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Q1 With over 20 years of experience as a nephrologist, what led you to specialise in diabetic kidney disease and the molecular mechanisms behind this?

The primary reason is that it's the most impactful disease that affects nephrology. When I was in training, there was only one medicine available to slow the progression of kidney disease and diabetes, and kidney disease in general. It is estimated that around half of all patients in a dialysis unit got there because of diabetes. So, I started my career doing molecular biology and the molecular biology of hypertension. But when I was starting to chart out on my own, I got very interested in molecular mechanisms of diabetic kidney disease because I thought it was an unmet need.

Q2 What was the key mission that you set out to achieve when you established the Bhalla Laboratory?

One of the main projects that we undertook was trying to understand why some people with diabetes develop kidney disease and why others don't. Diabetes affects millions of Americans and people around the world, but not everybody with diabetes gets kidney disease, eye disease, microvascular disease, or neuropathy. Only a portion get each of those complications, and about 15–30%, depending on how you ask the question, get some form of kidney disease with diabetes. As a researcher, that to me is a silver lining; that means that the majority of people with diabetes actually don't develop kidney disease, and I felt that this was

an opening to try to look at why that might be. After all, there are patients called 'Medallists' from a programme at the Joslin Diabetes Center, Boston, Massachusetts, USA. These are patients with Type 1 diabetes who have lived for several decades and have not developed the complications of diabetes. So, there are clearly people that have diabetes but don't get kidney disease. We started to ask the question: are there things in the kidney that could help to predict who gets kidney disease among patients with diabetes?

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Since I came from a molecular biology lab, the way to ask that question most effectively was to look at mouse models as there might be something genetic involved. In the mid-2000s, when I was starting my own lab, the National Institutes of Health (NIH) had convened to form the Animal Models of Diabetic Complications Consortium (AMDCC). Some of the original publications out of that group were trying to redefine what diabetic kidney disease was in different models. At that time, there had been very little progress made in the laboratory because many investigators were using different definitions of kidney disease and using different models. I'll give you an example: you can make a mouse diabetic in a variety of different ways; you can use a congenital model, you can use various genetic models of diabetes, you can use a toxin to model Type 1 diabetes, or use dietary changes to model Type 2 diabetes. So, there was a lot of heterogeneity, and the most common type of mouse models that were being used for all kinds of studies for a variety of different diseases actually didn't get very robust kidney disease at all. The consortium actually published several papers comparing different models of kidney disease in mice with the same diabetic insult, if you will, which allowed one to compare apples and apples instead of apples and oranges.

It was clear that there were certain strains of mice that are more prone to kidney disease than other strains of mice, even if they're all equally, or relatively equally, prone to diabetes. That was very interesting to me, and I began trying to understand what genes might dictate the susceptibility and resistance genes in these mice. And so, our lab has spent a considerable amount of time looking at these genes, and we started to really hone in on one in particular, simply because I felt it was more effective to dive deep into one gene than to cover a number of different genes more superficially. So, that's how we got started.

Q3 How was the Bhalla Laboratory impacted by COVID-19, and has the pandemic altered the way in which research is carried out?

Our lab has been very much affected by COVID-19; probably the most important way that it was affected is through laboratory personnel that have had very close relatives pass away from COVID. Probably second is that our lab had to completely shut down for a number of months, and could only open partially for a long time after this, which affected the laboratory enormously. We had personnel who had come from abroad to study with us, and their term was up by the time we were able to open again, so they were not able to accomplish any of what they wanted to accomplish. I had other personnel that needed to make a salary during that year, but weren't able to work, obviously because

the laboratory was shut down. So, at the end of the pandemic, we had this skewed budget left in the laboratory, where we did not have very much money for personnel, but a lot of unpaid money that was meant for laboratory reagents, supplies, and experiments. That was one of the major ways that our lab was affected.

Q4 How have you seen the treatment landscape of diabetic kidney disease change over the years that you have spent in research?

I think that the treatment landscape has changed enormously for the better and it's really exciting. I think we have to remember that, with all of these developments that have happened, particularly over the last 2–3 years, diabetic kidney disease is still not a curable condition. All of the efforts that were initially put forward for different molecular mechanisms have not actually yielded that many new targets. What has helped is that we've had a little bit of luck with diabetic kidney disease, a field in which we historically have had very poor luck. We've had a lot of perseverance around particular targets, along with a lot of help from industry to pursue those targets.

