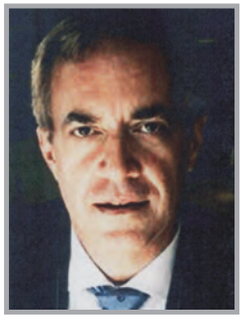
Encouraging collaboration in cure-focused research



Camillo Ricordi[†]: Camillo Ricordi is the Stacy Joy Goodman Professor of Surgery, a Professor of Medicine, a Professor of Biomedical Engineering and a Professor of Microbiology and Immunology at the University of Miami, FL, USA. At this institution, he also serves as the Director of the Diabetes Research Institute and the Cell Transplant Center. Dr Ricordi is also the Responsible Head of the NIH-funded Human Cell Processing Facility and has been chairing the Dean's Research Cabinet at the University of Miami, Miller School of Medicine (FL, USA), since 2006. Camillo Ricordi is an acclaimed scientist in diabetes cure-focused research. He is well known for developing the procedure for isolating and extracting human islet cells from the pancreas and he performed the first series of successful clinical human donor islet transplantations. Dr Ricordi is also currently researching methods for transplanting cells and organs without the continuous requirement for antirejection drugs. Over the years, Dr Ricordi has received numerous honors and awards; he has authored over 600 scientific publications and has been awarded 11 patents for his inventions. In 2010 he was inducted into the prestigious Association of American Physicians. Dr Ricordi also serves as Chairman of the Diabetes Research Institute Federation, which brings together over 24 leading international institutions with the aim of enhancing scientific collaboration and facilitating networking among scientists worldwide.

Q How did you first become interested in research related to the management of diabetes?

My career in diabetes began in an unusual way; originally, I started medicine intending to do brain research. My mentor advised me to go to work in a hospital for a while, in order to gain some exposure to internal medicine. The department that I was placed at was a major center for diabetes in Italy. Around the time I graduated, my little cousin was diagnosed with Type 1 diabetes, and at this point, I decided I would stay in diabetes research to find a cure within 2 years and would then move back to brain research. I have not found a cure yet, so I never moved back. The family mission became a life mission because I have met so many people along the way who I hope that I can help. It is no longer simply an issue of curing my cousin. Whilst at first I thought that brain medicine was interesting, at the time, in Italy, it was not very advanced. Ultimately, I thought that I could do something more effective in the emerging field of transplantation, so that became my mission.

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Q How did your career lead you to the University of Miami Diabetes Research Institute?

I was interested the idea that we could extract islet cells from the human pancreas but we did not have the resources within my hospital in Milan (Italy), so I was sent to the Washington University, St. Louis, (MO, USA). This is where the famous Professor Paul Lacy and his laboratory of world-leading scientists were working on experimental islet transplantation. I traveled there in 1985 and stayed for 3 and a half years. This is where we developed the automated method for human islet isolation, which was later named the Ricordi method, although this was not the name that I first gave the procedure. I then moved back to attempt the first transplant in Milan. Unfortunately, clinical trials were stalled for over a year and a half. During this time, Professor Thomas Starzl, Director of the Transplant Institute at the University of Pittsburgh (PA, USA), called me out of the blue; he told me that he had a list of names of experts that he was contacting to start a clinical program of islet transplantation in Pittsburgh and he asked me if I would like to join them. I had 24 h to decide and just 1 week to move. That is when I left Italy for good. I joined the University of Pittsburgh transplant team and that is where we performed the first successful trial of islet transplantation for diabetes, in January 1990, only 1 month from when I arrived in Pittsburgh. In 1993 I moved to the University of Miami (FL, USA). It was appealing because they were building a unique center to focus on a cure for diabetes. I was offered a lot of independence in direction and, thanks to the support of the Diabetes Research Institute Foundation, the possibility to really make progress. I have been here in Miami ever since.

Q Were there any particular colleagues that you worked with who really influenced the path your research has taken?

I would say definitely Paul Lacy, who was my mentor at Washington University, St Louis, and Thomas Starzl, the transplant pioneer who recruited me to the University of Pittsburgh.

