Groundbreaking arthritis research: What is Plan B?

Transcript

PG: Hello, everyone. My name's Pete Gowler from the research team at Versus Arthritis. I'm really delighted today to be joined by three really excellent scientists pushing the boundaries in arthritis research. And so it would be great if you could just introduce yourselves for the listeners.

CM: I'm Professor Claudia Mauri. I am an immunologist as a background with a long-standing experience in rheumatoid arthritis and lupus research.

DI: I'm David Isenberg. I'm now the Emeritus Professor of Rheumatology here at University College London. I was originally the Arthritis Research UK, became Versus Arthritis, Professor of Rheumatology here for about 26 years, and I have both clinical and basic research interests in lupus and related diseases.

ER: Hello, I'm Dr. Elizabeth Rosser. I'm an Associate Professor in UCL's Division of Medicine. Claudia was actually my PhD supervisor, but I started my group about two years ago. I'm interested about how B cells may contribute to disease in young people and children who develop arthritis.

PG: Excellent, thank you very much and welcome to all of you. So we're here today to talk about what we're calling ‘Plan B’ at Versus Arthritis. And this is the role of B cells in arthritis and how my three guests are breaking new ground with their research. Their work has shed new light on inflammatory arthritis and we really think it's going to bring us closer to new treatments and new management options for people living with arthritis in the UK. So I think where we should really start is, what is a B cell? Lizzy, could you maybe start us off there?

ER: So a B-cell is a part of the immune system and they're most well known for producing antibodies, which in most situations help us clear infections, so viruses and bacteria, but in people with arthritis these antibodies that are made by B-cells can start recognising parts of the body instead, which contributes to inflammation.

PG: Ah, excellent. And how long have we been interested in B cells in the research field?

CM: It's a long, long time.

DI: But in the mid 1950s.

PG: Oh, wow. Excellent, so it's been a long journey to get to where we are today. And I wonder if we could sort of go into a bit more detail about your research projects and research interests at the moment. Claudia, do you maybe want to start off?

CM: Yeah, so we started many years ago when I was still at the Kennedy Institute of Rheumatology and as many research discoveries come about, I encountered B cells, these white cells in the body. In addition to being considered pathogenic, there was a unique subset producing anti-inflammatory mediators which are really important to prevent our body to generate excessive inflammation. And at that point, just a little bit of a life journey, I contacted David Isenberg and asked him whether I could move from Imperial to UCL, as I know they had a great experience with B cells and they were pioneering the B cell depletion therapy, which I'm sure David will touch upon in a minute. And together with David and with Lizzy really, we all worked together for many, many years.

We pioneered this new field where in addition of B cells being pathogenic, we identified a subset of B cells which are protective. And in patients with lupus, for example, rheumatoid arthritis, these protective B cells are missing. And so all our life, I think, working life, we've been trying to understand why patients with autoimmunity, in particular in SLE [systemic lupus erythematosus] in our case, and rheumatoid arthritis, don't have these protective B cells compared to healthy individual. Any one of us that if you are healthy, in circulation, you will have roughly 5 to 10% of these cells which are constantly protecting against excessive inflammation. And this subset of white cells is missing in patients with RA and lupus, as well as many other autoimmune diseases.

PG: Oh wow, so we're saying they're sort of like the good guys and the bad guys in the B cell world.

CM: Yes, correct.

PG: And actually a lot of these people are missing the good guys that are protecting.

CM: I would correct. I don't like the bad guys and good guys simply because there isn't a bad and good guys in immunology. All cells are important but it's the concentration, the amount and their capacity to respond to what we call immune challenges. So you do need both and in the absence of one or the other there is a trouble in terms of disease.

Pete: So it's all about balance?

Claudia: Correct, it's all about balance.

PG: Excellent.

DI: So now to make some very important points about the question of balance, but I'd like to sort of move this towards the clinical arena if I may. Because there was a major idea in the 1980s, 1990s that rheumatoid arthritis in particular was largely a disease of T cells and inflammatory molecules called cytokines.

