

Dean Goldschmidt's Interview with Camillo Ricordi, M.D.

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PJG: So Camillo, I thank you very much for doing this. It's an honor and a pleasure to have such a distinguished scientist to talk about his work. Before we go to a more scientific level, I was just hoping you would tell us a little about your life...born in Italy...

CR: At least the part that can be reported.

PJG: ... which is also a wonderful country and then coming to America as a surgeon, to find a cure for diabetes Type I. It's such an amazing story. I was wondering if you could tell us, what in your upbringing got you to become who you became and the drive to succeed.

CR: I have to say, that the first big decision was that of not following the family business, which was the music business, for the generations who preceded me for a couple of centuries in Milan. So the second key factor was most likely the willingness to take chances and be very mobile, willing to move to wherever there was the best opportunity to be productive and learn/contribute the most. I was born April 1, 1957 in the United States at Doctors Hospital in New York City. At that time my father was working at the Ricordi offices in New York and was learning the newly emerging record business that transformed the music industry. My two "Godfathers" in New York were conductor Leonard Bernstein and Earl McGrath, who was from what was then considered by some the "dark side of music" and who eventually became the president of the Rolling Stones while I was a teenager. I grew up between rock and roll and classical music. Some say that a lot of exposure to music may influence your brain's development. Growing up I spent a lot of time sleeping in a box at Teatro alla Scala in Milan or in recording studios, this might have helped to develop some creative parts of my brain (or

damaged them ... I am not sure). I'll have to ask the Vances to do a control study for that. At the time I was in high school I wanted to do astrophysics or physics. I was pretty good in math and physics and I was already following university level courses. I finished high school with a "perfect score" on our SAT equivalent of one week long exams and that summer I started reading a book by Sir John Eccles, *Understanding of the Brain*, that completely changed my orientation and my life, as I decided to start medical school to eventually go into brain research. After reading that book I thought that the universe was actually within ourselves, as there was still so much to be explored about the universe that is our brain, including all of the potential still untouched, which we do not use. During the second and third year of medical school I started an internship in neurophysiology at the CNR, which is the Italian equivalent of the NIH. It was around that time that Professor Guido Pozza, the father of Italian diabetology and scientific director of H. San Raffaele Institute in Milan, convinced me that you cannot go through six years of medical school (that's the length of medical school in Italy) without actually doing an internship in a real medical department. So during the fourth year I moved to H. San Raffaele for an internal medicine and diabetology internship and I eventually graduated from medical school with a thesis on factors affecting prevention of diabetes complications. As soon as I graduated, I decided to switch to surgery and transplantation, because I was not really patient enough to deal with type II patients, diets and prevention. At about the same time my little cousin Serena was diagnosed with type I diabetes. I thought that by studying transplantation in diabetes, I could figure out a way to replace the insulin producing cells that are destroyed by the autoimmune process in type 1 diabetes. It was that year that I came up with the idea of how to isolate human islets from the pancreas through an automated system including a digestion chamber, etc. My mentors in Milan didn't have the expertise or the resources to actually allow

me to test the concept and so they allowed me to “emigrate” to the top islet isolation and transplantation center at that time, which was directed by Prof. Paul E. Lacy at Washington University in St. Louis. Lacy accepted me in 1985 with an initial salary of \$7,500 a year. The second year I was lucky to obtain an NIH Trainee Award which bumped my salary in 1986 to a whopping \$13,000. At the beginning in St. Louis there were several McDonnell Douglas Corporation engineers working in Lacy’s lab on a very complex system for the extraction of human islets from the pancreas. They were the same group that then put islets in the space shuttle from Wash U. They immediately didn’t like my idea and actually asked Lacy to send me back to Italy, as I was interfering with their planning and their IP development ideas. That’s the reason why I always tell my fellows and students that certain opportunities present themselves late at night or on the weekends because of my personal experience. One day a human donor pancreas arrived late on a Friday evening and Lacy’s team thought that the period of cold ischemia was already too prolonged to give any chance to obtain any significant islet yield (some 18 hours ischemia time). They decided not to process that organ and disposed of it in the biohazard trash container. Instead of leaving with the rest of the team that night, I remained behind, retrieved the pancreas from the trash can and performed my “unauthorized” experiment to show (only in case of success, of course) the result to Professor Lacy. I was lucky that night as I was able to obtain an incredible yield of very good looking human islets, that I obviously and proudly showed to Dr. Lacy. I realized that we were up to something major when he started calling people to the lab to view those islets at the inverted microscope. One of the people he called in was transplant surgeon Dr. David Sharp, who ran the cGMP islet cell processing facility in another building.

