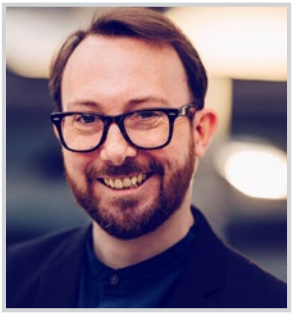
Interviews

Chris Wincup, Denis Poddubnyy, Christine Peoples, and Thomas Huizinga spoke with EMJ, sharing details about their careers and research focuses. The experts also discussed a range of field specific topics, including systemic lupus erythematosus, spondyloarthritis, and the value of telemedicine.

Featuring: Chris Wincup, Dennis Poddubnyy, Christine Peoples, and Thomas Huizinga



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Q1 What led you to pursue a career in rheumatology specifically focusing on systemic lupus erythematosus?

I think that I was slightly unusual in my career choices, in that I left medical school knowing exactly what I wanted to do. I went into medical school interested in sports, exercise, and musculoskeletal health, mainly because I was frustrated footballer, who was never going to make it playing at a professional level. But thought that I would like to work in the field of musculoskeletal health, particularly in relation to sport injuries.

During my elective at medical school, I gain experience doing orthopaedics, and I realised that I was not cut out for that. I recall being told that my history taking was overly detailed, but I enjoyed being inquisitive. However, it was at that time that I was introduced to a few patients with rheumatic conditions. The thing that really struck me was how fascinating it was that the patients did not just have problems with their joints, but they also had problems with their lungs, heart, kidneys, eyes, and skin. Something that I was really interested in is that it was not just a disorder of the joints, but it is systemic! I found that really fascinating and that lends itself to my very long and detailed history taking.

So, like that, I was interested in rheumatology! At medical school we had quite a few lectures on lupus, and I really found it absolutely fascinating. It was a disease that was very poorly understood. I remember being told that if you learnt anything about the disease, you are probably breaking new ground. The disease also seemed to be quite discriminatory in the way that it presented; it predominantly affects younger patients and is nine times more common in females than males. Patients also have worse outcomes if non-Caucasian. The disease has

significant impacts on quality of life, in addition to being immunologically fascinating and I think this is what drew me to it.

In my final year of medical school, I decided that I wanted to do lupus, and that I wanted to do a lab-based PhD looking at lupus, Then, 10 years later, that is where it led me, and I have been focusing on lupus ever since. Last year I was appointed as a consultant here at King's College Hospital, London, UK, to focus specifically on lupus.

Q2 As a Lupus UK funded researcher, what research projects are you currently involved in?

I have done lots of different projects in lupus! Being so passionately interested in the subject, I am keen to know about all areas. Some of my research is quite clinical; I am interested in outcomes, but also focusing on what the barriers to good quality care are. We are also currently working on a research project investigating patients' diagnostic journeys. For example, we are asking 'how long does it take to be diagnosed with lupus?', 'What is the impact of being misdiagnosed at the start of a patient's journey have on their future care?', and 'how does this impact on their trust in clinicians and future worries?' That is what led me to develop an interest in mental health and neuropsychiatric lupus.

We know that lupus is a chronic illness that is not curable, has flares, and can be associated with high levels of pain and fatigue, as well as other complications that ultimately have a significant impact on quality of life. We also know that patients suffer with poor mental health. In many cases, we see high levels of anxiety and depression; but we also know that neurological inflammation can occur as a result of the disease, which is poorly understood, and doctors may not be very good at picking that up. We have a major research focus on the neuropsychiatric and mental health manifestations of lupus at the moment and are doing a number of global studies, working with doctors and patients from around the world to get their opinions on when they may worry about these symptoms. This has really informed my clinical practice because when we know that these patients have these symptoms, it then prompts me to ask those questions to better identify them. It gets slightly tricky when patients do admit that they have these mental health symptoms and worrying symptoms such as feeling suicidal or having hallucinations. As a rheumatologist, we are not well trained in what to do once we have identified this. So, we are working on ways to collaborate better with neurologists and psychiatrists to support patients and provide better care.

