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TRANSCRIPT - GR 12 15 23 "Kidney Success: *Celebrating the Renaissance in Glomerular Disease Management*" guest speaker Brad Rovin, MD from The Wexner Medical Center for Clinical Research Management

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- Good morning everyone, happy to see everyone today. Welcome to our last grand rounds before the holiday season. Today we are so excited for the Bolton lectureship, and I'm going to introduce Dr. Marco Coosa to introduce our lectureship.
- Thank you, Kara. So welcome to grand rounds. This is the W. Kline Bolton distinguished lectureship, Dr. Bolton. Could you stand and be recognized.
- So it's a privilege and honor to host our guest, Dr. Brad Roven. He's a friend and a colleague. He's a professor of medicine at Ohio State University. And what I'd like to do at first is to say a few words about Dr. Bolton and about this lectureship.
- And so this is appropriate. This is this. Talk is going to be on glomerular disease, and Dr. Bolton is one of the pioneers in glomerular disease, and he's a pioneering nephrologist in many ways. Dr. Bolton is a physician, scientist.
- He's a leading authority on Rpg. And good pastor Syndrome, and through his work he's definitively shown a couple of different things. One is that cell mediated. Immunity alone can cause glomerulinifritis, and he was also the first to show that epitope spreading occurred during experimental glomerulus, much as it does in autoimmune diseases.
- He is also described and disseminated the use of pulp, methyl prednisolone therapy for rp, rpg. And something that we do all the time. Doctor Bolton Bolton really is one of the early promoters of this therapy. Doctor Bolton went to Washington and Lee university for his undergraduate degree, and then went to medical School at Uva. He then received internal medicine residences, training and and fellowship training at Harvard.
- This was followed by research training at the University of Chicago. Doctor Bolton then joined the faculty at Uva in 1973 became Division chief in 1988, and he was division chief for 20 years. He was an integral member of a number of national committees member of the Asci or the American side for clinical investigation. He's been on a number of NIH. Panels. He was well funded by NIH. Throughout his tenure at UV. A.
- And beyond his contributions to the field of nephrology, he was instrumental in establishing the foundation for the current Eva division of nephrology
- for his great vision. He, along with our Medical Center, created one of the largest academic dialysis programs in the country. This is served, and to build the division of nephrology in terms of the academic portion for me personally. Doctor Bolton hired me, and he shepherded me through the challenges of being a physician, scientist, and he was a mentor when I first joined the faculty in the 19 nineties, and he continues to serve as my mentor, so we are truly grateful for his incredible contributions, and we recognise this through this endowed professorship. So, Doctor Bolton, do you want to say a couple of words?
- First of all, I'd like to thank everybody for coming. The crowd gets younger and younger every year. For some reason I have never figured out. I've watched many of the folks that are here grow up. I recognize many of your faces now, although there are some places I don't see anymore. Especially proud that Brad Rovin is. Gonna be here to give the lecture today.

- He's been a stutter member of the nephew community, and I've watched him grow over those years to where he is now, and he is one of the major players in the pharmacy
- fits right in with Mark and Mitch, who are, I consider, major players as well. And I wanna thank him for coming. And Mark and Mitch and the others that are involved in establishing the lectureship so that this can happen every year. So thank you again.
- Thank you, Dr. Bolton. Such a treat to have you in person today
- I'm going to introduce Doctor Brad Rovin. He is the Lee Herbert, Professor of Nephroology at the Ohio State University. He received his Bachelor of Science in Chemical engineering from North Western University, in Evanston, Illinois, and his doctor of Medicine from the University of Illinois Medical School in Chicago, Illinois.
- He completed a Residency internal medicine at Barnes Hospital in Saint Louis, Missouri, and a Fellowship in Nephrology at Washington University School of Medicine, Saint Louis. He joined the College of Medicine Faculty in 1990, and became director of the Division of Nephrology in 2,004, and served as the vice chairman for medicine and research from 2,009 to 2,019. In 2,019 he became the Medical Director of the Ohio State University Clinical Research Management Institute.
- Dr. Rose verbin has had several leadership roles in the American Society of Nephrology, including running the glomerular diseases, pro precourse and co-editing. Nef. Sap, glomerulative Diseases, which is a continuing education program of the society.
- Most recently he was appointed deputy editor of the Kidney and International, which is the Flagship journal of the International Society of Nephrology. He is also Co. Chair for glomerular disease, guideline development for the kidney disease, improving global outcomes, effort.
- Dr. Robin studies the immunopathanogenesis of glomerular and autoimmune diseases. He is heavily involved in clinical trial development and design for investor initiated and industry sponsored trials. He is a founding member of Nefronet, which is a grassroots, nephrology, community clinical trial organization and the lupus nephritis clinical trials network he is, and has been the principal investigator on several trials of novel therapeutics for glamorous diseases. We are so excited to have you today. Please join me in welcoming Dr. Provin. Right? Well, it it's a real pleasure to be here. And and this is actually my third time coming to Uva. So always. Great. Thank you for the nice weather. Everybody talks about kidney failure, that's all you ever hear about. It sounds like our sub specialty sort of is a downer. So I wanted to talk about kidney success instead. And that's why I titled this these are my disclosures. I'm so conflicted that I'm not conflicted. I hope you'll agree this is going to be a non-conflicted lecture before I start. These are some of the papers.
- Dr. Bolton's that I was exposed to when I was a nephrology fellow. I knew I was interested in immunology and glomerular diseases, and there were very few people in nephrology at that time who did this sort of work. So Cline actually became a friend and a mentor, and someone who has influenced my career over many years, and these are a lot of the things that Dr. Okusa was just talking about.
- In terms of what his contributions are, and these are papers from the seventies and eighties, and I know from many of you weren't even born then. So but this really is the foundation of what we're doing now and has contributed to the success. So I hope to get you excited about nephrology. I hope that you will find mentors and role models like Dr. Bolton, and when Dr. Okusa said, Will you come and give this lectureship? I jumped at the chance, I think, took me like 5 s to answer that with an affirmative.
- So let's get started you can divide glomerular diseases broadly into immune, mediated and non immunated disorders. If you want to. And you can think about this in even finer categories antigen antibody interactions like lupus nephritis immunoglobulin deposition like

monoclonal gamopathy of renal significance. Remember we used to call it Muggus, at least when I was younger. Now it's mgrass when it's important for the kidney due to. Ii like to say, circulating factors or cytokines. We really don't know what causes minimal change, disease or focal segmental glomerulosis.