PJG: And what was this secret?

CR: It was the concept of performing the separation process within a digestion chamber that activates an enzyme mixture at its inlet, while inactivating it at its outlet where the progressively released islets leave the “disassembling” chamber to be collected in separate compartments of the separation apparatus (you can see an animation of the whole system at www.diabetesresearch.org). Before this technology, investigators in the field were using methods including some kind of meat grinder apparatus, or Velcro strips, tissue blenders, etc. All of these methods shared a substantial traumatic action to the islets during the isolation process. At that time, it was inconceivable (when I first proposed my idea) that you could put the whole pancreas in a chamber, and get islets from its outlet. To make the story short, we started alternating pancreases for two weeks to compare the traditional method used at Wash U versus this new concept and subsequently, all the engineers from McDonnell Douglas left while the center switched completely to the new “chamber” based method, which eventually was named the Ricordi method. Since that time we have trained hundreds of physicians, surgeons, fellows and technicians worldwide on how to better use this technology, with a complete open policy both for training and making the equipment available to all. I do have a patent on the method, but it was only to protect our ability to continue to use it and to freely teach and distribute the technology to others.

PJG: I understand that pretty much everybody doing this type of research is using it?

CR: Yes, and then I went back to Milan, Italy to bring this technology I developed to be used for the first clinical transplant at my institution, H. San Raffaele Institute. But when I arrived, after we had just shown that islets separated with this method could successfully reverse diabetes in experimental model systems, I met a lot of resistance in starting a pilot clinical trial. In fact, my mentor and leadership of the hospital were afraid to test a procedure that was not proven

successful in clinical trials yet, asking me why should we be able to succeed first, in a clinical islet transplant if neither St. Louis, Miami or Minnesota had succeeded first, they were afraid of failure or just to be first in something. So they started to slow down the project for more than a year. By that time I had become a “tenured” (di ruolo) attending surgeon after completing a residency in surgery that I started before moving to St. Louis and following a period of practice in emergency surgery. One day I was making rounds while complaining to a fellow surgeon, arguing that we could not get anything new done in the center, with that conservative mentality, and that if we could have just been in a center like Pittsburgh, with someone like the mythical transplant pioneer Thomas Starzl (who I did not know at the time), things would be different and we would already have done the first successful islet transplant. I was literally shocked when a minute later they called me from the nursing station, the head nurse called me and said “there is a certain Thomas Starzl on the phone.” I thought it was a joke since I was complaining and had mentioned his name. I was completely speechless and could barely answer Dr. Starzl’s questions, who was considered the Asclepius of transplant surgery. I was so surprised that Starzl asked me, “Do you understand English?” because I was completely paralyzed, speechless. “Do you understand what I’m saying?” He said ... “well, I want to start an islet transplant program and I asked several important people, from Dr. David Sutherland, head of transplantation in Minnesota to the chairman of the Nobel Forum in Stockholm, Prof. Carl Gustav Groth, also a leading transplant surgeon. For some reason your name comes up first out of ten possible candidates, but I have no time to lose, as I do not want to waste any time. You have to decide within 24 hours and should you accept this mission, you’ll have one week to move to Pittsburgh.” So a week later I was at the University of Pittsburgh with my little suitcase containing the “chamber” and all the key components of the islet isolation apparatus. That was December 1989 and when I

arrived in Pittsburgh I was very surprised (and initially upset) to find out that at the same time he also recruited Dr. Daniel Mintz and Dr. Rodolfo Alejandro from the University of Miami, a major competing group of Dr. Lacy's Wash U team. That was the first lesson I learned from Starzl, he would never assign one project to a single person putting all his eggs in one basket, but rather start a healthy competition between two groups with the same objective. Together with Drs. Mintz and Alejandro we decided to compare the "Miami" method with our method, head-to-head, splitting the pancreata in half and testing in parallel the two approaches, before making a final decision on which method to use and then moving forward as a team. When they took their apparatus out of the box for the parallel testing, I smiled as I was pleasantly surprised to see that they tried to replicate a "Ricordi Chamber" but with a slightly different shape (a round bottom). Within days we decided to switch to the "original" Ricordi Chamber and method and since then we have worked as a team. The rest is published history. Together with Dr. Andreas Tzakis, founding director of the MTI (Miami Transplant Institute), we performed what eventually was recognized as the first successful series of human islet cell allotransplants. The first transplant was on January 10, 1990, less than a month after my arrival in Pittsburgh, including the holiday period in the middle. We still had boxes in the lab when we performed the processing of the islet cell product for the first transplant (that was before the cGMP era).

