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News&Views

Islet Transplantation in the US - Quo Vadis? An Interview with Camilo Ricordi (CR), Ali Naji (AN), Peter Stock (PS), Piotr Witkowski (PW)

Dr. Ricordi, your pioneering work in the field over more than 30 years has laid the foundations for the burgeoning of national islet transplantation programs all over the world. It has allowed the completion of NIH-sponsored clinical trials that have demonstrated the clinical value of islet transplantation. However, US patients with brittle type 1 Diabetes are still unable to undergo this procedure, why is that?

CR: Well, the field of allogenic pancreatic islet cell transplantation is near extinction in the United States, with hardly any islet transplantation procedures currently performed (1). It has been a heartbreaking situation for me and so frustrating. I have spent my entire professional life developing the technology and performing clinical trials of islet transplantation in order to help patients with the most severe cases of type 1 Diabetes. I shared all protocols and renounced the enforcement or benefit from all patents to keep the field collaborative, academic, and non-for-profit - as it should be - in order to help the most patients. There is plenty of evidence documenting that pancreatic islets are not cells but rather that they are small organs and thus they should be regulated as such (2-5). In addition, the great variability of pancreas donor factors, islet cellular composition and potency, make it impossible to try to fit islets into the requirements rightly set for advanced cell therapies, or other biologics, where you can control and standardize the source material. To try to fit human islets into the regulations for cells and drugs is like trying to fit a size 14 foot of a basketball player into the slipper of a size 7 ballet dancer. The USA are the only country in the world where human islets, which are basically small organs, have been regulated as biological drugs instead of as organs. Everywhere else except the US, islets are regulated as any other

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organ/tissue for transplantation, which has allowed the field to advance and evolve to help patients worldwide! (1).

How was the Food and Drug Administration's (FDA) decision to regulate pancreatic islet transplantation as a drug, detrimental to the field of islet transplantation?

PS: NIH multicenter clinical trials have demonstrated the safety and efficacy of islet processing and transplantation. However, the next step, as for any drug development, was the submission of a biological license application (BLA) to the FDA. Academic institutions do not have proper infrastructure, administrative resources, or finances to undergo such a complex process for a single application. Consequently, as no BLA has been approved, islets are not allowed for clinical use in the US, except in clinical trials. Furthermore, research funding declined and almost no procedures have been performed in the US for the last 6 years (1).

But recently, a BLA was submitted to the FDA by a private company and it is expected to be approved.

CR: Yes. A for-profit company has submitted a BLA for human islets for review by the FDA. While we congratulate the team behind the company and recognize the effort and considerable resources invested, we cannot avoid thinking about the detrimental consequences this development will have for the field of islet transplantation in the US.

Don't you think that the BLA approval would finally allow the field to develop in the US?

PS: Unfortunately, no. It is a step in the wrong direction with potential detrimental and irreversible consequences.
First, a BLA does ensures neither the quality, nor the potency of islets. Since BLAs exist to ensure that drugs are safe, standardized and provide a clinical effect, this concept does not work for islets.
The biggest worry is that a BLA falsely reassures about islet safety by allowing islet transplantation without the appropriate clinical oversight.

Well, that seems to be so different from the common perception. The BLA requirement was introduced to ensure drug safety and effectiveness. Would BLA approval not confirm that?

PW: BLA works for drug manufacturing. The principle of the FDA safety and efficacy reassurance system is based on the final product *being well-defined with specific product characteristics, produced with consistency and that correlates with clinical effect and outcomes*

(6). Once it is verified and the BLA is approved, a new drug can be safely released for clinical use. Post-marketing monitoring, however, is not rigorous, with only volunteered reporting of side effects by patients and physicians to the sponsor and FDA.
Islets are not drugs, but human micro-organs (2-5). Like all human organs, islets are highly variable. Their specific characteristics cannot be ensured with consistency, and most importantly, there are no specific characteristics which correlate with clinical outcomes (1). Recently, the FDA reviewed the BLA data and concluded that the "**critical quality attributes for islet product purity and potency did not correlate with the clinical effectiveness and that the critical quality attributes may not adequately evaluate lot-to-lot manufacturing consistency"** (7).
In practical terms, quality and potency of the human islets manufactured as a drug according to the FDA standards, cannot be confirmed or verified before clinical use. Simply put, if a BLA is approved, the exact quality and the potential for desired clinical effect of islets provided by the commercial BLA holder remains unknown.

What do you think will happen next?

AN: The most rational strategy would be to exempt islets from the BLA requirement and allow islets to be regulated as an organ/tissue for transplantation by the OPTN (Organ Procurement and Transplantation Network).

How do you know that regulation of islets as organs for transplantation will reassure safety and quality?