- And now we are really getting very involved with diseases caused by the complement system. So those are all sort of immune mediated. But you know, diabetes is a glomerular disease, right? You have deposition in the glomeruli have abnormalities of the glomeruli. So I list some of these as due to metabolic disorders deposition of non immunoglobulin proteins genetic disorders and that could be focal, segmental, glomerular sclerosis, especially in kids, steroid, resistant, nephrotic syndrome, and then genetic disorders of the glomerular basement membrane so I'm just gonna do. This is a very broad, based audience. So I'm gonna try to show some fun stuff and things that are interesting. And then sort of get into. Why, I think there's a Renaissance in in nephrology and glomerular diseases. So for diagnosing glomerular disease, we should suspect that if a patient has proponor or hematuria. There's lots of reasons for that. And the patient may or may not have swelling hypertension visible blood in the urine or impaired kidney function. I put probably urine there. I hope everyone asks if their patients looked at their urine, because, you know, that's one of my favorite things to do, and if it's foamy, like the head of a bear, you should suspect something is going on like pro nuria and then, in the context of a systemic process, of course. The patient may have other symptoms. This is
- The urine dipstick, the way I used to do it, I suppose in your clinics. Now it goes into a machine and they give you a piece of paper. So you're losing that sort of contact with the urine. I include these because they're fun. And we were talking this morning, nobody does your analyses anymore. You gotta look at the urine of patients with kidney disease. So you see, these guys here are normal looking red blood cells and these globs. Here, you see these little bumps. Those are acanthocytes. Did you, Klein? Did you invent the acanthicite. Okay? So the acanthocytes are dysmorphic red blood cells.
- But they are very specific for glomerular bleeding. They're not so sensitive because you don't always see them, but if you see them, or if you actually look hard in the urine, you will often find them in Ged and then, of course, you have red blood cell casts which are conglomeration of red blood cells in the tubule that come out in the urine, and white blood cell casts white blood cell casts in the absence of infection. Remember, you can also get infection in the urine and get white blood. Cell casts, too.
- Protonaria can be glomerular in origin or tubular in origin. You sort of have to have a range. Glomerular propuria, or tubular protonura is generally a low molecular weight. Glomerular propuria can be of any range, but it's often nonspecific with higher molecular weight. Proteins. Hematuria, of course, can originate from anywhere in the in the ge tract.
- I thought, this is, I love this slide because it really shows you going from a microscope out into the urine. So this is an electron micrograph of a patient with lupus nephritis. And you see this is a glomerular capillary, and the red blood cells are in the capillary, and they look pretty pretty, normal, smooth, and really nice looking, and the ones that have come across into moment space, they look really crummy and they're all banged up. And when you, when you urinate these out. This is what you have is an acanthic site. Okay? And you have these blabs, and you can see where these might be blabbed because they're damaged going across the basement membrane. So this is a standing electron micrograph of an acanthus site. And I picked this one in particular, because if you put 2 eyes and a smile on it. It looks like Mickey Mouse and that's how we used to call them Mickey mouse cells. This is actually a tubule with a red blood cell cast in it, and you can see this when

you do kidney biopsies, and then when you pee them out, they look like this. And of course they don't last very long.

- Okay, so what is really our goal of treating glomerular disease? And if you look at all the trials that I do and everyone else does, you would get the impression that our goal is to make proenuria go away.
- and while that is something we like to see, because propuria improvement often goes hand in hand with improvement or preservation of kidney function. Our true goal is to stop the development of End stage kidney disease and to prevent chronic kidney disease. And why do I say that?
- And II think this is really important for a general internal medicine audience to know. These are our most recent Us Rds United States reel data system data. And you can see that this is the prevalent end stage kidney disease patients. And of course you know that the majority in this country are due to diabetes and hypertension. But you see that glomerular diseases account for a large portion of patients that do go on to end stage kidney disease. And I think we now have some some tools to help slow that down or prevent that. So that's why this is very why I call this kidney success.
- The other thing that I think is important. I'm afraid this is a little bit fuzzy. But this is what happens to your cardiovascular mortality and morbidity risk with chronic kidney disease. And this is why it's really important to not only think about preventing end stage kidney disease, but minimize or prevent progressive chronic kidney disease. So if you look here on sort of the vertical axis. This is glomerular filtration rate that's diminishing over time. And this is this is albu into creatine ratio, and this is low to higher levels.
- And you can see that even with pretty well-preserved glomerular filtration if you have propnuria that's fixed, you have increased your cardiovascular morbidity, mortality, risk.
- Similarly, even in the absence of much prouria. If you have chronic kidney disease, you increase. And this is, you know, this down here is 14 fold increase in cardiovascular risk. So having kidney disease is not just imply. There's problems with the kidney. This is something that those of us in internal medicine really have to grasp.
- So what can we do about this and the goals of glomerular management?
- Really, I've sort of outlined here. If there's an associated systemic disease control the disease. And of course, that makes sense in diabetes that makes sense for lupus etc., etc.
- We want to control inflammation as rapidly as possible in those glomerular diseases that have an active inflammatory component, because the inflammatory cells are damaging the renal parenchoma and the renal parenchyma heals with scar, which is called chronic disease, and that scar we can't reverse right now. We don't know how to do that. Okay achieve immunologic remission if we can, in immune medium kidney disease. And then we want to minimize chronic kidney damage in all the diseases. The problem with many of our diseases is that they flare, they recur, and when they flare you start an inflammatory cycle over again, and you have damage again. And each time you flare you're pushing yourself further down the road towards end stage kidney disease. Okay?
- So since 2020. So this is relatively recently, the FDA approved 5 drugs for glomerular diseases and 3 drugs for chronic kidney disease.
- And that's remarkable. Because in the preceding years we haven't had hardly any drugs approved specifically for kidney diseases like 0 drugs. So they're really modifying our approach to glomerular disease management.
- So I'm gonna give you sort of a survey. And you know, I'm not gonna get into the weeds on this because that's maybe for the nephrologists, rheumatologists, those sorts of folks. But I want to give you the impression of what you can do and what you should be looking for in our patients and how we're treating our patients. So this is the story of Inca Vasque