PJG: So this was 89 or 90?

CR: December 1989, when I arrived in Pittsburgh, to January 10, 1990 the first successful transplant, and six to follow, and the paper was published in the *Lancet* in March 1990 and then the rest of the world started performing islet transplants within a month. Everybody was waiting for someone to succeed first, and then Milan, Minnesota and Edmonton quickly followed, together with Miami where Drs. Mintz and Alejandro had eventually returned to. The isolation

method is still used today by most centers involved in islet transplantation and several investigators worldwide have contributed to improvements of the technology.

PJG: And how did you then get to Miami?

CR: My recruitment to UM lasted two years, from 1992 to 93 when finally Dr. Mintz was able to recruit me here. At the beginning I was resisting the idea because I thought Pittsburgh was the capital of the universe of transplantation. That was the time when Pitt was performing over 1,000 organ transplants a year. There were so many institutional resources that we were not allowed to write NIH grants because it would have been a waste of time. You just had to write on a piece of paper the total amount for the budget you would need for next year and Jeff Romoff would issue the check (that was of course if you were part of the Starzl team). Starzl used to say we would generate more revenue for the institution by transplanting two patients in one day, then by spending the time to write an NIH grant. See how much can change in a decade? It is completely different now, even in Pittsburgh, but it was interesting because in fact when I was recruited here at UM, I had zero NIH funding. Mintz in fact convinced me to move to UM in 1993 and this was essentially for two reasons. The first was that Dr. Starzl wanted me to only use FK506 (Tacrolimus) in islet transplantation and I had begun to feel limited in our ability to test novel concepts. But most importantly, I had met key leaders for the DRI Foundation (DRIF) in Miami, who explained to me the model of “affiliation” of the DRI with UM, and the extreme flexibility I would have to develop a program reporting directly to the Dean and to the President, since the DRI operates across schools at UM. In February 1993, I came to UM with Dr. Massimo Trucco for a serious visit (Dr. Trucco is now head of the Diabetes Center at Pitt). We came back to Pittsburgh with completely different outlooks. For me, the glass at UM was clearly half full as we had an independent foundation, a new building with space to grow and a

lot of potential with the sky as the limit. Massimo instead saw the half empty portion of the glass there was a building almost ready but empty, with no infrastructure. There was no endowment and too much risk in moving to such an environment, so he eventually decided not to come with me to Miami. After I arrived in Miami, the first person we recruited was Bob Pearlman to head the DRIF. In our first meeting Bob told me, “you know that \$9 million we were told was available to jumpstart the program, it’s actually more like \$900 thousand, so we have six months of oxygen.” So we started by hiring three post-doctorate fellows, Dr. Norma Sue Kenyon from Duke, Dr. Luca Inverardi from Fritz Bach’s lab in Minnesota and Dr. Alberto Pugliese from George Eisenbarth’s lab at Harvard. They have all been very successful and instrumental in the growth and success of our research programs, and are now Area Leaders and part of our Executive Research Council at the DRI, together with Drs. Alejandro Pastori and Jay Skyler who were already here at UM when we were recruited. We all started with no NIH funding and \$900,000 from the DRIF, and we made the bold decision to focus on fundraising, as there was no time to wait for a cycle of NIH review and funding and we had no “institutional” (UM) commitment or start up packages. And by that time I already had the predecessors of Ron Bogue’s team measuring my office space and labs at the DRI , a practice that generally makes investigators a little uncomfortable. Around that time, with Bob Pearlman and Dr. Mintz, we were successful in getting the first \$5 million gift from Rowland Shafer of Claire Stores, with whom I had developed a very good relationship since the time he hosted me on his mega yacht at the time of my recruitment visit. Rowland and his family eventually contributed much more and named the DRI building in subsequent years. In 1993, I actually got my first RO1 thanks to Eckhard Podack, who served as Co-PI. Then we progressed exponentially: the foundation

moving from raising \$1 million/year to now raising \$20 to \$25 million/year and our DRI team now with over \$10 million/year in NIH funding and other competitive grants.

