

## **Dean Goldschmidt's Interview with Norma Kenyon, Ph.D.**

**November 17, 2008**

**PJG:** Welcome. It is good to see you Norma.

**NK:** Good to see you.

**PJG:** So tell me a little bit...how did you decide to do what you are doing.

**NK:** That's a complicated question. I guess I first fell in love with immunology when I was at Duke as an undergraduate and took an immunology course and I liked it a lot. It was the hardest course I had--was not my best grade, but I really enjoyed it and when I graduated, I was offered a job at Duke in one of the immunology laboratories. I had moved to Virginia and I actually went to work as a tissue typist at first and, believe it or not, I was looking for an HLA association between Type 1 diabetes and rubella at the time, never knowing, of course that diabetes would end up playing a big role in my life. After a couple of years of working in the lab, I wanted to do more, so I went to graduate school in immunology and my true love really was immune regulation. How could you boost the immune system if you needed a better response in cancer and in HIV and how could you turn it off in the setting of an autoimmune disease or get a graft to get accepted. I was a post-doc at UCLA when I was looking in the back of *Science* and saw an ad to study Type 1 diabetes and I got really excited because where else could you look at immune regulation more intensely: transplant rejection, autoimmunity. So that's when I came to DRI, the Diabetes Research Institute, for my second post-doc. And the DRI at the time, I used to laugh, because the "institute" was a corner on the 7<sup>th</sup> floor of Rosenstiel, and that is where I learned about islet transplant. I had projects in regulation and islet transplant, trying to get grafts accepted, prevent recurrent autoimmunity and ultimately I ended up going into industry for a few

years because I had a baby during this time. I never saw her, it was a day and night job. Industry was great—twice the money, half the hours, but I got bored and I needed the challenge, so I took a pay cut and actually became a junior faculty at Duke. I had traveled to the lab to see how renovations were going, and when I went to the airport for my return trip to Miami, I called home and discovered that my 14-month-old daughter went into a coma with the onset of Type 1 diabetes. So, I got on an airplane, expecting never to see her alive again, and she is 16 now. After that happened I stayed at Duke, but I was looking—I wanted to go back to islet cell transplant. I wanted to go back to Type 1 diabetes, and I called the Institute. Dr. Ricordi had just been recruited there and I came back. It's been almost 15 years.

**PJG:** And so, tell me more about what happened to your daughter... remind me of her name.

**NK:** Laura.

**PJG:** Laura, so Laura had one of these presentations where the first manifestation of diabetes was diabetic coma.

**NK:** I left on a Wednesday and she was fine. I had just accepted the job at Duke and I was actually traveling to Harvard to meet the laboratory that was moving to Duke, so I called it my triangle trip... I'd go to Harvard and then I'd go to Duke, and then I'd come back to Miami.

**PJG:** So the team from Harvard was being recruited to Duke.

**NK:** Yes.

**PJG:** And you were being...

**NK:** I was being recruited to Duke. Right, so I was at Harvard, then at Duke and I got a phone call that she had a cold, and being a Mom, I was on the phone every day asking... how is she, how is she, and apparently there were symptoms that were missed, so by the time it was caught,

she was already in a coma and not expected to live. She was only 14 months old so I guess the reserves aren't that great and as it progressed she got very ill.

**PJG:** It must be more difficult at that age because when children are older, parents notice there is something going on because their child needs to get up at night or is losing weight, etc., but with a young child it must be extremely difficult?

**NK:** I think that probably it is because of the age, because when I left she was fine, she wasn't soaking the crib or anything like that and obviously she had had it for a while, she had a very high A1C but none of the symptoms. I noticed the day I left that she seemed a little thinner but she was also taller. Of course, I called the hospital expecting to hear that she had meningitis or pneumonia. I called home and my babysitter, who spoke no English, told me she was at the hospital, assured me she was fine, and of course, I didn't believe that and that was before cell phones, so it took me 20 minutes to get through to her bedside. I had to keep using a calling card, they kept passing me around and I expected meningitis, pneumonia, never, ever did it occur to me that she would have Type 1 diabetes.

**PJG:** And again, if I recall correctly, that is a little bit on the younger side of kids who develop Type 1 diabetes.

**NK:** Oh yeah.

**PJG:** Did she ever have what we call "the honeymoon?"

**NK:** So after she got through that crisis, she did go through the honeymoon phase where, it killed me, but I would inject her with 1 ½ units of insulin a day—and she needed it, and then it slowly progresses, and as an immunologist, that is torture, because you know there are beta cells and they are just slowly going away.

