

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