PJG: And the Diabetes Research Foundation was honored for being in the very small group of more than \$100 million contributors to the University of Miami.

CR: Yes, I believe we are now up to \$250 million, with our new pledge to the UM campaign, making the DRFI probably the largest UM contributor ever.

PJG: Let me ask you a question that is more about life than science...but when you were in St. Louis, you met with a young woman, from what I understand, named Valerie.

CR: Yeah, actually I presented Valerie to the diabetes world on two occasions, at the ADA Lilly Lecture in 2002 and this year in Rome, when I gave the Galileo lecture in front of 17,000 participants. This was the opening lecture of what has been the largest congress on diabetes worldwide. I always recognize Valerie as my major and number one achievement ever, since I was able to convince her to marry me, on August 6, 1986, the same year the automated method for islet isolation was developed. I always have a picture of our wedding in all of my major talks.

PJG: But you met her in St. Louis?

CR: Yes, we met in St. Louis. She was working at the St. Louis Art Museum at the time, but she came to a party of a medical student friend of mine who was in high school with her. I immediately noticed her and I started telling my friend "I want to meet that girl." He first replied "No, forget it, she is already engaged three years with this other guy, they will get married etc. Look next to her, the blonde one over there ...", but I insisted and introduced myself. Knowing how little of a chance I had, I had to adopt a strategy that could be effective immediately, so I asked this wonderful Midwestern girl: "Oh, you look so European, where are you from?" Well I

knew she was born and raised in St. Louis. I told her “your life is going to change completely but you don’t know it yet.”

PJG: I love it. And you had three kids...

CR: Three kids: Caterina, Eliana and Carlo. Caterina was born in St. Louis, Eliana in Milan and Carlo in Pittsburgh. We actually moved to Miami when Carlo was one month old, at the time I was recruited here in August 1993.

PJG: People who have the drive to get something done to the point that they have been in a pretty comfortable life in their home country and then come to America and get things done. I’m usually a bit of an entrepreneur type, but from time-to-time there must be something that you miss from home. What would it be in your case?

CR: Well, I loved Miami at first sight, because I always dreamed since I was a student in Italy that my ideal place to work would be a metropolitan environment but in a tropical setting. I love the ocean and fishing; every time I would have a little free time when I was living in Milan, I would try to go on the water. So, Miami for me is an ideal setting. Lifestyle-wise, I miss a little of Italy – especially the historic friendships that I have there. There is very little mobility in Italy. In Milan, we had a very close group of friends, maybe because our parents were also friends. As we grew up, we went to the same schools, the same holiday places. I know every one of my friends pretty much since before the time we were in high school and nobody has moved from Milan (except me and two others), so every time I go back, even now, we have little reunions, or we go out for dinner, it’s all the same people, maybe with a different composition of couples, but pretty much within the same group. Here in the United States, the first difference I noticed is that friendship is much more, not superficial, but mobile, people change. It is very rare to find somebody that is 20 years in the same place or 40. So there is this mobility that is also at the

basis of professional success. In Milan, you cannot move because once you leave your mentor, you are cut, with no chance to progress in your career, so you better make sure your mentor is not only powerful and outstanding, but also very healthy. For me living in Miami represents a great compromise, as I may see a little less of my old friends, and the life is a little different from life in Italy, like village squares, the atmosphere, the restaurants (except Osteria degli Amici of course), places where you meet people that you know or spend some free time with. But in any event, I had so little free time even when I was there that I feel like I see more of my old friends now, as many of them are visiting us here, or when I go back for meetings. Sometimes you idealize things that are far away. You think that life could be better there compared to here. Then you spend one week in Italy and you suddenly remember all the challenges that exist there, the bureaucracy, traffic, lack of funding, and you realize you can't wait to get back to Miami. One thing that I may be missing the most is the comfort of our family places, like our house in Stresa, on Lake Maggiore, or the Dolomites, where I spent my winters growing up, in Cortina d'Ampezzo, or Giannutri, this little island, the most southern of the Tuscan Archipelagus, those places are not reproducible here, but we discover better places every year, like Staniel Cay in the Exhumas or Triumph Reef just south of Fowey Rock.

PJG: I honestly thought that the answer would be either music or pasta.

CR: No, pasta I cook, and music we have plenty with the opera, Orchestra Miami and the Frost School of Music.