I am also doing some work in response to lupus therapy, in particular in the role of B cell depletion therapy. We use rituximab quite a lot for severe cases of lupus and I use it often in my practice; however, it does not guarantee a response in every patient. Some of my research into this area is trying to work out why patients may have a good or a poor response to treatment and why some patients have side effects from treatment while others may not. This is so that we can tailor treatment to patients a bit better. As a doctor, we all want to be able to tell patients when we are confident that a treatment will be both effective and well tolerated with confidence.

This leads on to my third main area of research interest, which relates to precision medicine. We are fortunate that, after many years and trials failing in lupus and not having many treatment options, we are starting to see new drugs become available. In 10 years, we will hopefully have even more drugs available, but it will be very difficult for us to know who gets what drug when and for what type of disease. Obviously, we want people to be on the right drug first time rather than go through a trial-and-error process. So, a lot of my laboratory research is now focusing on if we can find markers that allow us to identify if one person will respond very well to a certain treatment, whilst they may not respond to another treatment. This will allow us to personalise care for patients onto drugs that are effective and safe for them.

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Q3 What was the main finding of the paper you recently co-authored, entitled 'Anti-rituximab antibodies demonstrate neutralising capacity, associate with lower circulating drug levels and earlier relapse in lupus''?

Rituximab is a drug that depletes the B cells in patients with lupus, which we know is one of the main drivers of many people's lupus. We use it quite a lot here in the UK and I've got quite a lot of experience with it. I was interested that we also use the drug for other conditions, such as rheumatoid arthritis and vasculitis. For patients with lupus, there is risk of infusion reactions, in which they feel unwell when the infusion is being given. Some of these reactions can be more severe in very rare cases, such as full-blown allergic reactions to the treatment. But we do not usually to see that in other conditions that we treat with the drug, so this seems to be a problem only in lupus. We started with a study where anti-drug antibodies had been measured in several lupus patients. I wondered whether these antibodies drove the infusion reactions, and I looked back through the notes, and we published a study showing that if you have these anti-drug antibodies when you undergo retreatment with the drug, you are likely to have one of these reactions. If we knew that routinely in our practice, we may decide to avoid that treatment if we feel people are at sufficient risk of a bad reaction.

I was then interested to see what the effects of these antibodies were over time so I designed a second study where we recruited patients and measured the anti-drug antibody levels shortly after treatment: 6 months, 12 months, and 3 years post-treatment. What we found was that these antibodies persist for a long time. The next question was: 'what does this do to clinical outcomes?' Having shown that it can cause infusion reactions, we questioned if it affects the way the treatment works. What we found was that, if you have the antibodies, you respond well to treatment initially, as well as people who do not have the antibodies. However, patients with anti-rituximab antibodies saw the disease flare much earlier. The positive response to treatment was not as long lasting in patients with the antibodies. Then we took this to the laboratory, and we found the antibodies were capable of neutralising the drug. What we are seeing is a good response to treatment but then the antibodies knockout that response and people flare earlier. So, we now know that these antibodies play an important role in infusion reactions but also in preventing long-term benefit from the treatment. That is important because new drugs that target the same kind of mechanism are becoming available. Therefore, we may want to use those drugs in patients who have the anti-drug antibodies.

Q4 What do you believe are the common misconceptions around lupus?

Lupus is the most common rare disease, affecting approximately one in 1,000 patients, which does not sound all that common, but if you are working in a relatively small general practice surgery in the UK and you have a population of 5,000 people, that is still five people with lupus within that cohort, and four of them may have a diagnosis. But there may be one of those who are not yet diagnosed, and so there are often misconceptions that it is very, very rare. This problem is further compounded as many of the symptoms of lupus cannot be seen physically, which means that the delay in getting diagnosed. This is why lupus is often termed 'an invisible illness'.

One of the other misconceptions is that it is relatively mild illness, where there only mild symptoms like rashes, joint pain, and mouth ulcers. However, they are not mild symptoms for patients, and we know that symptoms like fatigue a very debilitating. It is not a disease to be taken lightly, and I think many people forget that is associated with kidney disease. We know that 50% of people with lupus develop kidney disease, and if that is not recognised, it can severely damage the kidneys, sometimes to the point where people may need dialysis. In a small number of patients that can be life-threatening. I think sometimes people see lupus as this quite benign condition that is very rare. But actually, it is probably more common than people think. It takes a long time to get diagnosed and it

does have very severe manifestations if it is not recognised. I often go around encouraging colleagues to consider that when you've got a patient where the diagnosis is not clear, think of lupus and test for it!