And it's important, I think, to mention some absent friends here. Two colleagues of mine in those days, Professor Jo Edwards and Jo [Geraldine] Cambridge, in the late 1990s came up with a rather heretical idea that B cells might be important in the development of rheumatoid arthritis. And I think they would have been burnt at the immunological stake by a number of people but this didn't happen fortunately! And the other big chance that they took was the discovery or the introduction of a drug in 1997, approved by the FDA in America, Federal Drug Administration, for the treatment of Non-Hodgkin's Lymphoma. This drug, or this monoclonal antibody, was called rituximab and what it had the capacity to do was in a sense to take out a number of these B cells. And Jo Edwards

and Jo Cambridge saw this as an opportunity, and they said to the world at large, “Look, if you look in the tissues of patients with rheumatoid arthritis, in particular inside their joints which are affected in rheumatoid arthritis, in nasty inflammation, you will find B cells - and they're not there for a holiday! They are there for a reason, and it's not a good reason. So if you can take these guys out maybe you see some financial benefit.”

So they went to the company who made rituximab – they have an office, large office about 30 miles north of London – and they said “Please, please, please could we have some of this drug to treat patients with rheumatoid arthritis?”. And the company said “Well we're a cancer company, we don't do this inflammatory arthritis, so that's not us”. And they had to be persuaded pretty, quite hard. But finally, the two Jos were given five doses of this rituximab drug to treat rheumatoid arthritis patients, and they showed some stunning results.

The patients’ swollen joints got less swollen, they got less tender, the markers of inflammation and the blood all improved. And so they went back to the company and they said “Look here are the data, this is quite interesting”. And they pointed out that in the UK there are maybe 500,000 rheumatoid arthritis patients in the United States over 2 million rheumatoid arthritis patients, so they were persuaded to give the two Jos another 20 doses and the first results of their work on 25 patients were presented at the American College of Rheumatology meetings in Philadelphia in the year 2000 – and it caused a sensation.

Because by then the TNF alpha drugs which we touched on were already reasonably well established these were good but it had also become clear by that point that about a third of patients given these drugs it wasn't going to work, so they had to develop other drugs – and lo, and behold there was this drug rituximab which clearly did work! And I remember coming out of the meeting when this was discussed because in order to get rid of the B cells they used a combination approach. They said we'll use rituximab but we use two other drugs steroids and cyclophosphamide because they are known to get rid of B cells in human beings. I remember listening to a good friend and colleagues, [thinking] “Using cyclophosphamide to treat rheumatoid arthritis? This is, this is unbelievable! I can't believe it!”, but actually they were right!

And eventually they did a big international trial which was published in one of the big American journals [in] 2004. NICE approved it in 2006, and rituximab has been widely used – I mean, literally hundreds of thousands of patients around the world have had rituximab to treat their rheumatoid arthritis.

So I, talking to Claudia and various other people at the time, said well if this approach is going to work in rheumatoid arthritis where the role of B cell is less clear-cut, this rather more sinister disease, systemic lupus, where B cells are definitely known to be produced - because the sort of B cells making bad antibodies which this has been talking about was very well established for a long time now – that really ought to work in lupus as well. So that's how we started. We were the first group to treat lupus patients, to 2000 – which

to my horror is now 25 years ago! Where did that go? So that's how it all kind of got started.

PG: Oh, excellent. It's really fascinating to hear that history there, and sort of like such an exciting time to be, I guess, a rheumatologist at that time in the early 2000s.

DI: Hugely, abslutely.

PG: Excellent. And Lizzy, do you want to tell us a bit about your research interests?