**PJG:** For those individuals who are not experts in diabetes, can you explain just a little about Type 1 and Type 2 diabetes and why Type 1 is so devastating when it happens in kids and we start to slowly see more Type 2 in kids because of the obesity epidemic, but it's still, by far, the Type 1 that is affecting most children.

**NK:** And they are both on the rise. Type 1 is also on the rise especially in young children.

**PJG:** Interesting.

**NK:** So with Type 1 diabetes, it's an autoimmune process in which the body attacks and destroys the insulin producing cells and without insulin, we can't utilize the food that we eat. So even though you are taking in the calories and the sugar, your body can't metabolize it and you start losing weight and of course, there is frequent urination, excessive thirst. She didn't have any of those symptoms before I left—she did afterwards, but she did experience a very rapid onset. I think at that time, I had never heard of a baby getting Type 1 diabetes. Now I hear about it all the time, probably partly because of where I sit, so a lot of people, while we were in the hospital, told me, “well, she'll grow out of it,” “this is no big deal,” and of course I knew better because you don't grow out of Type 1 diabetes. If you lose weight and exercise, you may reverse Type 2 diabetes but with Type 1, the cells have actually been destroyed by the immune system and unless we discover some new growth factor or can replace them with a transplant, they are not coming back. We were in the hospital for three weeks, I only left one night, my sister had her that night, and it was a completely different family when we left. I had a "new" baby, everything changes and of course, at that time, I didn't know families with diabetes and I've heard many families say this now, that you're in the hospital, you're in a state of shock, they tell you can't leave until you give the shot. Back then, the education part was very weak, so my education was, “here's an orange, you have to give her a shot before you can leave,” and I was

still squeezing diapers to get glucoses. The glucometers weren't nearly as good as they are now, we didn't have fast-acting insulin or long acting insulin so it was almost impossible to control with the type of insulin we had back then. Her blood sugar was either 40 or 500, just incredibly bouncing around, so it really changes the whole family. Once you have a child with diabetes, you are trying to understand how to take care of them and help them deal with it so if there are other younger children in the family, they often feel left out or ignored and these are things you don't realize while you're coping with having a child with diabetes, and I've heard that pretty commonly—that you have a new family, you're starting over... it's a big change.

**PJG:** Do you think that is true at any age or do you think it is particularly true when it's a very young child?

**NK:** I think it's particularly true when it's a very young child, because I ask all the parents I meet, of course. If it's a child close to 10 or thereabouts and they have an older sibling, often the older sibling can be drawn in and be engaged in the process of taking care of them and learning about it and I think that helps a lot. In my case, Laura's sister was only three years older, so you know being 4 years old was pretty confusing now to have everything change and all this focus on the baby. With babies, you can't even talk to them and ask them how they are feeling or ask them to eat something. So yes, I think there is a huge dependency on age, and support systems are so much better now, people are much more aware.

**PJG:** And I know that you are a huge part of the support system at UM because I have a personal friend who found out about the fact their kid has diabetes and they absolutely marveled at the way you talked to them about what would happen to them. First, they were amazed you knew so much about their life because you could tell them exactly what was going on with them

without them telling you and then how you prepared them for the next stages. They describe it as life changing...

**NK:** Thank you.

**PJG:** ...to have an opportunity to talk to someone like you. You have done so much for other families.

**NK:** Well, thank you. I was fortunate too, when Laura was hospitalized, two young mothers heard about her—not scientists. Their babies had also been diagnosed and they actually came over to see me and hold my hand, and just tell me that I'd make it. I've never forgotten them. I still see them periodically. So, I know what it means to have someone there and what I try to do, first of all, is say that it hurts and it's going to take about a year—it takes a year to come out of the fog almost, to really accept it and move on. I mean you go through so many changes. Just when you think you've got the glucoses regulated and you know how much insulin... they change, because they're growing and of course, puberty is a big change and as a parent, I can talk about the younger stages, but as my daughter gets older, I consult all the parents I know that have already been through that because teenagers and diabetes aren't a very good combination, so I have asked for lots of advice myself and I hope I can be there for other people when they need it.

