

# Why pancreatic islets should be regarded and regulated like organs

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## ABSTRACT

**There are strong reasons to say that pancreatic islets are organs before they are isolated and that they should be considered to be organs once transplanted. Thus, taking into account how much we have learned about the structure and function of islet micro-organs, it seems highly illogical to on one hand consider autologous islets be regulated as organ transplants and alloislets to be regulated with the very restrictive rules used for cell transplantation. It is particularly problematic that this policy has led to restrictions that have made it next to impossible for transplants of alloislets to be carried out in the US, which is a very sad situation for the country that made so many of the advances that brought islet transplantation to the clinic.**

We have followed the long-standing efforts of the United States islet transplantation community to make transplantation of allogenic islets available to at least some of the many individuals with type 1 diabetes who could benefit from this therapy.

For many years alloislets used for transplantation have been regulated as drugs which means that those wishing to provide this therapy must submit a Biologics License Application (BLA) to the FDA. We have been puzzled by why allogenic islets would be regulated as a drug while other countries regulate islet transplants as organ transplants, applying the same standards as they would for any other organ.

It seems illogical to develop a plan to regulate alloislets with rules used for drugs while autologous

islets transplants, processed exactly in the same way, are exempted from these drugs regulations in the US. Alloislets are exempt from drug regulation, and safely and effectively offered as a standard-of-care treatment option in a number of developed nations, with the notable exception of the US.

Some of the basis for distinguishing between allogenic islets and other organ/vascularized composite tissues lies in taking the position that allogenic islets are not to be vascularized organs, which led to the plan to regulate them as drugs, which is how cellular transplants are regulated.

Although there are many complexities, there is the simple question of whether islets are organs. The answer for many is clearly yes, and that would pertain to both autologous islets and alloislets.

The two of us have been working in the field of islet biology for decades and it is clear that islets have been regarded for many years as organs by the pioneers in the field; we can mention Professors Claus Hellerstrom of Uppsala, Lelio Orci of Geneva and Paul Lacy of St. Louis. Islets should be considered to be organs because they have four cell types, which are arranged in a highly organized structure that allows functional interactions between the cell types. They are richly vascularized with fenestrated capillaries that allow rapid release of insulin. The arrangement of blood vessels is highly structured, which facilitates communication between the cell types. In fact, the islets are a key part of what is thought to be the islet-acinar portal circulation. The way this works is that insulin-secreting beta cells are upstream from the glucagon-secreting alpha cells and acinar cells, which are influenced by the effects of insulin. In addition, like other organs, islets are innervated by both the sympathetic and parasympathetic branches of the autonomic nervous system.



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When islets are isolated, the structure and functional relationships between the four cell types are not disrupted. The endothelial cells of the islet connect with those of the transplant recipient. In addition, with time the cells of the autonomic nervous system grow into the islets to provide innervation.

We want to emphasize that the sophisticated structure of the islet organ before transplantation is very similar to essentially that seen in a transplant site. It is surprising that these highly organized structures would not be thought of as islet organs. Another key point is that this organized structure is important for optimal function. Thus, when we transplant autologous islets or alloislets, we think that their success depends upon their being micro-organs.

Of course, there is great interest in the prospect of using insulin-producing cells derived from stem cells for beta cell replacement therapy. But it remains to be determined if these derived cells will turn into micro-organs once transplanted. There are indications that they will, but time will tell.

In the meantime, we think there are strong reasons to say that autologous islets and alloislets are organs before they are isolated and that they should be considered to be organs once transplanted. Thus, taking into account how much we have learned about the structure and function of islet micro-organs, it seems highly illogical to on one hand consider autologous islets be regulated as organ transplants and alloislets to be regulated with the very restrictive rules used for cell transplantation.

It is particularly problematic that this policy has led to restrictions that have made it next to impossible for transplants of alloislets to be carried out in the US<sup>1-9</sup>, which is a very sad situation for the country that made so many of the advances that brought islet transplantation to the clinic.

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#### CONFLICT OF INTEREST:

The authors declare that they have no conflict of interest to disclose.

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