ER: So, we've been talking a lot about rheumatoid arthritis and SLE, which we're talking more about adults who get those kind of diseases. So we often think about arthritis as a disease of people who are older, but I investigate childhood onset form of arthritis, and we're interested now because a lot of these studies have been carried out in adults or people who are over 18, even the clinical trials that David's talking about. We want to see if we can see whether or not we can also look at how B cells are bad in young people and children who have arthritis. And this is very important because actually a lot more therapies are approved for use in the clinics for adults and older people with arthritis. So we need to do research on young people to understand whether or not we can use similar drugs or whether they're reacting the same way, also because we know the immune system changes as it develops. So that's what I'm really interested in now and obviously very passionate and making sure that children are also spoken about in the podcast and that we understand that arthritis can affect people over the whole age range.

PG: Yeah, I think it's really, really important for everyone to appreciate that arthritis can affect anyone and it's really that the work we're funding at Versus Arthritis does fund research.

DI: Could I say, I mean just to pick up on that, because it's a really important point, a lot of people think of arthritis [as a] disease of old people, but it's not true, it's found in children, it's found in adolescents, as well as young adults and older people, so it's very, very important to mention that.

CM: And if I can finish off about this, obviously developing autoimmune diseases at any age is never good news, but if you develop an autoimmune disease when you're very young, you have a long life ahead of different type of treatment and disability possible, possibly, so this is a serious issue that needs to be taken into consideration.

ER: Yeah, and what we're finding at the moment is that the B cells can look quite different in different forms of childhood arthritis. So I think we might be able to understand a little bit more what kind of treatments, B cell targeting treatments, we can apply to young people based on how their B cells are different in these kind of different subsets or different kinds of arthritis. Because we also talk about arthritis but then there's subsets of arthritis and when we get down into the whole clinical you know bits there they can present quite differently in different people.

PG: Excellent, thank you very much. I wonder if we can reflect a little bit on where we're really excited about maybe the next five years of research and sort of the ideas that might be really sort of like, you know, sparking interest for you for the next sort of five to 10 years around B cell research. So anything that's really sort of right at the forefront of research at the moment.

CM: Yeah, so if I can start, thanks to the contribution of, incredible generous contribution of Versus Arthritis, we have discovered now a few years ago that patients with rheumatoid arthritis, and now we have translated the results onto two patients with lupus, have a gut permeability, an increasing gut permeability. Now, it's really important to understand that we are talking about diseases, for example, in rheumatoid arthritis, where the major organs affected are the joints. And yet, I'm here, I'm telling you that it's highly likely that these patients also have a, what we call a very small inflammation in their intestine. And most importantly, the inflammation is located in the intestine, the brick, let's call it, that separates the actual intestine from the outside walls, where there is all the bacteria, et cetera, et cetera. And what we clearly showed, at least at the moment in experimental, by using experimental animal model, is that these bricks are slightly opened, and that allows the entry of, we don't know what really, get into the body and activate the immune system.

And so I think we're really, really excited, because hopefully, in a couple of years, we'll be in the position to start, perhaps even earlier, the first clinical trial, trying to reseal this brick in patients who have been diagnosed, actually, rheumatoid arthritis patients, that they have anti-CCP antibodies, rheumatoid factors antibodies, those antibodies that we know are markers for disease, but they don't have yet any inflammation in the joints. And the idea is that if we can close the brick, repair the brick of this building, the gut, we might be able either to prevent the disease altogether, development of the disease

altogether, or maybe, the disease is milder, and therefore, the patients will require less aggressive therapy.

PG: That's really, really exciting.

CM: Then there is the B-cell role, but I think it’s step-by-step.

PG: That's super exciting. Is there anything around the diet then that might be able to impact upon that?

ER: Oh, thank you so much for bringing up that question! So when I worked in Claudia's lab for my PhD, I was interested in how the bacteria, so the microbiota that lives on your body, so in the gut that Claudia's talking about, how that may affect the development of B cells. But now we're interested in the molecules that the bacteria breaks down from your diets and how that might condition B cells.

So, we know from speaking to young people and I know with adults that there's a real perception that diet impacts the immune system. And what I want to say for the podcast is – we're not sure what that looks like, but we're interested in understanding how these kind of, they're called metabolites, these products, may be able to condition B cell responses. And maybe in some patients you'll be able to use that to suppress disease, or maybe in other patients it will help with the response to therapy, but we're really, really early on in understanding what that looks like. So at the moment we're trying to, what's the right way of thinking about it? Like colour in the picture, like find the details, but we don't know what those are yet.