**PJG:** That's fantastic and thank you so much for doing that. So let's go a few years back. So here you are a crackerjack young immunologist, who is going through the steps of an academic career, as a stellar individual and you happen to be working on immunology core processes and you have a child whose beta cells have been destroyed by the immune system. Did you have a revenge to take on immunology—what was your professional feeling at the time?

**NK:** Frustration.

**PJG:** Yeah, I can imagine.

**NK:** Outright frustration and I have had the privilege of working in several NIH consortiums now, dealing with trying to prevent diabetes, treating it at risk, transplantation to cure it, and still the immune system evades us. We've got so many improvements, and we can prolong the honeymoon period, we can transplant and give the patient several years of enhanced function and better quality of life but still that immune system is outpacing us and one of the things I like about working at the DRI with Camillo is that we have the option to start new things that you wouldn't be able to do anywhere else. Whether you want to start in a small way--some drug discovery or you want to look at a new cell type. So, I think the biggest frustration in Type 1 research really is how do we safely stop the immune system, and we're getting closer and closer, but we need more hard work with a little bit of luck before we get there.

**PJG:** That is fascinating, because of course, about at the same time all this was going on there was an epidemic of AIDS that was devastating the world as well, which as we well know, is associated with the total destruction of the immune system and that, of course, comes with substantial consequences. I am just wondering between an immune system that turns against itself as in the case of Type 1 diabetes or an immune system that falls apart, what is the most significant challenge that needs to be tackled? Probably both are just as complicated and difficult.

**NK:** I think they are both complicated and difficult. I think as far as therapies, we've made great progress with both for maintenance therapy and keeping people relatively healthy, but I think they are both incredibly challenging and actually one of the things I like about... I call it immune regulation... I don't call it that on a daily basis, but if you can figure out how to turn it off, you can probably figure how to turn it back on. Of course, there are several people at the

University of Miami, working in different areas, looking at genes that turn the immune system on and off. So when I work with my colleagues in the Cancer Center or viral immunology, to me they are all connected in some way, so I feel that if I find—we're looking for small molecules that can block co-stimulation, turning on the immune system, and if we find, during this process, we may find some that block the pathway we want, most likely we'll also find some that turn it on and then we turn around and offer it to our colleagues in other areas where that would be an advantage, but I think that both are equally difficult.

**PJG:** Yeah, I know I totally agree with you. Of course, the drama with diabetes Type 1 is that once it is discovered, as in the case of Laura, the process is already going on and there is substantial damage to the islet cells, if I remember correctly, you need destruction of certainly more than 50% of the cells and maybe more than 75% of the cells by the time...

**NK:** Right, before you show.

**PJG:** ...symptoms manifest, and what I'm wondering is would there be an opportunity... so we know that the heredity of immune illnesses is a little bit special because it is not that specific to immune disease that everybody would have in the family, there is a susceptibility to immune illnesses in the family and I am just wondering whether we could become very good at predicting a susceptibility for developing that type of illness and then once the trigger comes, there would be already, in place, a preventive process that would prevent that process from going forth. Is that just dreaming?

**NK:** Oh no, not at all! I am a firm believer in that. I think a couple of things: I used to think that the reason we're seeing, very naively I might add-- so we don't have to write that down, that the reason we see so much more Type 1 now is because insulin was discovered in the 20s. If there was a young child with diabetes, I doubt they even knew what happened before the child

died and now people survive, so I figured that the genes that predispose diabetes are increasing the population, but actually, not too long ago when David Hafler visited the Vances, we were having a conversation about that and he said, “no, no, no”, because he’s really been getting into the genetics. He said, “there hasn’t been enough time for it to be a genetic effect—its environment.” So having said that, we know there is a strong genetic predisposition. My daughter has textbook HLA genes, HLA DR3 and DR4. So we have to identify a genetic predisposition and we know from the diabetes prevention trial and Type 1 diabetes TrialNet that you can predict people at high risk for developing diabetes. Right now they take an individual who has a sibling with diabetes—they look for autoantibodies. If you have two or more autoantibodies, and the appropriate HLA susceptibility genes, they’ll do a metabolic challenge. If you have already lost your first-phase insulin release, then they know with high probability that within five years you will have Type 1 diabetes. So you can predict it so far, in families that have it, but I think that certainly there have to be molecular signatures that, and in fact, I am doing some initial work in that area, that if you have someone who is at risk, how do you know that they are actually turning the corner where they will progress to disease. What I don’t know exactly is how to figure out all the environmental influences on the genes. I’ve heard the Vances talk about that—that there are newer ways emerging to look at the affected genes versus environment, but you can have twins, one of them can have Type 1 diabetes and there is only a 50% chance that the other twin will get it, so there is a strong genetic component and then the environment, but if you could have gene expression changes that suggest a progression, and I am a very firm believer in that, for not just Type 1 diabetes, but other autoimmune diseases...

