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Q1 What first drew you to nephrology, and how did your interest in IgA nephropathy develop?

At medical school, you rotate randomly around different wards, and my interest started when I was placed on nephrology, as I really enjoyed it. I liked the culture of the ward, I liked the consultants I worked with, and I found the subject area very interesting. I also liked the way that you would see a patient, take a history, and examine them. For the area that I'm most interested in, which are the glomerular diseases, the patient would have a kidney biopsy and then I'd be able to see what was going on inside their kidney, allowing me to relate what was happening in the kidney to the symptoms the patient was suffering from, the signs they had, and understand from a very basic perspective which immunological and pathophysiological processes were happening in the kidneys. So, I very much enjoy the bridge from basic science and physiology through to clinical medicine.

Q2 How has the field of nephrology changed since you started, and what excites you most about where it's heading?

If we think about glomerular disease, very little was happening for most of my career. In fact, it's all happened in the last 5 years, to be quite honest, and I'm almost close to retirement. So nothing much happened for 20, 25 years of my consultant career. We had some really important changes related to how we measure how a drug works in clinical trials, particularly in the disease I'm interested in, IgA nephropathy, which meant that clinical trials could suddenly be feasible, deliverable, and affordable.

That attracted pharmaceutical companies who were willing to invest in the area, because they could invest in a trial that would deliver a result relatively quickly and could get their drug approved. So we've seen an absolute explosion in clinical trials of new therapies, not only in IgA nephropathy, but many other rare kidney diseases.

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That has been predominantly driven by the fact that the drug regulators have changed how they assess whether a drug works in kidney disease by allowing earlier surrogate endpoints to be used. And that's tied in with the explosion in advances in basic science and the omics revolution that has allowed us to study kidney tissue in far more precise ways and better understand the pathophysiology of disease.

Q3 What do you see as the most important recent breakthroughs in understanding IgA nephropathy pathogenesis?

I think we've got a lot of data from genome-wide association studies, which have been global collaborations that have identified many different genetic risk alleles that are associated with IgA nephropathy and that has really pointed us to the underlying pathophysiology, which is at its heart, a dysregulation of the mucosal immune system, resulting in an excess of pathogenic IgA entering the circulation. And we've got a lot of really interesting studies from a variety of places across the globe, looking at the structure of that pathogenic IgA, how those immune complexes form, and what happens in the kidney tissue. We're seeing great collaboration globally, sharing of samples, and validation of results across populations, which is really helping us understand the underlying pathophysiology.

The other thing that's really changed is a better understanding of the natural history, identifying that IgA nephropathy does cause significant amounts of kidney failure, which has raised this disease up the agenda as an unmet need. If we can manage it, it will have a massive impact on the lives of young people. And again, that's been through global collaboration and sharing of data through the International IgA Nephropathy Research Network.

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Q4 Despite advances, what are the biggest unanswered questions that still frustrate clinicians and researchers?

I think the big challenge now is that in the USA, we have five approved therapies, with at least another three before the end of the year. And then we're probably going to double the total number over the next couple of years. The challenge is finding the right drug for the right patient, at the right time in the natural history of the disease.

Because at the moment, we just do not have biomarkers that I can measure in my clinic that can help me decide which patient is suitable for which drug. We're still using the same biomarkers we used when I was at medical school, which are serum creatinine and proteinuria. So we do need new biomarkers, and the hope is that over the next 5–10 years, we will have a panel of biomarkers, probably from urine and blood, that will help us better define disease activity, and better define which pathways are active, which will allow us to choose the right drug for the right patient and monitor the response. What we don't have at the moment is a very easy way of giving a patient a drug and then knowing whether it's truly working, other than looking at proteinuria and glomerular filtration rate, and they're very blunt tools. Each of these drugs is very expensive, and each of these drugs have side effects, so we really want to find the right drug for the right patient.

Q5 Are there any specific biomarkers that you think will transform early diagnosis and monitoring?