Inca, Associated vasculitis. This used to be called Wegner's Granulomatosis. The name was changed. But this is really a triumph of translational science. So for those of you. This is most of you know. This poly, immune glomerulin. Ephritis is a necrotizing glomerulinifritis characterized by minimal immune deposits in the kidney. But it's frequently accompanied by a rapid deterioration of kidney functions so in Rpg. As was mentioned before, and we do often treat or start treatment with high doses of glucocorticoid a posse immune glomerulin. Ephritis is generally associated with anti-neutrophil, cytoplasmic antibodies. Allah ancha Associated vasculitis.

- And what you can see here is this is a normal looking kidney for comparison. And then you can see there's a crescent here this moment's capsule, which is the around, the glomerulus disrupted. There's cells coming out. There's some scar tissue here, and you can see some proliferation and necrosis.
- When you get closer up in the glomerulus and you can see damage to the tubular interstitial space. The blue stuff is fibrosis, which is what we want to try and avoid. So this is a very inflammatory, very rapidly progressive disease, and you have to do something about it quickly and generally. What we do is high dose, glucocorticoids and cytotoxic agents, which really modify the immune system rather dramatically.
- So I want to emphasize that when we call these diseases posy, immune, glomerulinifritis posse is relative, and what I've highlighted here is that when you start to look at PR. 3 or mpos so protonase 3 or myloparoxidase, which are the 2 categories that we generally see of antibody specificities in Inca associated vasculitis.
- You can see that a lot of patients have a complement deposited often it's really of modest immuno fluorescence intensity. So it would be different that, for example, lupus nephritis, where we have a heavy complement component in the kidney. But almost 90 of patients have some complement. If you look at complement complement activation products in patients who have active Anca associated vascularitis. Who then are treated and remit. You see that the membrane attack complex declines c. 5 a. Which is the active component of the C 5 complement component C. Threea and Bb, they all go down, suggesting there is some involvement of complement in the kidney in this disease which we never really thought was a compliment mediated disease. So a lot of investigators. And this is some work from around faults group in in Chapel Hill. They started looking at blocking compliment, associated vasculitis. And so here's all the compliment pathways that you almost certainly hated when you were in medical school, and yet they have some importance, and they come back to haunt us.
- And this is a drug called a vaccopan, but it used to be called this name. And it blocks. It's a it's a receptor antagonist of the a receptor. A is an anaphletoxin, so it causes inflammation. It brings in leukocytes into an inflammatory mass. So it's a highly inflammatory complement component. And this drug blots its receptor. Okay? So when they looked at this drug in a mouse model of anchovascularitis. What they saw was crescents went away. Necrosis in the glomeruli went away clinically. Hematuria declined proponuria declined and leukocytes in the urine declined. So you get this idea that this drug is actually doing something to change the disease. This is a really great picture. This is the mouse that's untreated, or got a placebo, and this is the kidney of a mouse that got a vaccine. So it completely attenuates the Mpo ancha vasculitis in this mouse model. So we went back to humans. And we did this study. And this study was not done in the United States because this was an awesome leap of faith study.
- The investigators postulated that this drug would do better than glucocorticoids, and so in one of the arms of this trial they eliminated steroids. So this was a double blind Placebo controlled trial. It was done in Europe. Our FDA would not let us do the trial in this country

patients with anchor associated vasculitis. At the time most were treated with cyclophosmide. The standard of care arm got placebo plus prednisone 60 milligrams a day down to 10 milligrams by 3 months. The experimental arm review receive what would be evacuated? A receptor antagonist plus either low dose prednisone. So, starting at 20 milligrams a day or steroid free.

- Remarkable in the treatment of glomerular diseases. Right? We we almost never do this. But I'm gonna show you another time where we we're getting towards this. And you all are internists know that glucocorticoids are great drugs, uniformly hated by patients because of all the things that they do to patients. So this was again, this is the primary endpoint was a 50% reduction in Bvas. Our rheumatology colleagues are great at making these scoring systems with a lot of initials that none of the nephrologists can figure out. But I, you want to be best to be 0. That's inactive vasculitis. If there's rheumatologists in the room, I'm not insulting you on purpose. So here you see the people reaching this endpoint. But what I've highlighted here is a vaccin plus no steroid.
- 81% of the patients achieved a decline in this vascular score. So it looked like this was working in humans.
- And this is something that I think is interesting. This is a phrase that many of my faculty have adopted when I said it many years ago, when they were fellows. Time is Nefron, when you have an inflammatory mess in the kidney, and you let that continue. You are accruing to the kidney. That is so far irreversible. So you wanna get this patient treated as soon as possible, and control the inflammation as quickly as possible. And so what you can see here, using the Bvask score, you can see that this is high dose glucocorticoid, and eventually the patients get to the same point as those patients with Evac, but a large percentage of the patients in a vaccopan reach this in a much shorter timeframe, suggesting, not only can it substitute for glucocorticoid, but it works more rapidly than glucocorticoid. So we're hitting 2 checkboxes that we really want to hit.
- So this is a phase 3 trial. Our group participated in this. This was done throughout the world, and the Evac group got this complement inhibitor 30 milligrams twice a day, and then they were treated with cyclophosmide, followed by maintenance therapy with as a Thyrin or Auximab. They received no prednisone now they could have received prednisone prior to the trial.
- Okay, prior to entering the trial, but in the trial they were receiving no prednisone. But they got a pill. That look, you know, placebo that looked like prednisone. And then the prednisone group was treated with a regular prednisone taper, starting at one milligram per kilo per day. So let's say, 60 milligrams and they had in the Vaccine placebo, and then the same, you know, suppressive treatment.
- And this was a non inferiority trial. You don't see those trials very often in the renal space, but what the investigators were trying to show was that using a complement inhibitor in the absence of glucocorticoid was just as good as using the glucocorticoid. And you can see here that looking at clinical remissions at 26 weeks, so at about 6 months, there was no difference between the 2 groups when we looked at sustained remission at week 52.
- You can see that actually, a vaccine is starting to look a little bit better than the glucocorticoid, and that turned out to be statistically significant for being superior.
- So now, what about the kidney? Because we're here to talk about the kidney? This is propnuria in patients with Angiomasculitis, and you can see. Talk about quick action. The Avoca Pan group really drops their propnuria. Eventually the control group catches up. I'm not saying the glucocorticoids are not effective, they are effective, but this is more rapidly effective without the glucocorticoid side effects. And you can see we get down to a about an 80% decline in propnuria here.