**PJG:** Wow, that’s terrific and maybe a genetic impact in the way we have been able to help all patients with autoimmune diseases is actually more likely in total to impact upon the disease

epidemic because there are many more people with autoimmune disease in general than diabetes, in particular. Now, going back to your work specifically, your most quoted paper was about transplant and the field of curing diabetes and that is what everybody wants.

**NK:** That's what I want. I would say there are quite a few people that want that as well, and ideally, to prevent it.

**PJG:** My recollection is that what you brought to the field is not only a transplant approach, but also a protection of the transplant cells by creating some immune tolerance for these cells through modulation of the immune system.

**NK:** Right, I don't think that our animals were actually tolerant, so if I was a mouse scientist, my animal would go 100 days without immune intervention and then they would say it is tolerant. I'm very rigorous, I had an animal go 1,000 days, but eventually it lost the graft so it wasn't quite enough for me. It depends on how you define the word, but clearly the reagent we were using with one dose a month and very low levels in the blood—the animals maintained beautiful function and didn't suffer from infection.

**PJG:** Can you tell people about that molecule?

**NK:** That was quite a period of my life. I was actually communicating with a gentleman at NIH, Dr. David Harlan. I had met him at an immunology meeting in a very strange way. I have always worked in clinical models and Dave Harlan was working on a mouse model at NIH and he was looking at co-stimulation. So the T cell has to see the stimulus that turns it on and that eventually will kill, but then it needs a second signal called co-stimulation. So I was trying all kinds of approaches to prevent islet rejection in non-human primates and nothing worked. And actually, no one had ever gotten it to work. There had been some transplant

people who could get mice to survive, but as soon as you went up to a larger animal model or human, it didn't work. So, my passion was, "how do we translate this--how do we make these things work in preclinical models?" So this individual happened to see another scientist in our Institute, Ricardo Pastori, cloned and published a larger animal CD44, an adhesion molecule, so he wrote asking, "Is there someone in your Institute working on a larger animal, preclinical model—it was very rare back then that anyone was doing anything other than mice, and it was a struggle, I can tell you. The letter got passed on to me and we made arrangements to meet at the poster session at an immunology meeting and we kept communicating back and forth and one day in frustration I e-mailed him, I said, "You know, I'm really frustrated. Can you think of anything different, anything that you've heard of?" And he e-mailed me back and he said there may be something, and I knew this person well enough that I just had a feeling, and what it was was a molecule being made by Biogen that blocked the CD154 molecule which, when a T lymphocyte, which is the ultimate destructor of a transplant, when it encounters its' stimulus, it rapidly and transiently up regulates CD154 on the cell surface, and so it's an activation marker and it goes away very quickly. Only the cells that are stimulated would express it. So it's not a global activation marker, it's not a pan T cell marker. One of our problems is that we can turn off T cells, but usually, it's like a sledgehammer approach where you turn them all off and then you are more "at risk" for infection and cancer, so we are very excited to potentially try this in an islet model. Up until that point, I might have gotten insulin dependent animals for two weeks—they always rejected no matter what I tried so we were able to start a collaboration with the National Institutes of Health and with Biogen to get access to this antibody. We were able to show that by giving five doses around the time of transplant and then one dose a month, that we could keep the monkeys insulin independent with like-stable blood glucose levels for as long as