I was particularly lucky when I went to Washington University because at the same time Professor Lacy stepped down as Chairman of the Department of Pathology, so he became a full-time researcher and my mentor. It was like having a personal instructor for 3 and a half years; every day we spent time together reviewing slides and he taught me everything from how to recognize an islet to how to write a paper, a grant submission or an abstract. He was really influential in giving me a base for my future research career. Yet it was not just his teaching; from the beginning I also identified some differences in our opinions – I noticed how I would diverge from the traditional academic standards and way to do research because I was constantly interested in testing the next step. I did not wish to stop to work out the detail in a mouse model that could prove to be insignificant when compared with human disease. I found that I was more predisposed to the translation of research; I do not want to spend 5 years working on a model if it is not relevant to the next step towards curing diabetes in humans. At Washington University, I was exposed, for the first time, to the way that academic research was carried out in most US institutions, where performance indicators, promotion and incentives are generally more closely linked with the amount of funding you bring to the institution rather than the clinically relevant steps you have completed towards the development of a cure. Therefore, I decided that in the future I would always work to try to reach a cure in the fastest, most efficient way possible. Now, as soon as we begin a basic research project, we always think about whether there will be a predictable road block to implementation, or, if it works in the mouse, what is the next step towards translating this into a new therapy.

The second mentor who had a major influence on my career is Professor Thomas Starzl, one of the pioneers of transplantation: he developed most of the organ transplant procedures we are now carrying out, from kidney and liver transplantation to multiorgan transplantation. He taught me a lot about how to implement a strategy that makes the best progress. When working in Milan, waiting for the trials to begin, I felt that my research was somewhat paralyzed, but when I had that telephone call from Professor Starzl, he gave me support and expressed the urgency of getting started. I was there within the week with my bag and all of the equipment we needed. When we did the first transplant in January, we still had boxes in the laboratory that were not completely unpacked. He always had a "show me what you can do" kind of attitude. He was incredibly positive and motivated, and although he worked his team very hard, I learned a lot from him.

Q What do you consider to be the biggest achievement in your career so far?

Scientifically, it has been developing the method for extracting human islets from the pancreas and performing the first successful series of islet transplants in patients with diabetes. I am very proud of having contributed to the discovery that it is possible to perform a clinical islet transplant and successfully reverse diabetes. The challenge now is finding how to make it work in all cases and how to do so without immunosuppression. I feel that at least I have helped to set up the field, ready for the next steps.

Maybe the most important thing I have done is not a scientific discovery, but has been to achieve goals by breaking geographic barriers to collaboration. I am proud of forming The Cure-Focus Research Alliance ('cureforall') that brings together scientists worldwide, while providing them with, and further developing, the technologies that allow them to interact. No matter where you are you can now work together, as though you are physically in the same laboratory, looking at the same microscope. I have also worked to encourage people not to compete and to share research findings in a timely manner. If you are dealing with a disease that kills one person every 4 s and you keep secrets, working in isolation to build your own little ivory tower, then you are actually contributing to the delay in finding a cure, and in my opinion, that is indirectly a criminal behavior.

In a way, I hope that if I will be remembered for one thing, it will be for having worked tirelessly to develop and promote collaborative strategies to enable us to be as effective as possible in order to reach a cure in the fastest and most efficient way.

Q What is the largest project you have been involved in whilst working at the University of Miami?