- This is Anca associated flares. So one of the problems with Anka associated, or all the vascularities is that they relapse, and when they relapse. They really take out another large chunk of parank, and so you can't sustain many relapses and Anka associated vasculitis without losing your kidney function.
- And so this is, this is a way to sort of preserve kidney function. And you can see that with this drug we reduce the hazard ratio for relapse is reduced significantly.
- Now, this is really a cool thing that we didn't know that we were gonna see. But this goes a long way towards this Ck. D. Goal that I was talking about, and that is, if you look at the Gfr. Of the patients who were treated with prednisone or Evac, and especially the Gfr. In those patients who started out with severe decline in kidney function. These patients benefited dramatically with a recovery of Gfr.
- Much superior to our standard of care treatment. So we are actually seeming like, we're preserving kidney parenthuma in these patients. Again, getting towards the goal of kidney success.
- Okay. Ig, anthropathy. This is a triumph of a society trying to work with the FDA.
- We in the Asn developed a public private partnership with the FDA through the kidney health initiative and the idea was to start looking at how to make trials doable so we could get a drug approved for any kidney disease. The problem is, if you go back to the old way of doing things.
- The FDA wanted us to show that our drugs prevented and stage kidney disease. Well, that is a lifetime of following a patient which was impossible for Pharma to do impractical, and we couldn't get anywhere through this Iga we wrote a white paper, and I was lucky to be part of the committee. We developed a new way to look at drugs for Iga. We know that if you reduce protonurian Ig anthropathy, that is a good prognostic indicator that the kidneys gonna do well that's not sufficient as a surrogate marker for the FDA. So, we added, after you got the prop Nara reduced, you could potentially get your product for accelerated approval. But you had to continue the trial in a blinded fashion and show that it benefited Gfr. Again getting back to preserving kidney function and this gave us our ability to go forward with Iga trials and a floodgate opened. So first of all, just to review Ignephropathy is the most common primary glomerular disease in the world. So this is not a few people. This is a lot of people especially affecting folks in Asia, in China and Japan, etc. It's characterized usually by Massangio proliferation. And then, when you do immun fluorescence. You have a Massangio pattern of Ij deposition and just real quickly. This is the presumed pathogenesis of Ij anthropathy. It's a 4 hit idea. So the first hit is development of circulating Galactose deficient ij, one secretory ij, one.
- All of us have Galactose deficient. IJ. One. Those of you in the room who don't have I? Nephropathy, which I'll assume is most don't have a lot, but I've measured it myself. I have it and so do you? And that's not a deficit.
- Okay. Now, where does the IGA. One come from? Well, you know the mucosal surfaces are immunologically active. The gut is the largest immunologic organ, if you will, in the body, and we think that the gut and respiratory mucosa make Iga. That's secreted. We know that. And we think that in patients with I nephropathy, the gut makes too much Galactose deficient iga, the Galactose deficient iga can be recognized by antibodies. Igg antibodies against this aberrant form of Ig nephropathy of Iga. And then these galactose deficient, immune complexes deposit. That's the green stuff here in the glomerular massandum when they hit the glomerular massandum they cause proliferation of the mass. Angel cells extracellular matrix production. They induce cytokines and growth factors. They activate complement and they cause inflammation. So this is the presume pathogenesis of hygiene aropathy. Now if you look at modifying kidney injury, we now

have 2 drugs approved for Ig nephropathy and the first one I'll talk about is called is an Endothelian antagonist. But first I'll I'll sort of blow this up here if we look at hit number 4 this, we want to do something that will modify the effects of iga in the kidney.