we treated and we were excited that maybe if we stopped, they would become tolerant. They all ended up rejecting within 100 days or more after stopping drop therapy. Interestingly, the longer you treated them, and then stopped, we had animals that would keep function for 500 hundred days and I had the one that went for almost three years without evidence of rejection. So we are getting close. Now back then, I had two young girls and I was working 100 hours a week because I believed, with every molecule in my body, that Laura was cured and that all these other children and families were cured and I actually found out from an Internet release, from the head of our Foundation, Bob Pearlman, who walked into my office and showed it to me that they had discontinued the trials because they had seen thromboembolism in about 10% of patients being treated with the antibodies in different indications: lupus, ITP, and that was devastating because once the company saw that, they would not even let us continue the work in the non-human primates because anything that happens in a monkey has to be reported to the FDA. Interestingly, in over 40 transplants, we never saw a single clot. They were calling me every week, asking what I did different, I sent tissues. One of the things that's different is that it's a cellular transplant. You don't have reanastomosis like you do with the kidney, and the furry patients weren't hypercoagulable, but we never had a problem and we were really hoping we would be able to use it with the appropriate anticoagulation therapy but it didn't happen. So for many years, a lot of scientists said, "You'll never use this clinically; it's dead—you shouldn't even study it experimentally." I felt that, not only has nothing ever worked that well before, and not since—nothing has worked liked that. The really striking thing, not even immunological, the first evidence that islets can last long term—not only can they last, but unlike what we see clinically, they actually increased in function over time, until the animal met the level of function it had in its own native pancreas before we induced diabetes. So if you have the appropriate,

effective anti-rejection agent and it's not diabetogenic, you can actually enhance the individuals' response up to the level they need to be regulated appropriately.

**PJG:** Because you showed earlier that a classic drug used for transplant rejection like cyclosporin A is actually a potent diabetic that it damages.

**NK:** It's potent for a third of kidney patients, and FK-506...I think all of them have some impact. We actually had a normal animal we treated with steroid free, the thinking was always that it's the steroids we use in transplantation that adversely affect islets and that is true, but as it turns out, the steroid free immunosuppression with calcium inhibitors like cyclosporin A and FK also appear to be diabetogenic and that's actually been shown now, not only the effect of the drug on the islets that people have published—that if you put pregnant animals, for example, on rapamycin it'll inhibit proliferation of the cells in the developing fetus, so good to avoid these drugs.

**PJG:** I've always been surprised that beta islet cells are in the pancreas. I mean, you know, one may challenge the location, in terms of its suitability, and sure enough to be native of an organ that produces some of the strongest enzymes that can digest anything...

**NK:** Right.

**PJG:** And it's kind of an odd idea. I know that your transplant was done in liver tissues, if I recall correctly.

**NK:** They were transplanted into the liver.

**PJG:** And that's a much more welcoming tissue, to some degree, but one wonders whether that's one of the reasons why the beta islets cells are so challenged by the immune system—is because of that kind of odd location... you're pretty recognizable when you're a beta islet cell in the middle of the pancreas. I just wonder if the basis of the rejection that leads to diabetes in the

first place could have something to do with a finding that—I think that came first from Antony Rosen at Hopkins, where he was looking at dermatomyositis as another autoimmune process and found out that actually and this more of a hemo-rejection with antibodies and things, but what he found out is that the target cells are primarily not the muscle cells, in the mouse islets but the precursor cells and so muscle cells you know get challenged and die from time to time, and need to be repaired, etc. by the satellite cells, but the fact that makes the disease so dreadful is that the precursor cells that repair the muscle cells actually targeted by the immune system. I'm wondering if there is a precursor to the beta islets that may be targeted by the immune system when diabetes...

**NK:** I've never heard anyone ask that question. We are always looking for those precursor cells, but I have never heard anyone actually address that. I would have to ask Camillo too, but I don't think anyone has looked at that. There is newer data and actually I have talked to Dalton Dietrich about it some, that Schwann cells, that the neuro cells surrounding the islet may actually be a primary target, maybe if you have precursors—it has been argued where they are, there have been publications that even people that had diabetes for 70 years, at necropsy you could see that there were scattered insulin positive cells trying to make a comeback and so I don't know—that's a very good question.

**PJG:** Truly fascinating.

**NK:** Because anything that tried to come back would also get nuked, so very good question.

**PJG:** That's the thing that is so... the uniqueness of autoimmune disease is that for disease that not necessarily has to do with a specific infection or something you get from the environment necessarily, although there may be a component of that environmental attack, is the fact that they usually affect younger people, you know the typical autoimmune illness affects a young to

middle-aged woman and that is very different from chronic illnesses, which have a tendency to develop at increasing age and age is a major risk factor for them, which is not the case for an autoimmune disease. So the fact that the young have a great repair process going on in all of their tissues and therefore chronic illnesses have no chance to take over at that time. If you destroy the cells responsible for the repair, then that may explain the fact that they occur much earlier in life. So it's something that again, we've seen that it's the case in dermatomyositis, interestingly, looking at the process of scleroderma, Dr. Chunming Dong, who is now at UM, found that endothelial progenitor cells in that case, it's a disease where you have negative vessel balance, which is very puzzling, the endothelial progenitor cells are the target for destruction. The skin of patients with scleroderma is very able to trigger an androgenesis reaction, but somehow...