PJG: And Miami is such a wonderful place to be when you were born abroad.

CR: That's why I started a restaurant.

PJG: There is a huge responsibility on your shoulders with thousands of new patients every year and their parents who want you to find the cure for diabetes type I. When you are in your

secret-thought process - what do you see the opportunity that will be first to really cure the disease process? What's your imagination taking you to?

CR: Well, first of all you are right, there is a tremendous pressure to get the job done. I'm fully aware and I make sure that everybody working with us is fully aware that every 24 hours, one thousand people die with diabetes in the U.S. alone. 1,200 new cases are diagnosed. But I also took these elements at the center of the rationale that led us to change our research strategy at the DRI, keeping our focus on our primary objective and not where funding opportunities may lead us. I tried to learn from leaders in industry, from old strategies and models like Quality Function Deployment (QFD) that was used in the automobile industry in Japan to beat the American industry, putting the consumer at the center of the web strategy, and then using modern techniques to increase productivity and efficiency in your day to day operations, organizing your operations to aim at the strategic objectives and structuring your operations to fulfill your central mission. I tried to develop our strategy and the re-engineering of our research operations, putting patients and a cure for diabetes at the center of the web organizational structure and strategic decision making process. Then everything else falls in place and has to fit this model, contributing to reaching a cure in the most efficient, fastest and safest way possible. So every decision we make has to respond to these questions and prove that it is in the best interest of the patients we serve and the research of their cure. If a project fulfills these criteria, then it has high priority and can enter a process of milestone-based management. But it still has to meet strict performance indicators that reflect our mission and strategic objectives, to move forward, or be cut through our periodic phase-and-gate decision making process. We have to be constantly ready to accept new proposals and skim the least promising ones, to avoid wasting resources, even if they are available. We never stick for five years to a project, because we have

NIH funding for it, for example. If we think we are not going anywhere with a specific research project, we stop and redirect our efforts and our project teams to a more promising area. The key research objectives right now are still related to a cure of type I diabetes. We first need to develop successful strategies to restore self-tolerance, to block the autoimmune process and re-educate the immune system to no longer attack insulin-producing cells. Otherwise you will have the same problem of recurrence of autoimmunity after islet cell transplantation or following a stem cell regenerative strategy. After restoration of self-tolerance is achieved, the path is split in two ways. On one side you can have the cellular replacement therapy. That could be islet transplantation, stem cells or tissue reprogramming - other cells being trained to become insulin producing cells, with tolerance induction to the new cells that you implant. And the other option is instead obtaining regeneration of insulin-producing cells from native precursors that we may already have present in our own bodies -- regenerative medicine instead of transplantation, like in a clinical trial that we are just starting now using autologous bone marrow stem cells and hyperbaric oxygen treatment in patients with diabetes. But in regenerative strategies, the autoimmune process would keep attacking the beta cells that try to regenerate so if you can restore cell tolerance, you may not need to perform a transplant at all, but just work on the regenerative potential.

PJG: You'll always have that very strong commitment to modify the immune system in a way that you shelter the beta islet cells from the dreadful impact of the immune system on them, right? I mean that is an approach that's always a driver.

CR: We are working on two big areas. One is sort of an intermediate step to tolerance that is local immunomodulation, like delivering anti-rejection drugs and immunomodulating only the micro environment where you put the islets in this hybrid device concept so that instead of

treating systemically a patient with let's say 100 mg of anti-rejection drugs, resulting in 1% of those drugs that are actually needed to protect your cells and 99% that are responsible for the known side effects of immunosuppression, organ toxicity, etc. With the hybrid device concept instead, we deliver only 0.1 milligram of these drugs only where the islets are, in that 1-3 ml volume and then you have virtually no systemic levels of immunosuppression, virtually eliminating its side effects, which are currently limiting the clinical indications of islet transplantation to the most severe cases of type 1 diabetes. The other key approach is to increase or infuse regulatory T cells to achieve immune tolerance, both for restoration of self-tolerance and to induce donor specific tolerance to the newly transplanted cells. The local immunosuppression strategy includes all the areas of tissue engineering and nanotechnologies headed by Dr. Cherie Stabler at the DRI, who was recently recruited in a joint effort with the School of Engineering. Cherie is developing nano-encapsulation technology that could allow us to protect insulin producing cells within a hybrid device, maybe following a temporary immunomodulatory local treatment. Right now we have some very advanced technology that Dr. Raj Pahwa, the husband of Dr. Savita Pahwa, is developing at the DRI and I think we'll enter clinical trials this year to transplant regulatory T cells for tolerance induction using a novel purification-expansion protocol. We already performed the first transplant of regulatory T cells together with Dr. Tzakis's team, in a liver transplant recipient. We now need to go through a full IND process following this initial patient treated on a compassionate release basis. This process will take at least six months.