PG: Excellent, I think that's a really important point to get across is that research isn't just done in a day and it's, you know, we wish it was, don't we? But it really is about building that picture up and sort of adding evidence to what we know at the moment.

DI: So even Isaac Newton said that he made his discoveries by standing on the shoulders of giants! So I think that's right. You don't go to work one day and say, “oh, I'm going to discover a world-beating discovery today”. I wish that it worked that way!

ER: Yeah, so your question was about what's the next nice, you know, in the 5 years' time. I think that's, I'm not sure about what it will look like in 5 years' time, but maybe in 10 or 15. At the moment, the B cell targeting therapies we use target all B cells. So the B cells that Claudia was talking about and the antibody producing B cells that I'm talking about. And I think maybe in 10, 15 years time, we might be able to have more specific ways to target different kinds of B cells rather than everything together. But I think that will be definitely past 5 years' time.

DI: A huge step forward potentially has been taken by a group in Erlangen in Germany, run by a guy called Georg Schett. And what he's done is more sophisticated. And I'll try to keep it relatively simple. Essentially, you go into hospital, you put your arm out, they shove a big needle in it, and they take out a lot of blood. And from that blood, within that blood, they identify not the B cells, but these other cells that we mentioned called the T cells. And they are genetically modified to recognize a slightly different marker on B cells called CD19. And then you get those cells given back to you. And in the meantime, your body has been, as they say, prepared. You get some quite powerful drugs actually, so that you won't reject these cells. But the great thing about these T cells, which are known as CAR-T cells, is that they are able to get into the tissues to hunt down the B cells, which are producing the antibodies which Lizzie was telling us about right at the beginning. So, in other words, you get a more complete removal of the B cells.

And the results that they published are absolutely amazing, actually. Now it's only eight patients that they published in detail, and maybe the next eight patients won't be quite so successful. But what they showed was that after 12 weeks approximately, they were able to stop all the lupus drugs that these patients, they'd chosen, rather young patients. So with short histories of lupus, but very aggressive disease that had failed all sorts of other drugs, they were to stop all their lupus treatment. And the patient that had this, the longest now goes about four years, hasn't flared. The antibodies that we used to find in the blood of these patients have not reappeared. Now, to be fair, with more conventional treatments, you can see very long-lived remissions in some patients. So in that sense, it's not completely unique, but nevertheless, it's potentially very important. There's a small problem around price, but we'll come back to that a little later, I've no doubt.

ER: There's always a problem with price and science. Sorry.

PG: I think that is a question I wanted to ask which is what is the biggest challenge at the moment in terms of this area of research and I guess

DI: Oh, I can sum that for you very easily. The manager of Rolling Stones' tour around America once said very famously, "It's only rock and roll, but it's expensive". And the same is true of medical research. It's only medical research, but it's incredibly expensive. I mean, the sort of work which Lizzy and Claudia and I, and our colleagues, are doing doesn't come cheap. And yet the capacity to improve the quality of life of patients to save the lives of patients is undoubtedly there. So that's obviously what fires our imagination, but it doesn't come cheap. We need a lot of support to make this happen. And it is happening, but now we really want to sort of move forward as fast as we can with some of these newer ideas that my colleagues have been talking to you about.

PG: Excellent. This is such an exciting conversation and really, really just so inspiring to think about the future of this. Can you reflect on any really important moments you think in research and in science that have really changed the lives of people with arthritis?

DI: I divide my career very simply into pre-biologics and post-biologics. And although we're focusing on B cell depletions today, we've touched on TNF-Alpha blockade and there are other ways that have moved forward, especially in the context of rheumatoid arthritis. But I do a general rheumatoid or rheumatology clinic once a week. Before the year 2000, when the biologic drugs began to become much more available, I would expect to see, in the 12 to 15 patients I'd see every week, every week, three patients in a wheelchair because of their arthritis. Every single week. Subsequently, now, one in six months, maybe? I mean, it's chalk and cheese, it's sort of, and it's happened in front, it's happened in my professional lifetime and it's been truly wonderful to observe actually and very, very exciting.