The largest project is the one I am chairing, which is currently, ongoing; the NIH Clinical Islet Transplantation (CIT) Consortium, which was made possible by a US$75 million grant from the NIH, intended to contribute to the next generation of clinical trials in islet transplantation in the USA and Europe. This has been a massive undertaking because we have everything from trials of new islet strategies to two registration US FDA Phase III trials, seeking the approval of islet transplantation as an insurance-reimbursable procedure for the most severe form of Type 1 diabetes. The Diabetes Research Federation has now evolved into the more globally oriented Cure-Focus Research Alliance, in order to expand the collaborative platform technology and global attack to disease conditions beyond diabetes while focusing on a cure for diabetes worldwide. This major effort involves dealing with governments, institutions and individual scientists and will certainly be a major project in 2011. It began 10 years ago with the establishment of the Diabetes Research Institute (DRI) Federation, but now it is evolving to a new level with cureforall – the Cure-Focused Research Alliance. It started last year as a concept and we now have a formal nonprofit entity already comprising several of the DRI Federation members, while expanding the scope beyond diabetes and covering themes that cross over disease conditions. For example, we are working with cancer groups who helped develop technology to target metastatic disease, while we are using the same targeting strategy to deliver molecules and growth factors to individual stem cells or target tissues. There are therefore platform technologies that one may develop in cancer that can be applied to diabetes and *vice versa*. We are currently developing strategies in diabetes that could help neurodegenerative disease conditions, so we thought it was important to be inclusive in the scope of the alliance, expanding our concept of breaking the geographical barrier to collaborative research efforts, always with the same objective, to reach cures in the most efficient and fastest ways possible, by linking investigators and individuals worldwide who want to share this mission and work beyond individual and institutional interests.

Q Could you tell me a bit more about the clinical research you are working on at the moment?

The three most exciting areas we are working on at present are as follows.

First, we are aiming to induce tolerance by re-educating the immune system to no longer destroy the introduced cells. Some of the strategies, such as infusion of the expanded regulatory T cells, are already at the clinical level. We will be moving to clinical trials in the next 3 months.

The second big area is the potential to localize immunoprotection to transplanted cells and tissue, either through the local delivery

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of immunomodulatory drugs, using either a hybrid device with local delivery of immunosuppressive drugs, or a tissue engineering approach, using biomaterial scaffolding technology with local delivery of molecules and/or conformal coating encapsulation with immunoprotective membranes, instead of immunosuppression of the whole patient. We are working on immunosuppression of the site in the microenvironment where the transplant will occur. Within this area, there are also the developments of nanoencapsulation and conformal coating encapsulation technologies that help to put a small layer of semipermeable membrane, very thinly, around the introduced cells, so that you can protect them from immune attack without the use of systemic, life-long immunosuppression and antirejection drugs that currently limit the applicability of the islet transplant procedure to the most severe cases of diabetes.

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The third area is actually that of stem cell tissue reprogramming and β-cell regeneration. When we have achieved tolerance by attaining goal one or two, or a combination of the two, then everyone will want a transplant of islet cells because they no longer face the limitation of antirejection therapy. Clearly, it will be impossible to meet the demand with organ donation or out-of-human islet transplantation, so it is important that from now on we begin to look at stem cells and alternative sources that could be unlimited, or to reprogram other cells to become insulin producers. This is one of the most exciting areas we are working on.

The work on tolerance is already at the level of clinical trials and the scaffold tissue engineering hybrid device for local immunosuppression will be in clinical trials, in 1–2 years. In terms of looking at alternative sources of insulin-producing cells, I think we are still a few years away at the moment.

Q What advances in the field do you expect to see in the short & long term?

In 2011 I expect that the Cure-Focus Research Alliance and the Diabetes Research Federation will be able to start clinical trials for tolerance induction in China, in Argentina and eventually in the USA. This new pilot technology will be tested and I think we will begin to move towards clinical translation with some of these basic concepts that have been explored at a clinical level.

In 5 years time, I hope we will have established definitively that cellular therapy can be successful with fewer toxic drugs and more localized forms of immunomodulation. I hope that we will already be planning for the first trials with alternative sources of insulin-producing cells, possibly derived from embryonic or adult stem cells. One of the most exciting sources we are exploring at the moment is adipose-derived stem cells, which you can extract from fat tissue obtained from the same patient by mini liposuction, and then these adipose-derived stem cells can become insulin-producing cells. This is a very new area but I hope to see an advance in this and similar technology over the coming years. It is certainly an exciting time for diabetes research.

Financial & competing interests disclosure

Camillo Ricordi is the holder of several patents in islet cell processing and transplantation-related technologies and holds an equity position in two University of Miami (FL, USA) biotech start-up companies (Converge Biotechnology, Inc. and Ophysio, Inc.) that are developing cell culture systems, local delivery of immunosuppression, hybrid devices and immune barrier technologies for treatment of diabetes. Camillo Ricordi has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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