We don't have anything that's validated yet. The Phase III clinical trials all have blood and urine biorepositories, and are all looking at specific biomarkers to see if they add value above what we do already. For instance, the complement therapies are looking at complement fragments in the urine that may be emerging. The B cell-directed therapies are looking at galactose-deficient IgA1 and other immunoglobulin targets, and we really don't have any data at the moment to say any of these add value and are worth the expense of measuring in clinical practice.

Q6 Are there any therapies in the pipeline that you believe could be truly game-changing?

The ones that we don't have Phase III data for that I think are interesting are the CD38 depleters, so mezagitamab and felzartamab. From their early phase data, these drugs look like they could give patients a treatment-free holiday while maintaining disease control, but we need to prove that. And then we have newer therapies that actually degrade the IgA without affecting the immune system, and

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therefore potentially have less of a longer-term immunosuppressive effect, but they're in very early stages. So those are the two sets of therapies that are untested at the moment, in terms of having any Phase III data, but we've certainly got exciting data for the proliferation-inducing ligand and B-cell activating factor class of drug. We've got data for the complement inhibitors as well, so I think there's lots of opportunity for new treatments for our patients. We've got two in the NHS at the moment, with more to come, hopefully. One of the big challenges is that for one of those drugs that we trailblazed in the UK, the company have decided not to bring it to the UK. That's both for complement 3 glomerulopathy and for IgA nephropathy, and so that's very disappointing. It's something healthcare systems are going to have to try and face in terms of whether the price of these drugs are truly cost effective.

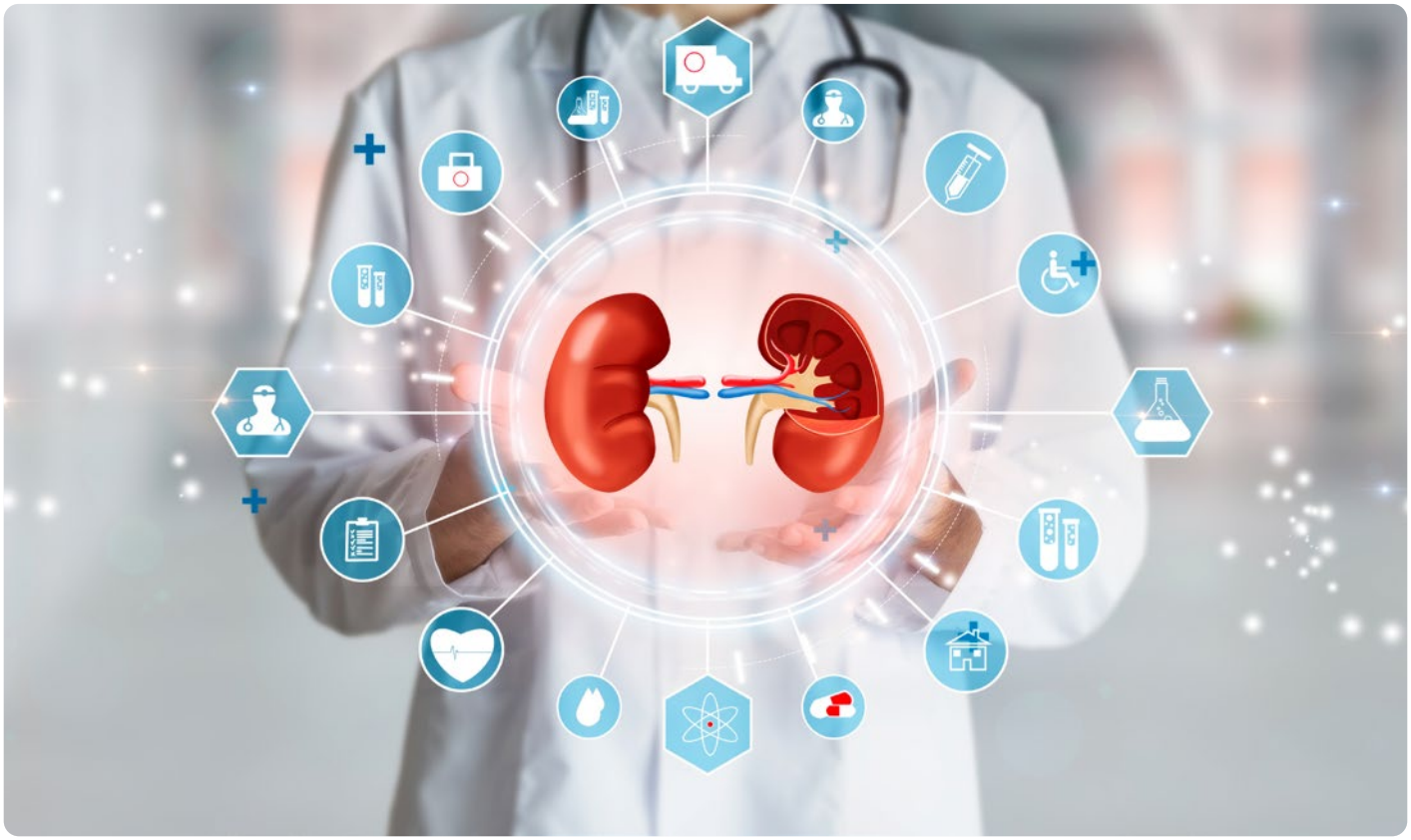
Q7 How has your research influenced the way you personally manage patients with IgA nephropathy?