**NK:** So it must all be linked—and I wonder about this, I'm not equipped to understand all the science, I'm trying...but what is the link between injury and repair. Therein probably lies, you're right, somewhere in that pathway, may lie the answer to many of these diseases especially if there is a viral infectious etiology that can damage that way too.

**PJG:** Absolutely, that revs up the immune system and there you go. But sure enough if you can't repair tissues with progenitor cells, it really seems they degenerate much more rapidly, whether brain or pancreas, beta islet cells. So how do you think we're going to cure diabetes?

**NK:** Diabetes? To cure it, I do believe a biological replacement, at least some threshold and then if we can effectively turn off the immune system, your body may be able to bring up the level of cells to what we need. I've had arguments with people that think if you can stop immune response and give growth factors, that you can regenerate and cure, but I think when you're that depleted, you need to have a boost. Honestly, I think that, and I'm sure Dr. Ricordi

will talk about his new idea with local delivery of immune intervention since the systemic part has been so challenging. I really think that pathway we were studying several years ago when we showed that it is possible to get islets to graft over the long term and not only survive but increase in mass over time, a very interesting pathway and we actually—it's small, but we started a small drug discovery program specifically looking at that pathway

**PJG:** Phenomenal.

**NK:** And we've made some progress. I'm not the scientist in it, I'm just the driver—his name is Peter Buchwald. I think if we can find the right agents to safely turn-off the immune system, then we need cells—we need some kind of a threshold mass to get the jump-start and I think they will regenerate on their own if we can turn off the immune response.

**PJG:** And so the problem with the drug that was providing you with that opportunity was thromboembolic complications.

**NK:** Yes.

**PJG:** Has anybody tried to identify with a GWAS type of approach, individuals that would be susceptible for thromboembolic complications.

**NK:** To my knowledge, no one has done that. CD40 ligand is expressed by activated endothelium and platelets and there is a lot of soluble CD40 Ligand in the serum so people tried to understand the mechanism and it's given at a very high dose, 20 mg per kg, so everybody always felt that it had to do with the Fc receptor of the antibody so attempts were made to have a glycosylated or modify it, make a single chain, but as it turns out it was important for the efficacy of the antibody so I keep that in mind as we try the small molecule approach because you don't know if the antibody structure is important for depletion or modulation—then a small

molecule may not work, but no I am not aware of anyone doing GWAS studies. Back then, they weren't so predominant as they are now.

**PJG:** No, that's true. What is the thromboembolic complication that was noted, by the way.

**NK:** So, some of them were right away and some were delayed. I'd have to go back and get all the technical names for you.

**PJG:** Were they arterial or venous?

**NK:** There were both so it wasn't something that they could pin it on.... All of the patients, however, if you look at it, they either had anastomosis for an organ transplant or they had a disease where they might be hypercoagulable, like lupus or ITP, so we are the only ones that never saw it. Even in the animal transplants for heart and kidney they saw these clots. The other interesting thing it seemed to be very epitope-dependent. So there were several antibodies made but only one was as effective as the one we tried—so effective as a matter of fact and so powerful that now, after all these years have gone by, now everyone has agreed that the NIH should produce the antibody again so people can study it and try and understand why it worked so well. I always thought that, but the vast majority opinion was “no, it's a waste of time”, but there hasn't been anything else that even comes close.

**PJG:** That's what genetics are for, right? We studied the human genome for that specific reason. I can tell you that in the field of cardiology for example, drugs as common as statins can induce, in very rare cases, a very bad muscle disease that can lead to rhabdomyolysis and very recently there was a beautiful paper published in *The New England Journal of Medicine* where they have identified a gene that accounts for 60% of the variance of the susceptibility to that specific side effect, which is extremely rare.

**NK:** What's the percentage of people that had that side effect.

**PJG:** You know, there are two side effects that you get with statins, primarily. One is the liver challenge, which occurs in about 2-3% of the patients. The muscle disease is 10-100 times more rare and again... if you have muscle pain, etc. you should stop taking a statin, but so many people develop muscle pain.