PJG: The drug that Norma Kenyon and you developed for immune suppression of transplanted patients seem to be an almost ideal compound to use in prevention of a rejected transplanted beta

islet cells, and in that case the reason why they didn't go further is because of side effects of the drug. This would be typically benefiting from your approach of locally impacting.

CR: Definitely. And also, we don't see side effects in the islet cell transplant context, but they observed serious adverse events following administration to kidney transplant recipients and some other patients affected by other autoimmune conditions. So the drug was pulled from the market. I am actually very concerned about our ability to access drugs that could make a difference, because the decision making process in big pharma is driven by the marketing and financial levels in industry and not by the R&D group, based on their research potential and scientific impact. Several very promising drugs disappear before our eyes, because there is not enough market and profit potential. So one of the worst things that you can experience, is to be working with a most promising drug and then suddenly witness its disappearance, they do not even make it available for research purposes, it is like it never existed.

PJG: Yeah, I know...that's terrible.

CR: And when you talk with the executives of these companies, they'll tell you that this is the case. In the last year three different companies pulled a drug or technology from cell therapy, cure-focused applications, because they say our strategic investments are in the area of new molecule identification, where you can patent and have a higher profit margin, because other molecules are going to become generic drugs and the whole investment/revenue strategy is based on new proprietary molecules. In addition, if you see in a big company how much of what they are funding in R&D is going towards development of better treatments or support technologies versus a real cure, you may be surprised by the answer. In the diabetes field, for example, there are a lot of investments in better needles, better insulin molecules, infusion pumps, glucose meters and all kind of products that can help manage diabetes, but very little is invested in

strategies that could eradicate the disease, wiping out this “market” altogether. I am not complaining against the better drugs and technologies, as they are undoubtedly and greatly helping millions of patients now living with diabetes, improve their every-day life. But how much is invested to eradicate this disease? If you look at the big pharma, this is close to zero. That is another reason why we are so grateful to the DRI Foundation for allowing us to keep our eyes and efforts focused on the cure.

PJG: I can assure you that people were producing the iron lungs were not financing the vaccine research of Salk?

CR: Definitely. There was an evolution and also antibiotics. You have a lot of situations in which industry was curing – like if you developed a successful antibiotic or an antiviral, you can actually witness a cure in the subjects treated. But when you witness an exponentially growing market, now for diabetes in the U.S. alone equal to \$170-200 billion/year, and your R&D doesn't invest anything into something that could lead to a cure, then it becomes morally and ethically complicated.

PJG: And tell me, you have also looked at a specific protection of the beta islet cells taking advantage of the brain blood natural barrier that seemed to modify at least, for example, in the eye environment – the stability of the beta islet cells to the immune system. Can you tell us more about that?

CR: Yes. We've been looking for decades at immunoprivileged sites - we started with the brain and then also the testes were explored, and then co-transplantation of Sertoli cells. Now, most recently, there has been a resurrection of the anterior chamber of the eye. There have been a lot of implantation studies using this site, but we initially tested it to develop a model for in-vivo microscopy, a window for in vivo imaging; and then we saw that it was actually pretty

effective also to reverse diabetes in experimental model systems. Per-Olof Berggren and Alejandro Caicedo's group at the DRI and in Stockholm are working on this together with our Bascom Palmer key collaborators, in a collaboration that stretches across the campus at UM and across-the-ocean, all the way to Stockholm. Clinical islet transplantation in the eye remains a remote possibility and we must proceed with cautious optimism due to a series of technical limitations and risks, including blindness or impairment of vision, sympathetic ophthalmia, etc.

PJG: Sure.

CR: But then talking with the Bascom Palmer team, they were actually much more reassuring; and Jean Marie Parel and collaborators have already developed several devices and strategies for implantation in the eye. There is already technology available for local immunomodulation in the eye and the number of islets required to reverse diabetes might be less than what we need to transplant in the liver, or we may just be able to aim at stabilization of the disease condition, if it can be done with local immunosuppression, even if the total volume transplanted is insufficient to achieve complete insulin independence. We are now working on a pre-clinical model, an experimental model.