I'm involved in all the clinical trials and I help write the Kidney Disease Improving Global Outcomes (KDIGO) guidelines, so I try and do exactly what the guidelines say. I try and diagnose as early as possible, I have a low threshold to treat, and I have a very high target I want to achieve in terms of control of disease. I utilise the drugs I have available in the UK, and, wherever possible, I get my patients into clinical trials.

Q8 How important has international collaboration been in advancing IgA nephropathy research?

We have the International IgA Nephropathy Research Network, which has a research group that has facilitated sharing of clinical data, and has led to the generation of the International IgA Nephropathy Prediction Tool. It also led to the generation of the Oxford classification for how we classify kidney biopsies. It is doing more work looking at how you can use risk prediction tools and treatment response tools to look at identifying patients who are going to do better or worse with particular treatments.

At the moment, we are looking at collaborating to gain and collect even more clinical data, so that we can look more clearly at the kind of questions we've just been discussing, which is can we identify the right patient for the right treatment? So, it is a global collaborative that is collecting a lot of clinical data from populations around the world, bearing in mind it's really important to understand that IgA nephropathy behaves very differently in different patient populations. And so, we need that breadth of data to understand and compare populations with IgA.



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Q9 Do you think we will see a cure for IgA nephropathy in the foreseeable future?

I think we will see a way of controlling this disease. The genetic data tell us that patients have a genetic predisposition to mucosal immune system dysregulation, and we can't cure genetic changes, but we can control them. What we're seeing with the new therapies is that we can control this disease to the point that patients do not lose kidney function. Now, how we can do that with a minimal amount of drugs, we don't know yet. But I do believe we will be able to control this disease and prevent kidney failure in the long term for most patients.

The biggest challenge we face now is actually finding the patients early enough, because most patients in the UK, and in fact in most countries, present when they've lost at least half their kidney function already. Because it's an asymptomatic disease, most of the time patients are just identified through luck and having a urine dipstick or a blood pressure check for a completely unrelated reason. So, one of the challenges we're going to face now we have the treatments is going out and finding these patients, so we can start treatment when they have good kidney function, and therefore give them the best chance of avoiding kidney failure in their lifetime.

> **"What we're seeing with the new therapies is that we can control this disease to the point that patients do not lose kidney function"**

Q10 What advice would you give to early-career researchers entering nephrology today?

I would say it is the most exciting time to enter nephrology. We have fantastic opportunities across a full range of kidney diseases, utilising the most cutting-edge technologies to really understand the pathophysiology of disease, identify new drug targets, and really make a difference for patients by identifying new ways to treat kidney disease and prevent kidney failure.

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