Q5 How important is the early diagnosis of lupus and how can we move towards this?

In the UK, we have an open access healthcare system, where you do not need to pay to see a doctor; you can see a general practitioner and then you can go to hospital and there is no charge. However, the time from the first presentation of lupus symptoms to getting diagnoses is, on average, about 7 years. And that is in a system without any financial constraints to prevent an individual from going to hospital, seeing a doctor, and getting tested. That is probably because the symptoms are very subtle early on and then, as they become more severe and more obvious, it is easier to make a diagnosis. But early diagnosis is important in lupus as the main aim of treatment are to suppress the inflammation in order to control the disease activity. If you do not do that quickly, then you get damage. For example, if you do not pick up kidney disease quickly, and treat it quickly, then the disease will progress; your get more activity in the kidney and that will lead to scarring. When you do eventually recognise it and treat it, you can switch off the inflammation, but if the damage is done and there is scarring, this cannot be reversed. This is why early detection is really important from a clinical point of view.

From a patient's perspective, 7 years is a very long time to be ill without a diagnosis, and that causes a lot of anxiety. Patients will often get a wrong diagnosis before they are being told that they have lupus. So, a patient is often told that they have another condition by a doctor, and then they see me, and I tell them that it is something else. Being diagnosed incorrectly to begin with, and being unwell for so long, can be difficult for patients, and they may struggle to trust doctors again. An earlier diagnosis means that the patient journey is shorter, and they are more confident in the long-term care that they receive. It is all about getting the diagnosis right. But I do appreciate that many doctors are unfamiliar with lupus.

Q6 Across all medical disciplines there is a focus on personalised medicine. Do you believe this will ever be possible for lupus?

I certainly hope it will be! We have had a lot of years where drugs have not worked with lupus and have had to adopt drugs used in other conditions that we think are similar to lupus. We are using the limited number of medicines that we have available to us in the instances when someone is very unwell. But, as new drugs become available, we now have a choice, which is new for lupus. Before we would have perhaps two drugs for someone who is very severely unwell before, but now we have up to perhaps three or four, if the trials are successful. In 10 years, we may have considerably more than that!

As I mentioned with my work in rituximab, we know that this drug works very well for a lot of patients, but some may not tolerate the treatment because of a reaction, or they may not respond to treatment where we had given them medicine that depletes their immune system but not made them better. So, it is absolutely vital that, in the future, we say: "This is what is driving your lupus, and this is the drug that switches that off, and we are very confident that it will work." It is currently not as simple as you have lupus in your kidneys, so this is the treatment that will work for that. I think that we need to find more molecular or tissue markers to give us a clearer idea of what is driving the lupus. A good analogy might be the way we treat cancer. You would not treat it without a biopsy or an idea of what is going on at the cellular level. You can tailor the treatment more appropriately that way, and maybe we need to think in that way with lupus.

Q7 What are the main focuses of your roles in the BILAG Lupus Expert Group and the European League Against Rheumatism (EULAR) Lupus Guidelines Group?

The EULAR Guidelines Group is meeting very soon to update the guidance treating lupus. This is a revision of the guidance from years ago and really does kind of show how much has changed in the lupus landscape and how much we have learnt over a very short period of time. This is because new drugs are becoming available. However, not all drugs are available in every country, and the way that drugs are commissioned and licensed varies from country to country. So, the EULAR task force is looking at Europe and we will look at all the evidence and make broad suggestions on how to treat with the evidence that we have got at the moment. But there will probably be caveat as to what is available locally. I am looking forward to those discussions because I think a lot of people feel drugs work well in different scenarios. I am sure that it will be very educational to participate in.

The BILAG is a group of lupus experts based in the UK and we are updating the UK guidance on the management of lupus. Again, it will be a very big update given that lots of new drugs are available, and it will be more bespoke and tailored to what we do in this country. We are looking at the main healthcare system and the accessibility of various drugs to that system. The group is also working on a number of studies to look at how lupus is diagnosed, what treatments we use, how patients should be monitored, and how we should appraise their disease activity.