PJG: Wow. Fascinating. There was a huge response in the field to the discovery published in Nature Medicine.

CR: Yes, we had received mixed comments, but mostly positive, especially from cell biology experts, as there are a lot of applications for what you can do using the eye as a window for in-vivo microscopy, especially with the level of sophistication of current multiphoton microscopes. Then from this to also say that it will become a clinically relevant immunoprotected site may be a stretch, but worth exploring in limited pilot experiments before the next phase and gate decision making process step which will occur in the next quarter.

PJG: Wonderful. I know that you tell people in your group that if they don't believe that a cure will be happening in one year then they should go work elsewhere. What do you tell yourself?

CR: I think that you have to believe that the next trial you are doing could be the breakthrough that makes the whole disease condition disappear and be cured. But at the same time, you cannot tell this to patients and their family because they have been exposed to such an emotional rollercoaster every time there is a new little biotech or a new paper claiming a cure for diabetes. In mice there have been over 400 ways to cure diabetes, but nothing has actually been successfully translated to clinical trials. So we have to work with the optimism and the intensity like the cure is around the corner next year, but with the awareness that it may take seven or ten. But the intensity of the project has to be as if it's next year. It's more of a psychological attitude issue. If you think you're working on something that may happen in 10 or 15 years, the first thing you take is a two-week Christmas holiday, or a weekend off to go fishing. If you think that the experiments we are doing next week could be the ones, then you cannot pause or take your eyes away from the objective.

In science, there is some times a very relaxed and casual way to be contemplative and investigate a phenomenon of nature, or understand a mechanism in a biologic system, but there is often very little mission-oriented focus in understanding the urgency. But when you have to cross a waiting room with patients before arriving to the labs, patients who represent a disease from which 1,000 people will die in the next 24 hours in the U.S. alone, then it becomes a little like working at a Manhattan Project to develop nuclear power or the atomic bomb, you have a different kind of pressure, intensity and focus. In other words I believe we should work with the same intensity like if we would have a meteorite approaching Earth and we have to find a way to stop it or

divert it before impact, like in the Bruce Willis movie, but for diabetes there are over one thousand of these meteorites per day that actually make impact, in the lives of affected patients and their families.

PJG: Obviously you are extraordinarily accomplished and you are internationally renowned, perhaps more than anybody else in the field, you are a distinguished professor at UM, and one day you will come up with a cure for diabetes type 1. Have you ever thought what Professor Ricordi would do next?

CR: Cancer. Definitely a cure for cancer.

PJG: Amazing.

CR: Because it's affected so many people in my family and friends. I think autoimmunity, cancer and HIV pose the ultimate challenges to the regulation/control of the immune system, one way or the other – everything we are doing for tolerance could be a mirror image of what Eckhard Podack could do for cancer, that's why I keep a close eye on everything Eckhard and his team are doing, because every time he discovers something useful for cancer treatment, we may be able to look at the mirror-image strategy. When he looks for co-stimulation, we look for co-stimulatory blockade, when they want to block T reg expansion, we want to enhance it, etc. But for me, after diabetes it will definitely be cancer – I think in three to five years from now it will be cancer.

PJG: Awesome. Well we are so proud of having you at the Miller School of Medicine and of all the work that you are doing with your team. I know it's teamwork, but having a leader of your caliber and your incredible drive and intelligence, it's just a fabulous opportunity. So, on behalf of the University of Miami and the Miller School of Medicine, I thank you for the opportunity that you bring to this place.

CR: Thank you. I really appreciate that. I would really like to underline that it's teamwork. Maybe my best contribution is to be able to be a cheerleader and keep the intensity and the team together, trying to keep scientists working together as project teams, when they naturally tend to grow apart from each other, but I am very lucky to be able to work with an incredible team of scientists and dedicated staff. They, together with the DRIF, are the ones who deserve the credit for everything that is going on at the DRI.

PJG: I agree. But again, the person who is at the helm and carrying the load of knowing how many people are waiting for the cure, and at the same time keeping the spirit to never give up and to always look at a better step, a better opportunity, a better chance is invaluable.

CR: Thanks.

PJG: So, keep up the wonderful work that you are doing. We thank you for that.

CR: Will do. Thank you.