- Now, if we modify the effects of Ig in the kidney. We are addressing the kidney injury of Ig nephropathy. We are not addressing the pathogenesis of Ig and aphropathy. Okay? So just understand that we're not gonna cure ig anthropathy with this drug. But I think all of you probably have seen some patients, and you know the nephrologist. Wanna put everybody on ras inhibition?
- Why do we do that? Well, this is what happens when the wrap, the Renan Angiotensin system is activated in the kidney, we get vaso constriction. You all know that we also get endothelial cell dysfunction. We get mass, angel cell proliferation and excess, Miss Angela matrix production. We can get abnormalities in the potocyte and then we can induce inflammation and fibrosis in the tubular interstitial.
- Well, it turns. And of course we've known for many years that patients who are put on wrasse inhibitors, aces, or arves with ig anthropathy. If you can control their pro Nora, they actually tend to do pretty well over time. That perfect but pretty well.
- So we figured well, if inhibiting all of these diverse activities of the Renan Angiotensin system would work.
- What if we inhibited it even better? And it turns out, and as you can see here, that Endotheline, A actually has much the same function
- when it's activated in the glomerulus as does the Renaang Angiotensin system. So some smart Pharma person said why not combine these drugs? And that's what they did.
- And so this is called Sparsentan and Sparsentan is a dual endotheline angios tensen receptor, antagonist, Adira.
- Ok. So new abbreviations that you can try and learn. But basically it hits the angiotensin one receptor and the Endothelene, a receptor in the glomeruli and other kidney cell types.
- And so we did a clinical trial, using the mechanism that I just told you about how drugs can be approved with the FDA, and we compared Sparsentan, the dual inhibitor to Urban, which you know, is an arb alone. So we're looking at one component versus knocking out 2 components in the in the pathway of injury and the primary efficacy endpoint was 9 months. What happened to the pro nuria? And then the end at the end of the trial was 2 years, and the key was to show that the Gfr. Was better in the group that got Sparcentat.
- And this is what happened. So if you look here, this is what happens to proton area over the entire course. And you see what happens when you put patients in a clinical trial, it's highly likely that they may take their medication as opposed to what you think they're actually doing when you're treating them, and you think you're doing a good job because they go home and say, Ha! Ha! Fool the doctor. I took the pill today, and that was the only time I've taken it this month. So look at the drop in propnoria. It's dramatic, and you can see that this was about a 43% decline versus overall, a 4% decline from when they entered the trial. And this was at week 36. This delta in pro nuria. So the improvement in pro nuria at this point met the criteria for FDA accelerated approval of this drug. So then we continued the trial for another 12, another 15 months to get to 24 months.
- And this is the confirmation long-term kidney function. So what you see here is Gfr. Over time in in the Sparsentan group and the Urbis Sartan group. And what you can see is that there's an initial decline because both of these drugs are hemodynamically active. So they decrease glomerular profusion pressure. So you have a small decline in Gfr, then things sort of stabilize. And when you follow these patients over 2 years, the patients in the placebo group or the control group lost 9.5 mill per minute for 1.7 3 meters squared of Gfr. Compared to only about 6 mill per minute per meter squared in the Sparcentan group,

confirming that we have a benefit on Gfr. And you can say, and rightly so they both declined. They did. We haven't cured this disease. Okay, we have not cured this disease, but if you slow the decline in Gfr by even a little bit. You prolong the life of the kidney and avoid end stage renal disease therapies like dialysis or transplantation for a number of years. So this is good. It's not the end, but it's good.

- Okay. how about if we wanted target the real pathogenesis of the disease? And so this is the idea is, can we eliminate or reduce circulating Galactose deficient Iga? And so you might say, if you were to do this, you would want to intervene with a B cell drug, and I'll show you that we are doing that.
- Or you may want to intervene with the production of Galactose deficient Iga in a mucosal organ. And so what we did was we looked at Nef. Nefacon in this Nefagard trial. Neficon is a really fancy encapsulated. You know what viewes an idea is, Buddhismide is an oral glucocorticoid that is not very reabsorbable and people use it for Crohn's disease or inflammatory bowel diseases, and they inhale it for asthma that sort of thing, but we encapsulated it, and when I say we, I participate in the trial, I didn't have anything to do with the chemistry of it, and it was in a capsule that is set to release theoretically at the pires patches. And the idea is, could we reduce Galactose deficient Ij production. And so we trial this drug.
- And it was the same sort of setup we had nef con or placebo. All of the patients were receiving Wrasse inhibition, because that's sort of our standard of care for Ig nephropathy. They were followed along for 9 months on the drug, and they had 3 months off the drug, and then Part B was 12 months off the drugs. So, in other words, 2 years, with a look at propnoria as a qualifying endpoint for the FDA at at 9 months.
- And these are the data.
- So I want to point out several things. You can see that there's a sort of a dramatic reduction in pro nuria, in the patients receiving nef con. And at 9 months there was a 30% difference in pro nuri reduction favoring nef con. At the 9 month time period.
- The FDA approved the drug under the accelerated approval format. You can see that over 3 more months. As the drug was being tapered off. It is a steroid, and some of it does get systemic.
- There's a further drop in propnoria. Now look what happens as you're off the drug. You're starting to see the pro nuria come back, and in the end, at 2 years, 24 months, there was a 30% decline in pro Nuria. But the suggestion is again, this is not a cure. You don't give it once the disease doesn't just go away. Like most autoimmune diseases, we may have to think about maintenance therapy in the treatment of these diseases, but nonetheless this is what we saw, and then we confirmed that in the Gfr. Endpoint at 2 years. And this is something I want to point out. This is this little bump in the Nef in the nefaciy group in Gfr.
- Really is the same thing we see when you give systemic glucocorticoids, there's a little bump at the beginning in Gfr, and that suggests that
- Nefcon may have some systemic effects. It's not necessarily only related to what's going in on in the gi tract. About 7 of it gets absorbed. It's or it's it comes out to about 7 milligrams of Prednisone, my predecessor who was in Dr. Bolton's era, he said to me 1,000 years ago, well, he yeah, sorry, client, you're not that old, he said. Why don't we just take you design? This is before any of this, and just treat patients with that?
- Or why don't we take a little tiny dose of glucocorticoid and treat Ij patients with that. And I learned that he was almost always right, even though he had never had any data for anything. He said he was almost always right. It really begs the question, do you need high-dose steroids? Or could you get away with a little bit of leukocorticoid in these patients.