And at the individual case level, I'll give you a simple example if I may. I saw a GP as a patient, and she comes to see me with hands that look very gnarled and twisted and all the rest of it. And she said to me, "Well, I think I've got rheumatoid arthritis". I said, "Absolutely". And I said, "Well, so why have you come to see me today?" She said, "I've come because I have read about these biologics, and I would like one". And I said, "Well, it's not quite that simple", but let's say within a few months, we were able to give her a biologic drug. And she came back to see us with her husband who seems to be an endocrinologist. And he said to me, "I knew she was better day two". I said, "How could you possibly say that?" He said, "Because I observed her going upstairs and I called up to her, I said, darling, do you realize how fast you've gone upstairs? And she said, oh yeah, it doesn't hurt anymore".

PG: Wow. That's so powerful, isn't it? It's so amazing to be able to do that.

DI: Took my breath away.

PG: And where do you think the next wow moment like that is going to come from?

DI: Well, I've really talked to you about a couple of approaches. The fully humanised antibodies replacing rituximab, which they will do eventually, I'm sure, and whether CAR-T cell therapy can be made cheaper, more off the shelf, because currently at the moment, it's about €350,000 per patient, according to Schett and his colleagues, and that's a lot of money. And I can't see NICE approving that very quickly or easily. So we need to find ways in which we can get the patients not having to stay in hospital for two weeks to have this therapy, which is what they do at the moment. And I won't get too technical about this, but there are some very good ideas about doing that. And some, again, very exciting stuff in which newer forms of these so-called biologic drugs are being produced which can interfere with the function of B cells and T cells at the same time. And they can be given as outpatient intravenous infusions, possibly subcutaneous injections. So I think we are on the threshold at an incredibly exciting time. Actually, the next decade will be really fantastic, I think. Excellent.

CM: In addition to this type of treatment, I think the excitement from Lizzie and I, and from my perspective, I'm always very, very happy to see that people that work with me continue to work and they share the equal excitement, is really the possibility to be able to change the diet. And again, we have to be very careful when we think about changing diets. And I know that lots of patients come to us and ask, what should I eat or what should I not eat? It's not that straightforward. Science is moving very fast in this field, but unfortunately it's also contaminated by a huge amount of non-scientific based evidence. And that when you have a certain, depending on the condition that you have, it's drawn towards or not. But the immune system is so incredibly sophisticated and it's very, very complex. And there is this interaction that we know between the bacteria that live in our body and the immune system. And if I, whatever I say to, I always start this teaching lessons to medical students, to undergrad students here at UCL, when I do the microbiota, the interplay we call it, between the microbiota and the immune system. And I asked the question, do you think you're human? And we always said, yes, of course. And then I shared my favorite pictures, where it's a man. And virtually the only the hands are made of human cells. The rest of the body is made of in comparison. So the percentage of bacteria that we have on our body outweighs far more the amount of actual human cells that we have. And so I think we, at the moment, we have just scraped the tip of the iceberg. And if we can capitalize on what mother nature has empowered us and trying to understand what the bacteria do, what do they make, what

are the metabolites, and then using these metabolites to prevent or to cure, or in addition to existing therapy, I think that would be super exciting and very promising.

PG: Wow, that's so interesting to think about as well, and I guess it's another complexity when you think about the complexity of the microbiome. In combination with the complexity of the immune system, it's a very complex picture.