**NK:** As you get older, yes.

**PJG:** ...this actually identifies the patients who are homozygous--have substantial risk.

**NK:** How many patients do they have to study to see that?

**PJG:** You know, not so many because actually 25% of the homozygous develop it so it's not like it's a rare instance in that group of patients. Now, the people who have that...

**NK:** Out of the total it's not much

**PJG:** ...are very rare but if you have it, you have a 20%...

**NK:** It sounds like Type 1 diabetes, if you have a certain predisposition, you won't necessarily get it, but out of the people that have it, a high percentage have a certain genotype.

**PJG:** And of course, it turns out to be a gene that codes for a molecule that modifies the metabolisms of statins and so the interaction of statins with liver cells...and so it makes sense that it would do what it does, but it's the kind of finding that tells us, "Okay, so we're getting there", so if that type of antibody could be resuscitated and then try to find out, where...because animals would also get thrombosis, from what I understand...

**NK:** Yes, they do.

**PJG:** So try to see if there is a group that would be more prone than others and identify the genes that are involved

**NK:** There might even be archived samples.

**PJG:** ...substantially reduce the exposure of those individuals.

**NK:** See, that's something you've brought to this University. I've struggled for a long time trying to get the genetic molecular part in there and thanks to you and all the people you've brought here, we're finally going to be able to look at those things.

**PJG:** It's a team effort.

**NK:** It's a team effort, but I think you started the ball rolling.

**PJG:** ...you contributed too, but it's an opportunity that we can't glance over. I mean it's too important. In life, the best thing we can do is to predict, right?

**NK:** I don't know if you are aware, we actually have published in monkeys and humans gene expression changes associated with rejection, predicting rejection.

**PJG:** Fantastic.

**NK:** Because when, by the time the patient becomes hyperglycemic, it's too late. Most of the islets are already gone. One day one of my dog transplants, years ago, would be completely normal, and the next day 500, and C-peptide, you know, it doesn't change until that happens. So we actually saw a paper that was published showing changes in gene expression in mice and people that were experiencing immune mediated kidney transplant rejection vs those that had non-immune related loss.. I was just talking to the Vances with Camillo about this, they wanted to confirm that an elevation of creatine was an immune-mediated rejection and not something else, because if you decrease—if you think it's rejection and you give extra immune suppression and it's actually a viral infection, you're putting yourself at risk, so they looked at cytotoxic effect for gene expression, urine and blood of human and mouse kidney recipients and they showed they could confirm immune-mediated rejection. Well, I read that and I said wow, I wonder if you could predict? So we started trying to work at it and in our patients, and we don't have that many, it looked promising, but nothing we could really grab onto, so we took four

monkeys that were actually finishing this anti Anti-CD154 study and discontinued the drug and we followed them serially, and we were actually able to show that you could predict impending rejection by several days and then we also showed it clinically. The only problem is, what all my colleagues challenged me with the first time I presented it, British scientists got up and said, “Well, Norma that is all very well and good but what will you do about it?” and we don’t have the best immune intervention agents to turn it around, but we do have ways of predicting rejection and what we really need to do is expand the panel and try to better distinguish between rejection and infection because these genes also go up with URIs.

**PJG:** But, can’t you do what people do for other organ rejection, which is to try to knock down the immune system for a little while at least until...

**NK:** Yeah and we try, we just don’t have that many drugs that are effective and so actually our new trial that is starting will be the first time that we prospectively look at this in a clinical trial, I’ve been in so many consortiums where we try to understand what’s going on in the immune system... take a snapshot, is the patient progressing to autoimmunity or progressing to rejection, is the therapy working? So, I’m in Type 1 diabetes transplant islet consortiums, and I am the mechanistic chair, and the bottom line is you plan a trial like this and you say, okay, I’m going to get a sample pre-treatment, three months, six months, nine months, twelve months, right, and if you look through the literature, related to diabetes whether it’s prevention, treatment and onset transplantation, it’s full of papers trying to make some kind of association between some immune assay and the patient status and you can’t find anything consistent. Why? Well the cells come and go from the blood and we’re sampling blood and every patient progresses at their own rate. So, if I take a three month sample, I may or may not catch the cell I’m looking for in the blood, it may not be there, so I have this idea actually years before all this other stuff started

