and perhaps multinationally, and large-scale studies to dilute out the heterogeneity.

Dr. Gipson: I think it is important here that we talk about the FSGS minimal change pathology continuum, to sort of get you in the neighborhood. We really are not going to be successful performing 500 or 700 patient trials. That is not this disease. It is a rare disease. We recognize that. And the guess-and-check mode of continuing to throw medications at patients is really not where we should be in 2014. The goal here is to be more precise about that patient. The neighborhood is that you have a pathology in a certain range, and now let us think about what the real molecular phenotype of that patient is. What is their molecular profile that says, this is who I am today, regardless of whether I have minimal change, or FSGS, or perhaps diabetic nephropathy or hypertensive disease, what you really want to know is, what is the path that is active today that is causing difficulties?

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Podocyte-Targeted Treatment for Proteinuric Kidney Disease

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The story I want to share with you today started in 1994, when I was struggling to get my laboratory going. My friend Matthias Kretzler, who had been my anatomy student in Heidelberg, was a postdoctoral student in Josie Brigg's laboratory in Ann Arbor, Michigan, at that time, and told me about differential display polymerase chain reaction (PCR), which was the coolest technique at the time. On Josie's invitation, I went to Ann Arbor and learned the technique. Two years later, Jordan Kreidberg, a friend and colleague, had just published the α3 knockout mouse,[1] which was noted to have podocyte foot process effacement and proteinuria. Because we were interested in podocytes, Jordan and I decided that we would cross the α3 knockout kidneys to the Immortomouse to isolate podocytes out of kidneys from these mice.[2] This is how we were able to perform differential display PCR, which is how we discovered B7-1 (CD80) in podocytes.[2] This also is how we come to podocyte-targeted treatment for proteinuric kidney disease, the subject of my talk today.[3]

Before we continue our story, I also wanted to make another point. As we will hear from the keynote lecture, in the cancer field it is a given that tumor cells proliferate, but by now we also understand that there are at least 50 or 100 pathways that can drive proliferation of a tumor cell. In nephrology, focusing on the podocyte, we have been searching for a unifying, single pathway that drives podocyte injury and proteinuria. In my opinion, this is a false assumption that has led us down the wrong path. Although foot process effacement looks the same in many different models of disease, as well as across many human proteinuric diseases, I believe there are many

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distinct pathways, and I will share with you today one example that we discovered, namely B7-1–mediated podocyte injury.

If we accept the idea that there are many different pathways to injury, then this also means that therapeutic efficacy can be arrived at in a targeted manner: if you can detect the 20% of your patients, for instance, whose disease is caused by a particular pathway, then you can treat them with greater efficacy and fewer side effects. In this scenario, capturing 20% of the population with focal segmental glomerulosclerosis (FSGS), for example, is not a failure, but quite the opposite, a tremendous success in targeted treatment.

As we have already heard this morning, FSGS is not a disease. It is a histologic pattern that presents with familial, primary, and recurrent forms.[4] We think that podocyte injury is central to the pathogenesis of FSGS. As we all know, therapies for FSGS have been nonspecific, often ineffective, and fraught with side effects. Efforts to prevent or delay proteinuria and ensuing loss of kidney or allograft function also have not been successful. Relevant targets have not really been discovered, therefore drug discovery and development has been difficult. Within this space, there is therefore a great unmet need for podocyte-specific treatments of proteinuria and prevention of podocyte loss.

B7-1, also known as CD80, has been studied extensively in an immunology context by many investigators including Arlene Sharpe here at Brigham, who has been a leader in this field.[5] B7-1 classically is found on antigen-presenting cells, from where it signals to T cells as a co-stimulatory molecule, contributing to their activation through CD28 or inactivation through CTLA4. This is the classic paradigm.[5]

When our differential display PCR experiment back in 1994 showed B7-1 induction in α3 integrin knockout podocytes, I did not initially understand what it meant, and initially might have been inclined to dismiss it as an unrelated immune molecule. However, I was intrigued and we persisted, with confirmation by real-time PCR.[2] In our initial B7-1 report, we found that B7-1 is induced in genetic podocyte injury mouse models, including nephrin-deficient mice, but also after toxin exposure such as puromycin.[2] At the same time, we showed that podocytes have Toll-like receptors, and thus lipopolysaccharide and activation of TLR4 receptors also could induce B7-1, causing proteinuria. We also showed that this was possible in SCID (severe combined immune deficiency) mice, therefore podocyte B7-1 induction was independent of T cells.[2] These experiments established a role for B7-1 in the pathogenesis of proteinuria.

Interestingly, our immunology colleagues already had developed abatacept, a fusion protein containing CTLA4-Ig, which effectively can bind and inhibit B7-1. Abatacept has been used safely and efficaciously for the past 10 years for the treatment of rheumatoid arthritis.[6,7] Taking together the excellent safety profile of abatacept and the fact that our work showed that podocytes express B7-1, but not B7-2 (CD86), we reasoned that abatacept would be an excellent agent to treat B7-1–mediated proteinuric kidney disease.

In work performed by George Burke, an excellent transplant surgeon in Miami, FL, a pre-implantation biopsy and a postreperfusion biopsy specimen was taken from patients at high risk of recurrence of FSGS. In this experiment, B7-1 was induced in postreperfusion biopsy specimens in two patients with recurrent FSGS who already had failed efforts at mitigating the risk of recurrence with rituximab treatment. Based on these findings, the patients were treated with abatacept with good results[8] and all remain in either partial or complete remission up to 4 years after transplant. However, the four patients with recurrent disease had received many therapies, including plasmapheresis and a full immunosuppression regimen, therefore there was justified concern about our conclusions regarding abatacept. This brings us to patient 5 in our article,[8] who had primary steroid-resistant nephrotic syndrome owing to biopsy-proven FSGS. The patient was diagnosed at age 7 and had an initial biopsy that showed minimal change disease, however, as is often the case, two subsequent biopsy procedures performed because of her lack of response to steroids established the diagnosis of FSGS. The patient was given a number of therapies including calcineurin inhibitors with very limited effect. Her latest biopsy specimen in 2012 also showed signs of hyalinosis, which was concerning for calcineurin inhibitor toxicity. This biopsy specimen also was stained for B7-1 based on our experimental protocol and was thought to be positive for podocyte B7-1 expression. Therapy with abatacept was initiated in this patient, and was continued as monotherapy over the course of many months, which resulted in a durable partial remission.[8]

If I may make a comment here, when we discuss the difficulties in nephrology in terms of bringing new ideas to the clinic, one issue is the lack of communication between people such as myself, the scientists, and the clinicians taking care of the patients. Had I not had a close affiliation and collaboration with the clinicians in this case, this patient would have been very unlikely to receive the off-label use of abatacept for primary nephrotic syndrome.

This patient is now at 600 days past abatacept initiation and continues to enjoy a durable remission on monthly infusions of abatacept monotherapy. The patient, and that comes back to what Dr. Debbie Gipson mentioned regarding patient-reported outcomes, is for the first time in her life feeling well enough to be optimistic, to work full time, and live a full life.

Now, let me come to the issue of biomarker development around B7-1 detection to support clinical decision making and to enable clinical trials. In collaboration with