- That wasn't the point of this trial. The point of this trial was to show that over time and the patients in the Placebo group lost 12 mil per minute per 1.7 3 meters squared over 2 years of Gfr. And the patients in this group lost only 6. Okay. Again.
- Loss on both arms much less loss, better preservation of renal function.
- But now I hope you can see. Say to yourself, well, wait. He showed us one mechanism where we saved Gfr. And then he showed us a completely different mechanism. Where we saved Gfr.
- What if we put the 2 together could we have an even better benefit on Gfr. And I think that's where we're going in, ije. Nephropathy. We're going to use combination therapies in the future to try and achieve the lowest decline in Gfr possible. And I think that's now within our grasp.
- Okay, so once we proved to the FDA and to the pharma industry that we could actually do these trials. keep a trial going for 2 years, maintain patients in the trial, keep the double blind because we don't know what the patient's getting. The patients don't know what they're getting. We now have. I'm on soon of drugs that are being tested in a disease in which we've never, ever had a drug. Okay? And those drugs include, of course, the ones that are approved are neficon.
- Then we have another, an endothel and antagonist. We have a whole slew of complement inhibitors because complement is activated during this disease again, not as prominent as lupus nephritis, for example. But certainly there, I'm gonna talk about inhibitors in a minute, because they're really hot topics, but they are approved for chronic kidney disease. And then this is what's particularly interesting to me.
- These are all drugs that modify B cells. This is a plasma cell inhibitor, and the rest of these are Belumimab or blue map, like drugs. So in other words, they're inhibiting B cell survival factors that really maintain auto reactive B cells and those again tend to look and work at the pathogenesis of Ig nephropathy. And I don't have time to show you the data. But the initial data from these B cell drugs is absolutely beautiful, and these drugs are now moving into phase 3. And what's really important. I said, we need to get rid of Galactose deficient Iga. These drugs are causing about a 60% decline in the aberrant iga molecules. So we are actually, we think, affecting the pathogenesis of this disease. So that's exciting. Now, my favorite disease is lupus nephritis. I've been studying this for a really long time.
- We just had our first 2 drugs approved since 2020, for the treatment of lupus nephritis outside of glucocorticoids.
- And let me just show you sort of IIII put this on here because we put this in Jason in 2,016. This was the trial landscape in patients with lupus nephritis at that time, and these were all different drugs, having different targets. These are all immunologic mediators, and you can see the target is B cells aisle, 6 plasma cells.
- Inflammatory. Cytokine failed, failed looked good development discontinued. This is a whole different conversation over a bottle of beer. Because I was heavily involved in this, and this company really pissed me off it to the point where I we wanted to buy this drug and trial it ourselves in in Lupus, and they said, No, it might impair their Ms program. So they said, No not that I could afford to buy the drug, but anyway, I couldn't even afford to buy the drug. If it's out there for use. Nobody can afford these drugs, which is a whole different conversation in our medical system. Failed, failed. Stop! Stop for toxicity failed. So you could see how someone like me might have been discouraged in doing this, because I was on many of these failed trials, and my nickname at work at the Ohio State. You said it right. The Ohio State University was. Oh, if Robin's on a trial, it's gonna fail. So you know. Luckily that changed so 2 trials which I participated in. We're successful. This is the Bliss Ln study. So bliss ln patients were active lupus, ephritis biopsy proven. They

were treated with. The investigator could choose high dose glucocorticoid, or with Michael phenylate or high dose, cyclophos, or idos glucose quartercoid low dose cyclophosmide, the euro lupus regimen, and then followed by as a Cyprin maintenance, and then they got randomized. To belum a map belum is an inhibitor of bliss. Bliss is a d cell growth factor that is elevated in patients with lupus nephritis and then or just placebo. And then we looked at the primary endpoint which was called the primary efficacy endpoint at week 104. So at 2 years. What's unique about this trial is that it was the first 2 year trial in Lupus. We had previously done retu lab, which was a V cell antagonist at one year, and we really didn't find an effect. Okay? And we started to think maybe one year wasn't sufficient the other thing that's unique in this trial is that we loosen the definition of protein to create ratio for response and loosen the definition of Gfr response. But we also looked as the primary secondary endpoint at the traditional complete renal response. And I I'm not gonna go into a big discussion of what complete renal response means, because I think we have it wrong in most trials. And pro Nuria is a nice endpoint for us, but it's not the correct endpoint. There's too many things that can influence Propuria. We we do repeat kidney biopsies, you know, as protocol for a lot of our research most patients don't really want to do more than 0 kidney biopsies. And when we do 4 or 5. They're very patient with us and what I'm showing you here is this is the primary response and complete renal response in the Placebo group in the Belummab group, and this was a large trial Ii don't think I showed it the number of patients, but there's over 250 patients and belum gave about a 10% more effect size. So, in other words, 10 more of the patients achieved the endpoint and that was statistically significant. Now statistically significant is that clinically significant? Is this what we're looking for in one of our drugs. And I would argue, it's not necessarily what we're looking for but what was more exciting to me was the post-toc analysis. We did. The Bliss Ln trial. Now you have to take this with a grain of salt. This is a postdoc analysis. We weren't necessarily powered for these outcomes, but this is very suggestive. And what we saw here. This is a forest plot for those of you who are used to looking at it. This favors Balluma map on this side this favors placebo, and if we look at whatever the starting background therapy was, or the class of lupus nephritis was. the Lumimab patients had fewer renal flares. Then the placebo treated patient. Now why did we get to look at this? We got to look at this because this was a 2 year trial, and we'd never done that before. So that's really important. The other thing that

- I will tell you is that this is entirely consistent with the long set of observational data using belumab in non rena lupus, where major flares decrease in non rena lupus as well.
- Okay. So this suggests that this might hit one of our goals of therapy, which is preventing flair. The other thing that you can see here is we looked at Gfr. And we were able to look at this over a 2 year period. Egfr slope is those lines, is the slope of the line of Gfr. Either declining, improving, or staying stable over time. A negative slope means a decline of Gfr. What you see here is in the Placebo group. The Gfr decline was about 3.2 mills per minute versus point 9 9 in the Bloomamab group. Not quite statistically significant, not powered for this, but it's starting to give the suggestion that this drug may help preserve kidney function. So when I think about the Luma map I don't think about. Bloomer map is the most exciting induction therapy for lupus nephritis, because it's going to get a lot of people into remission quickly. I think of this more as maybe a long-term therapy, where we will preserve kidney function and avoid flares and contribute to kidney success.
- The other trial was the Aurora trial. This is vocal sporn. This is a calcine urine inhibitor. It's like other calcine inhibitors, but perhaps with fewer side effects put on a background of Michael Phenylate versus placebo. What was unique about this trial, and I told you I get back to steroids is this was the glucocorticoid taper that was used in this trial. This trial

started with far less. It was getting. You gave a dose of intravenous pregnant alone at the beginning. started with about 20 milligrams of prednisone, and then you were down after 3 months, to two five milligrams of prednisone. This was remarkably low dose for a lupus trial, remarkably adventurous if you will, and very low dose sustained over any period of time which really begs the question of, have we been overdosing patients with glucocorticoids for really long time? And my answer to that is probably yes. So this is. I took the phase 2 and phase 3 together. And this was a complete renal response. So at 6 months in one year you can see that there's 11% more at 6 months of complete renal responders in the vocal sporing group. And then there's about 20 more at one year. So this is a one year trial, and both of these drugs received approval from the FDA.