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The partnership with cardiology was not anticipated; usually, cardiology and nephrology are at odds in terms of how to treat patients best. The therapy for heart failure usually adversely affects the kidney, and vice versa. But within the last 2–3 years, there have been therapies developed that work to slow down the progression of heart disease and kidney disease in tandem, for which there has been one successful trial after another. There are now two classes of medications, and soon there will hopefully be a third. So, it was 20 years of drought followed by a deluge of new therapies, and that's been enormously gratifying both as a researcher and as a physician. We now have many more options to treat patients than we did before, and we can do this aligned with our colleagues in cardiology, which makes things so much more collaborative and productive.

Q5 You have also researched Bartter's syndrome, a rare genetic disorder that causes kidney defects. Do you know of any new developments on the horizon that may be implemented to treat this disease?

Bartter's syndrome is interesting. I mentioned at the outset that I was doing research on molecular mechanisms in the kidney that were primarily related to the sodium transport of the distal nephron. As a researcher in sodium transport, one is keenly aware of most of the conditions, however rare or common, that affect sodium handling. Bartter's syndrome fits under that umbrella as a disease that makes the kidney less avid for sodium, and there's a lot of consequences of that. It's fairly rare, but it's a good model to understand how the normal kidney works. It's also a genetic model of a condition that we use to treat patients in cardiology and nephrology every single day.

There are 22 million people in the USA who take furosemide, which is a pharmacologic version of Bartter's syndrome. So, understanding what happens in Bartter syndrome can provide insights into understanding what happens when you take furosemide. We have tried to exploit this in the laboratory, and have had an

interesting time doing this while trying to better understand what happens to the nephron in that condition. Right now, I would say that there aren't any new therapies for Bartter's syndrome, but I think what's really important is that the study of this disease has become quite a bit easier from the human side due to the advent of clinical renal genetics, which is something that has happened completely in parallel with other things that we're talking about.

There have been a variety of very prominent studies looking at the role of genetics in renal disease over the last 5 years, and that has sparked a wave of much more affordable genetic testing. Patients who had a condition of Bartter's syndrome before were assumed to have that condition and there wasn't a confirmed genetic diagnosis that was associated with that. There now is, and, for a large majority of patients, coverage for genetic testing has improved enormously, which makes human disease much easier to detect and much easier to track and follow. Going forward, there will likely be larger scale studies of patients with these rare genetic tubulopathies in the near future.

Q6 Have you found that patients are generally receptive to the shift towards new technologies such as artificial intelligence, or have you experienced any resistance?

I have not had a lot of experience with artificial intelligence. The limited experience I've had with that as a clinician is that patients are interested to learn more, but they still favour the one-on-one human interaction, either in-clinic or in a virtual setting following the pandemic. I would say that every patient is different, but in general, they are still sceptical of the idea of artificial intelligence. If we can harness those types of technologies to make human–patient interactions more productive and efficient, then I think that it will be accepted quite broadly.

Q7 How do you use your role as a member of various institutions, including Stanford Bio-X, to positively impact the field of nephrology?

The Bio-X institution at Stanford is a partnership of scientists and engineers that are interested in collaboration. At this point, I have not been able to utilise my Bio-X affiliation as much as I would like, although I have had many discussions with different engineers about interesting topics in nephrology. I have tried to use my other affiliations with other organisations, such as the American Heart Association, to impact nephrology, primarily to increase its visibility in the world of cardiovascular disease, which I think is a much-needed effort.

Q8 Finally, as an educator, where can we expect to see your focus lie in the coming years?

As an educator, I will continue to showcase my enthusiasm for the field of nephrology, for both physiology and pathophysiology, and probably let people know that the field has changed a lot and is changing still. Compared to 5 years ago, we know much more about renal disease mechanisms; from rare diseases to common diseases, we now have many new therapies. There have been successful trials in chronic kidney disease for the last 2 years now, and many successful trials in the area of hypertension. So, we have different therapies and options for patients that we didn't have 5 or 10 years ago, and the idea that nephrology is a specialty where you have a condition that you can't do anything about, and you're waiting to place patients on dialysis, is no longer the case. We have made and can make enormous headway with our patients that we couldn't before, and debunking that myth will be a major focus, as well as highlighting how rich the field of nephrology has become.