coming out, but I didn't have the sophistication we have now—I just had three genes I was looking at so now we're actually going to use the molecular flag. If we see it elevate, because the data is very strong, it's held up, then we will get another sample, confirm it and at that point, we're going to get our bigger cell-based assay that's more labor intensive and determine is this autoimmunity, is it rejection, what's happening?—because I think you know, like I said, if you take that sample at six months you don't know where that particular patient is and that's why you never get statistically significant correlations so we actually use the molecular flag to divide each patient's clinical status: molecular, negative, clinically stable. They actually become molecular positive, they increase gene expression for cytotoxic effector genes before there are any clinical symptoms, it goes up and it's not until you can't detect it in the blood anymore that now they go back on insulin. Because why? I think, and I would love to do imaging studies on monkeys, I think the cells are in the blood as they migrate to the transplant and the sensitive molecular technique that we can do more frequently allows us to see the cells come and go from the blood. If the signature is there, the cells are there, and it is when they are gone that you're in trouble because the cells are in the transplant site mediating destruction - we've actually seen this over and over again in monkeys and people. Once there's significant graft loss and they're back on insulin or hyperglycemic, now you get a huge spike in gene expression, I guess, as the cells egress back out of the affected sight. I don't see any reason that that can't work for autoimmunity and therapies for autoimmunity or other diseases, but it's just, our technique is unsophisticated because it's only three genes and we've tried to expand the panel, but really you need to go to a higher level. Since then a group out of Stanford has published a signature that they associate with graft stability and I guess Harvard now is getting data also saying that they can predict. We did that for islet.

**PJG:** That is a fascinating area.

**NK:** I know you like that area—I do too.

**PJG:** And tell me, so how many new children develop Type 1 every year?

**NK:** Oh my gosh, you know I don't know the actual answer, I do know that the incidence is going up dramatically. I know one endocrinologist in Palm Beach, actually Hollywood, who sees six new cases a week.

**PJG:** Wow.

**NK:** But, there aren't very good numbers on that. I'll go to New York—and that's the other reason I think that the environment is playing a strong role. You see these clusters of kids, for example on Long Island, in a ten block radius or at a school, and so I think that genetics is really strong, but that environmental piece...

**PJG:** No question...

**NK:** Is playing a huge role.

**PJG:** And so Laura is?

**NK:** Sixteen.

**PJG:** Sixteen and how does she feel about it?

**NK:** She hates it... like any kid that age. She doesn't want to think about it, which is a challenge for a parent who is trying to get their...we can't say anything about that; I'd get into a lot of trouble, but she obviously would not like to have diabetes. She said to me once when she was younger and she'd see me in meetings to discuss projects and things and we went home and she said, "Mom you're not going to cure diabetes in a meeting, why aren't you in the lab?" Hard to argue.

**PJG:** But she knows that you're going to cure it, right?

**NK:** She's funny. She actually started telling people, "Well, ask my mom about CD154." I think she worries we won't. Phil Lansman, from NPR, asked me "will this disease be cured?" Actually his child was just diagnosed and I said without question we will do this. I just can't say when. Dr. Ricordi probably will because he says if you don't believe it can happen in the next year, you shouldn't work for him and he's right, but I don't put a timeline on it because of what happened. I know what can happen, that you have to have a prepared mind, you have to have the tools, and some serendipity, but absolutely it will happen.

**PJG:** I totally believe it and I think that the world is very lucky for having someone like you.

**NK:** Thank you-- likewise.

**PJG:** ...and your talent and you know, your unique understanding of the disease process for having lived it through two people. It's very rare to have one individual that has two experiences with diabetes.

**NK:** And you know the monkey model that I developed and then taught everybody? I don't think I could have done it if I hadn't had an infant with diabetes. I really... there was no model like that and that's what gave me the background and the drive to develop it.

**PJG:** Amazing. Well listen, on behalf of the Miller School of Medicine, I want to thank you for the work you are doing.

**NK:** Thank you.

**PJG:** And we are very lucky at the University of Miami for having you and your team, for being there to find a cure for this disease and I know that Laura is right—that you're going to find a cure and that you know, the spark may happen when you are at a meeting but the reality will be in the labs of UM, so thank you for everything that you are doing. The Diabetes Research Institute is just, you know, a formidable bastion of science and the people that you have

brought in as your team are second to none, so carry on and thank you for everything you do.

Thank you, Norma.

**NK:** Thank you.

**PJG:** Take care.