- Now what do I think is important for the calcine inhibitor? You know that we use calcine inhibitors is anti T cell drugs in patients with kidney transplants and other organ transplants. But the other thing that the poto site, or that the calcine inhibitor does.
- Is it medi calcium urine itself mediates the dephosphorylation of synaptopodon, and then synaptip potent can be degraded. Synaptopodin is an essential element of the cytoskeleton of the potocyte. And so when your pathologist, when you do a kidney biopsy, and the pathologist says, Oh, the foot processes are fused. You see what they look like here. They look like this compared to this. This is a really cool experiment in which they took lupus prone mice.
- These were MRL. Pr. Mice, I believe, and the mice were approaching the age where lupus nephritis starts, and then they either didn't treat the mice or treated them for 8 weeks with a calcineuran inhibitor in this case to chromos and then they harvested the kidneys and the disease mice.
- The foot processes are destroyed, and the foot processes are actually remain intact here in the calcine treated mouse. Why is that important? Well, if you look at protocytes or epithelial cells, if you look at epithelial cell number and a glomerulus and the epithelial cells get lost. Then you scar the glomerulus down. Okay we don't know that we can replace potocytes, they may be end differentiated. There's some controversy as to whether we might be able to replace potocytes from the parietal epithelial cells, but the point is they're hard to replace. You lose them, you sort of lose them, and when you lose potocytes your Gfr. Drops. So I think this is a nice component of something we can add to the treatment of patients with lupus nephritis, maybe to mitigate or modulate T cells. And maybe we're gonna use your medication to modulate T cells better in the future which we have. Some. You guys have some really cool research going on right here. That, I think, is really interesting.
- But we can preserve podo sites and preserving poto sites. Preserves could be function. Okay, now, we started a little late. So I'm gonna finish up. Yes, okay, and I only have a couple of more slides and then we could have questions if you want. So the other thing that we have to do is we have to start thinking about our diseases as chronic kidney diseases like any other chronic kidney disease. You don't just have lupus nephritis. Treat it, and it goes away. It's a lifetime that you need to take care of that person's kidney, and so we now have sglt inhibitors, and for those of you who are not well versed in Sglt. 2 inhibitors. What's all the fuss about? And this is sort of the normal way things go. And you know that sodium and glucose are co-transported in the proximal tubule, and the Sglt 2 inhibitors are sodium glucose to transport inhibitors.
- So they inhibit the reabsorption here, and so more sodium and glucose goes down and comes up through the nephron, and when the nephron crosses back up by the glomerulus and the macular density it says, oh, there's too much sodium here, and we better constrict the effort arterials. That's why this goes down compared to this and glomerular pressure

drops. That accounts for the acute decline in Gfr. That you are likely to see if you start a patient with some kidney disease on an inhibitor. It also accounts for decline in pro. It's just working like a wrasse inhibitor in that sense hemodynamically decreasing. Pro and gfr a little bit. If the Gfr keeps going down, you got a problem. You gotta stop it. That does happen sometimes. But I don't think that's really the mechanism, and I don't think we know what the mechanism of action is, but I'm gonna throw this out there, and you can believe it or not believe it, because this is just my opinion, and it remains to be proven. But when we block sodium and glucose reabsorption.

- I believe it's reducing the workload at the level of energy production. You know, mitochondria, etc. Energy metabolism reduces the workload of the proximal tubule and may help to preserve real mass in that fashion. There are a lot of lot of works being done to figure this out. There's a lot of other things that the Sgl inhibitors actually do. But this is sort of interesting. Maybe blocking. Some of the inflammatory zone responses may be related to macrange. Polarization may be anti fibrotic, so there's a whole bunch of fairies out there. I don't know that we know the effect like any other drug. This probably has multiple different effects that may, in fact, be beneficial. And you say? Well, what difference does it make? And the difference it makes is that in a in a Ckd population when you give epiphuglosisin or dappofugosis in compared to Placebo. You see this decline in Gfr. In Gfr. As we expect, so don't panic and don't just stop the drug. Talk to your next door, neighbor nephrologist. And then, you see well, this placebo continues to decline and these SGLT. 2 inhibitors sort of stabilize on the basis of these studies the FDA. And we looked at these in mostly diabetic kidney disease. But then we saw that it was having this beneficial effect. So now Ampa and Dappa would send, and I hope I'm saying that right. But I can't say any of these names are approved for mitigating chronic kidney disease, and you can prescribe them in your clinic.
- Okay? And then and then the data that show this is, we did a sub-analysis of these very large trials, and they did this sub meta analysis. Looking at Ij Nefropathy, for example. And you can see that these are the 2 big trials. This is a forest plot again favoring this is the summary, the Meta analysis part favoring the Sgl tues as preserving kidney function or protecting against progressive Ckb and glomerular diseases, and then, when you get down to the bottom here, this is looking at any glomerular disease. Not just ig, Nephrophathy, and let me be very, very clear.
- Inflammatory diseases on immunosuppression were excluded from this trial. So no lupus before this, no acrobesculatis, etc., etc. You see that there seems to be a beneficial effect of the inhibitors very quickly. Second to last slide. You could also potentiate in my day.
- We potentiated ras inhibition by adding an ace and an arm together until we found that when you do that in patients with advanced kidney disease and cardiovascular disease, they died probably because of Hyperkalemia, but still they were pretty effective at inhibiting the Renan Angiotensin system. So now we're much more interested in adding Aldosterone antagonism with an ace or an arm to try and more completely inhibit the ring and Angiotensin system. This was Funeranone, which is like Spirona lactone in a sans. It's now vastro and antagonist. But presumably with less hyperkalemic effects. And you can see here, that. This is what happens to placebo or patients with diabetic kidney disease on funer known. So there's a benefit now the human area. And then, if you look at this endpoint, which is a sustained decrease of over 40% in Gfr from baseline. Fewer patients in the Funeranone group actually developed that. And on the basis of these studies, funer known was recently approved for chronic kidney disease management. So I'll end here. I think when we go back to this idea that we want to stop and stage kidney disease and prevent chronic kidney disease we can say we have several new therapies for glomerular