Q8 What do you believe are the biggest challenges for clinicians working with patients with lupus and what advice would you give them?

It is important that clinicians think about lupus as a diagnosis. If you are not a doctor who specialises in lupus or a rheumatologist and you have a patient where the diagnosis is unclear or you have tried different treatments and things are not working, it is often useful to consider lupus and referring to a rheumatologist. I think that the number one challenge is to make sure that people are aware of the disease so that they think about referring patients to rheumatologist who then have an easier job of testing for lupus, which is something we are very familiar with. It is very hard for us to diagnose lupus without someone saying, 'could this be lupus?' and then sending the patient to us.

The main challenge for rheumatologists looking after lupus is that the treatment is still imperfect. In some cases, the treatment can be quite toxic and associated with side effects. So, one of the main challenges Is making sure that we have good communication with our patients. If we are going to start them on a medicine that they may get side effects from, we need them to still be confident that when we offer them another medicine, the results will be different. I think that it is really important that we have good relationships with our patients, and that patients feel confident and comfortable in telling us how they feel they are getting on without fear that we will be very paternalistic and tell them they must take their medicine. One of the key challenges is to make sure that we are focused on the patients and how they are tolerating their treatment.

Q9 Are there any exciting innovations on the horizon within the wider rheumatology field?

In lupus, as with all of rheumatology, we are now getting a better understanding of how these

diseases occur. As we better identify what is driving the illness immunologically, we are finding better ways of targeting them with therapeutics. As lupus doctors, we often look at our colleagues caring for patients with rheumatoid arthritis enviously, given that there are multiple different drugs that can make rheumatoid arthritis better, especially as there is a lot of knowledge about that disease now. I hope that we will move onto similar horizons in the treatment of lupus soon.

One of the main challenges that we need to think about is if we can catch patients with rheumatic diseases (particularly lupus) earlier in their diagnostic journey. In some cases, by the time patients come to us, they are very unwell with symptoms, and we then confirm the diagnosis. But is there a window of opportunity where the immune system is starting to change towards an autoimmune disease, and that is the point that we may be able to catch them and switch things off before it even starts. In the future, it would be interesting to see whether we can do this.

Q10 There has been talk of moving to a spectrum definition of lupus, do you think this will be beneficial for patients?

I have patients who are close to lupus, where they have some positive antibodies and some symptoms but not enough to give them a diagnosis of lupus. In some cases, they then pick up symptoms or blood tests that, then in a few years, this becomes or confirms lupus. Whereas others will then pick up other symptoms that may develop into another condition such as Sjögren's syndrome or scleroderma, while others will just stay in that group that we call 'undifferentiated'. I often say to the patients do not yet fall into one of those categories or on a spectrum of a lupus-like disease that it does not often impact their care hugely. I would treat that very similarly to the way I would treat lupus based on the symptoms. The only impact it would have on them would be if we were doing a study in lupus where we have to be 100% sure that the meets criteria for lupus. So, it means that they may not be able to go into certain clinical trials. In clinical studies or trials, we have to be completely sure that that person has lupus because we really need to see whether that drug makes it better to be completely sure of it before going into clinical practice. I tell patients to watch out for symptoms, and if they get these extra symptoms (I usually give them a list), then then need to let me know and we may then reclassify things. Ultimately, if they have some joint pain and rash, I may start them on hydroxychloroquine, which is exactly what I would be doing if they had lupus. It is important to have consider that telling patients that they are on a 'spectrum of lupus' that can induce some anxiety, and I do appreciate this. There is actually quite a lot of anxiety in patient groups where we tell them that they had undifferentiated diseases that could progress into something more serious or might actually not progress at all. This is because rather than saying you have lupus and you can read about lupus, we are saying that you may get lupus or you may get these other conditions, which can contribute to anxiety. It is important that you communicate that with patients. I want patients to let me know if their symptoms change because then they may ultimately be moving along the spectrum towards something different. Clinically, a lot of us do think of many autoimmune conditions to be on spectrum already.