CM: But we do have a huge amount of technology that we didn't have, certainly, when we all started. And now we have so many high power technology that allowed us to look at each individual cells, all the gene in each individual cells, and how do they change according to the environmental input that the cells receive. So this becomes very complicated, but what I'm trying to say is that we have the tools nowadays to understand more and to move forward much faster than we were able 20 years ago. And I know that, you know, when you, I mean, I myself, I have an autoimmune disease, so, you know, I mean, I'm very lucky in a way. I've got celiac. I don't have any issue to declare it. So, you know, for me, it's relatively simple. I just have to eliminate the gluten, which is the molecule to activate my own cells. But as you can hear from my accents, I'm from Italy, and I do love pasta and things. I can't eat it. That is nothing, you know, gluten-free pasta and pizza is not exactly the same as the real ones. And so, but I am, I know that we will get to the point one day where I will take a pill and I will be able to eat my beautiful pizza without worrying about the side effect of that might occur if I do that.

PG: Oh, that's excellent. That's amazing.

ER: I think what will be, I hope what we can do in the next, you know, the next big discovery will be in a way, is that when you get diagnosed with an autoimmune condition, what that looks like for people is quite different. So speaking about a child with arthritis, some children can have, you know, one injection of steroids in their joint and then never have a flare again. Whereas another child will not respond to many kinds of therapy and then they have disability that goes on into their life, later life. Then also talking about anti-TNF and rituximab. Some patients will be taken off those drugs and it will be able to control their disease, they won't flare. Whereas other patients, you remove the drug and straight away they have a flare. So I think the more tools that we have and the more that we can understand about these nuances, I love that word that Claudia said earlier, maybe we'll be able to say when somebody comes into clinic and they've just been diagnosed, what kind of disease trajectory, what their life will look like with that disease. Because I think the unknowing how you're going to respond, whether or not you respond to steroids or methotrexate, another drug that we use or anti-TNF or rituximab is

very confusing. And I hope that if we have used these kind of high throughput, these really in-depth tools, we'll be able to give people a little bit more of an idea about what their disease will look like.

And if you think about kind of cancer immunotherapy and how that's kind of improved in the last five, 10 years, because we have biomarkers that when a patient goes into clinic, we can say, you have this kind of cancer, so this kind of drug will work best for you. I think that now we're getting more and more and more information, we might soon be able to kind of start thinking about that for autoimmune conditions like rheumatoid arthritis and juvenile idiopathic arthritis and lupus. And I think that that will be, you know, a really great thing to be able to do.

CM: And if I can also add, because I think it's really important, particularly now in the era of immuno-checkpoint therapies for cancer, and many of these patients might develop autoimmunity, and in particular, rheumatoid arthritis, and so on. And I think one big satisfaction that I'm having at the moment is that we have really, in this place, exactly in this place, we have pioneered the study of B-cells, both pathogenic, as well as regulatory, the good one, let's call it for simplicity, in the field of autoimmunity. And this finding now, we are and many others are translating this finding into the cancer arena. And the knowledge and the speed that we are going in cancer and the progress that we are making in cancer is thanks to the years that we have been dissecting in a very, very minute way, the role of B-cells in these patients. And I always say to David's patients when I had the chance to meet, David knows you very well outside, but we know you very well inside. We know everything our immune system does. And I think this really has been our strength and will continue to be our strength in this place.

PG: That's incredible to think that we're leading that field.

DI: Could I just pick up on a very important point that Lizzy made, that although the biologic drugs have led to a great improvement in the lives, quality of lives, the length of the life of our patients, we are invariably not talking about cures, and that's the problem. And as Lizzy has just told us, you treat a patient with a drug, but for various reasons that drug has to be stopped. For example, if they have to have an operation or something like that, the disease comes bounding back. This is classic in rheumatoid arthritis, it can be back within days or weeks. And so we still don't have cures, but maybe the work that Claudia is talking about and some of the stuff that Lizzy has been talking about too will ultimately lead to that. But that's what makes it so exciting. We're on the brink of some significant breakthroughs which will take us from that. OK, we can get the patients a lot better, provided the patients continue to take the medications for years and years and years to the point that we can give you a finite course of treatment which changes

something radically within your immune system, gets it back to normal, and then we can start talking about cures. That's what we've got to push for. That's the next phase, I think.