disease. I would say their effects on how well we do on preventing end stage kidney disease remains to be seen. We have to learn how to use these drugs and how to use these drugs in combination. They all appear to at least slow the rate of Ckd progression. And I believe this is an important first step in reducing end stage kidney disease development. So a little bit late. Happy to entertain questions. Thank you very much. Thank you, Brad, for that terrific review and holiday all the recent successes. I have one question. Sure you know these diseases are heterogeneous yet in the trials we treat them as homogeneous diseases. Where are we with regards to biomarkers to identify some endopen effects? Yeah, so when, when we design trials. I went into designing trials with the idea that we would look at decreasing heterogeneity and no drug company wants to do that because they want the indication to be for everybody. So for obvious financial reasons which is wrong, and no one drug is going to treat everybody.

- Now, I think we're coming full circle. The problem is qualifying a biomarker to try and lead you in the right direction is is really difficult at the FDA. Okay, it's a completely different process, and it's very rigorous. We have one biomarker for glomerular diseases. I think you've all heard about pla and membranous nephropathy.
- This is about the best biomarker we have, and we put together trials for the FDA, looking at Pla, 2 positive membranous nephropathy, because this is a biomarker in which we can find immunologic remission by which kidney disease, the kidney disease remits afterwards after it heals and the FDA said, we don't want pla to our positive, restricted patients. We want it to be for all membranous. So the FDA is being a little difficult, in my opinion, almost the antithesis of precision. Medicine sort of slide one slide 2 is that many of us, including me. This is sort of what my laboratory looks at are really trying to define biomarkers that will help us segregate a heterogeneous lupus population into patients that are appropriate for the drug target. And if we can do that, my belief is we can do smaller trials because the likelihood of a delta would be much higher if you're focusing on patients in which that particular target is active. So I think we're partway there but we gotta get buy in from the FDA. And the answer is done a much better job at this. And right, I mean they just have. And but a lot of their biomarkers are genetic. And we're just sort of poking the surface of the genetics of our diseases.
- Yes I have a question from the chat from Jonathan Truitt. With the accelerated drug format approval. How did you deal with the ethical issue of maintaining the control group on an inferior regimen.
- So at the time there was equipoise because we did not know that we had Would have a Gfr benefit. Okay, so understand your question.
- And it's sort of relevant for Iga, because it's a very slow-moving disease. So most of us thought that even if the drugs were blockbuster drugs. we weren't gonna lose or put the patients that much at risk.
- Now his next question might be, or the person's next question might be, now that you have these drugs and you show benefit. Can you ever do a clinical trial in, for example, hyanthropopathy with placebo arrest and addition. Only that's a very difficult question, right? Because now the equipoise is gone, we definitely have some data which suggests that these drugs are beneficial. And so we really have to start thinking about redesigning trials to incorporate the new drugs. And I think that's okay. Because, as I showed you, the new drugs provide some benefit to Gfr. But they're not providing the benefit that we need. If you look at a recent paper from the UK.
- They did an exercise with a very large Ija population to actually preserve kidney function for Iga patients over their entire lifetime. So remember, this is largely a disease of younger people. They have a very long time window.

- You really need to get the Gfr. Decline down to less than one mill per minute per meter squared per year.
- You don't do that. So I think it's the ethics are gonna be take the new therapies and add to them and see benefit beyond that. So I think that would be my approach going forward.
- Yes, great talk. Thank you. So commented question. The comment is, it seems like with targeting the disease, modification, and the potocytes and pertinary. You're getting towards goal, directed medical therapy kind of like our cardiology colleagues. Thank you. Cardiology. The question is, I'm a transmit person.
- How would you reflect some of these things so often, especially the immunologic diseases, when they recurrent transplant, have already blown through the tech? Really, miss there on some steroids often, and so they seem to be a different beast. So you have immune, remediable disease that's already going past immunosuppression.
- How do you interpret this, and how would you?
- I'm not sure we know enough with the new drugs to have gotten those experiences yet.
- But, You know, when we look at the transcription mix of the glomerulus and the 2 learners, to some in patients that are brand new de novo lupus nephritis, for example. And then those who have sort of relapsed on or with tapering therapy, they're not the same.
- Okay. One of the things that decreases is the interferon type. One interferon signature. So W. What I would love to do, and we can't do this in clinical trials. It would be wonderful to do clinical trials into nova lupus, and then in relapse, Lupus, to see how these drugs work. I don't think that's ever gonna happen. It's just really hard to recruit but what I do think is sort of to Mark's point is, can we start to look at the pathways that are different in these immune educated patients, and then see what's still active. One of the things that we found was when we were treating patients with standard of care therapy and we looked at the we did protocol biopsies. So there's a biopsy of diagnosis. And we did the transcriptome. And then we looked at the transcripts. 9 months later, when patients either got better or didn't get better.
- It was remarkable. The interferon Alpha signature went away, and the ones that got better in the ones that did not get better. It was hotter. Okay? So you could say maybe now I come in with an interferon drug because I haven't treated them with an interferon drug at that point. The other thing that was really cool was complement. Signatures didn't go away in the patients that were not responding compared to the ones that were responding. And now we have anti compliment drugs. So the idea would be, can we do something at the time of the flair, or whatever you know worsening of disease, to try and see what are the remaining pathways that are active, and then come in with something more targeted to get those pathways. Specifically, I think that might be effective.
- I think we should close. But, Brad, thank you so much for a wonderful lecture. Alright, thank you. It's still very. That was marvelous.