PW: The rest of the world capitalized on the results of clinical trials and introduced regulatory frameworks for human islets developed not for drugs, but specifically for organ/tissue transplantation. That is the way it is done in Canada, United Kingdom, France, Italy, Switzerland, Sweden, Norway, the Czech Republic, Poland, Japan, and Australia (1).
There is sufficient scientific evidence for the clinical safety and effectiveness of islet transplantation **without** implementation of a drug manufacturing system and BLA approval. This has been demonstrated in multiple clinical trials in the US and abroad and also supported by data captured from over two thousand islet transplants by the Collaborative Islet Transplantation Registry over last 20 years (1,8-10).

How exactly would it work?

AN: The quality and potency of the human organs (including human islets) can only be reassured by the transplant team via a continuous assessment of complex parameters and constant supervision - from the moment of donor selection through pancreas recovery, processing, preservation, transplantation and, finally, post-transplant patient care. Based on this rationale, human organs are, and human islets should also, be regulated under the aegis of the HRSA (Health Resources and Services Administration) and submitted to OPTN and UNOS (United Network

for Organ Sharing) regulatory – notably outside the drug regulations of the FDA. This proposed framework was specially designed and developed to ensure human organ quality and potency, as well as safety and effectiveness of transplantation (1,11).

How does this system ensure islet quality, safety and effectiveness ?

AN: OPTN and UNOS set comprehensive policies and bylaws to regulate every element involved in the therapy, including the organizational structure, personnel, quality and safety measurements, and post-procedure monitoring. Transplant programs obtain and maintain accreditation for transplantation based on rigorous requirements and evidence of pre-set clinical outcomes. Transplant programs can take full responsibility for clinical outcomes only if they control the entire process of transplantation including islet processing.
Importantly, the clinical outcomes are also subject to public scrutiny as they are available on the UNOS website as well as taken into considerations by payors when signing transplant reimbursement contracting (1).

So you propose to regulate islets as human organs, but are islet cells really organs?

CR: The term, *islet cell transplantation*, results in a common misconception that we dissociate human islets into single cells and then transplant them suspended in media. This is very inaccurate.
We isolate islet as small independent micro-organs from the surrounding exocrine tissue and transplant them still intact. Each islet, as any other human organ, consists of thousands of cells, of many different types, forming a complex well-defined structure which is functionally integrated into a single unit with its own internal vasculature and innervation. Additionally, islets, just like any other organ for transplantation, exist this way naturally in the human body and are not artificially manufactured. They make connections between their own vasculature and the recipient's blood supply after the transplantation and they can be preserved out of the body only for a short period of time (2-5).

Including islets into organ regulations seems to be a reasonable solution but is it legally possible in the US?

PW: Yes. Moreover, it has been legally overdue. The current law – the National Organ Transplantation Act (NOTA) – was amended in 1988 to also include subparts of organs in the definition of human organ. However, the definition of human organ under the OPTN Final Rule has not been subsequently amended to include human islets, which are subparts of human pancreas (11). Consequently, for the past 20 years, the FDA has taken the position that islets are a biological drug requiring BLA.

The Secretary of the HHS has the legal authority to amend the Final Rule and to include human islets in the list of human organs. Thus, islets would be regulated primarily as organs by the

OPTN/UNOS, and a BLA would not be required. Moreover, there is precedence for this. In 2007, human blood vessels for organ transplantation and again, in 2013, human vascularized composite allografts were removed from FDA oversight and placed under OPTN/UNOS organ regulation (11-13). The latter was done for patient safety concerns, as we now advocate for islets.
We have approached the previous and current Secretary but unfortunately in both situation we received rejections from the FDA on his behalf.

If the oversight of islet transplantation is given to the OPTN/UNOS, how will this result in the reassurance of safety and efficacy of islet isolation itself?

PS: The short answer is - the same way as we have been reassuring for the last 20 years, without need for BLA approval but with transplant centers being responsible for the entire process including clinical outcomes (1). We follow a set of rules and regulations established by the FDA under Section 361 PHS Act, designed for human cellular and tissue product exempt from BLA. Islet processing for *autot*ransplantation has been regulated that way for over 20 years, and islet isolation for the purpose of islet *allo*transplantation is exactly the same (the same personnel, facility/clean room, equipment, supplies and processing technology), so the same regulations are sufficient (1).

If islets are regulated as organs, negating the need for a BLA requirement, would there be a place for a commercial entity with expertise in islet isolation, like the one which submitted the BLA?

AN: Absolutely. OPTN/UNOS accredited transplant centers being in control of islet isolation could choose to do it themselves or outsource it to a reliable commercial entity specializing in islet processing. Transplant centers will have many different options and we anticipate this will lead to healthy competition, improvement of quality, and lower costs.

What are your goals now?

CR: We hope that our voice will be heard. The scientific evidence is unequivocal, and we urge the FDA and HRSA to re-consider the inclusion of human islets in the list and definition of human organs. Regulation under OPTN and UNOS is the way to ensure safety and future progress. We ask the Secretary of the HHS to take action to ensure this happens before it is too late (11,14).

Well, we all hope so and wish you all the best, thank you.

CR, AN PS, PW: Thank you very much.

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