PG: So this is all about rebalance, rebalancing the immune system

CM: Resetting, is the right word. And this is what we all want to do, you know, moving forward, we want to reset the immune system to what we see in a healthy individual.

DI: Absolutely right.

ER: Watch this space.

DI: Yes. That's true.

PG: I think it'd be great to sort of, yeah, think a bit more about sort of just for our listeners what you'd like them to remember about B cells. If you could just give them one sort of key takeaway message about B cells and why we're so excited about sort of, you know, working in this space, what would it be?

DI: Well, for me, the fact is that although, as we've heard, the cells within the immune system work together, B cells clearly are very prominent in the sense that when they go wrong and start to produce these antibodies which bind to the body's own tissues, this is not a good thing. We have shown in the last 20, 25 years that you can block that. We can show that has major clinical benefit. And we're now on the brink of improving the quality, if you like, and the quantity of the removal of these harmful B cells, which ultimately should lead to even better outcomes, longer duration of life. This is a good thing.

CM: Yeah, I don't think I have anything to add to that.

ER: I think, what would I like to say? So I suppose what I'm interested in, because I'm a very basic immunologist, is I'm interested in how B cells are different over age. That's

why I'm interested about them in childhood onset arthritis, and also why women are more at risk of developing autoimmune conditions and rheumatoid arthritis. So we're also trying to understand maybe the risk of developing autoimmunity is greater in women and females because of differences in the B cell compartment. So it's about kind of more population dynamics of understanding how B cells can change over age and change in different situations and how that might affect disease. And I think once we know a little bit more about that, we might be able to kind of tailor, target our treatments. but taking a little bit into consideration kind of background of the individual that you're giving the therapy to.

CM: So I suppose it's the 3 ‘B’s - bring, I don't know, 4, bring back B cells balance.

PG: Excellent, excellent. I think we're getting sort of close to the end of our time together, but thank you so much. It's been a wonderful conversation. I wonder if we might be able to just finish with a message for our supporters. So what would you like to say to those people that have made this research possible, those people that have donated very kindly to the charity?

CM: Well, if I can tell because I mean, I've been very, very fortunate for all my career to be funded by, supported by, the Versus Arthritis. As David always said, we've done well, we went we have gone far, but we really, really are continuously and relentlessly carrying on and working to try to cure. And we're not forgetting, obviously, patients that already have rheumatoid arthritis and lupus. So we will continue to work to try to improve existing therapies. But really, what we’d like to do is to try for the new generation to come to defeat these diseases.

DI: Yeah, no, I agree with that. The charity has been very open in trying to advance not just the careers of the researchers, but also the ideas that researchers bring forward in the hope that better treatments will follow and they have. But as I've said, we've got improvements in treatment, but we haven't got cures. We need to look now to take it on to the next step, the next level. We need cures of rheumatoid arthritis, lupus and those related diseases. And it may not be as far away as we once thought, perhaps even 10 years ago.

ER: So the supporters for the charity, thank you - Versus Arthritis funded my PhD and then my foundation fellowship. And I absolutely love being a scientist. It's the best job in the world. I don't think many people get to say that. So, thanks. And also exactly what

Claudia and David said, that we hope to move towards a cure and to hope to improve the lives of people with arthritis and to give them maybe more, not just about cure, but more surety in what the journey will look like when people are diagnosed. And I think that we can't do that without funding and as medical research is very expensive and the tools that we need to push science forward are now very expensive. So the more support we have, the more we can find out and the more I get to do a job that I love.

PG: So thanks very much for talking to me today. It's been fascinating to learn so much about the work you're doing and reassuring, I think, to know there are scientists like you working so hard for people living with arthritis right now. And to our listeners, thank you for joining us today. It's been a pleasure. And if you or someone you love is living with arthritis, you can find free support at versusarthritis.org. From our friendly helpline to our welcoming online community, please do reach out. So once again, thank you very much, Claudia, David and Lizzy.

CM: Thank you.

PG: And thank you for listening.

ER: Thank you.