

## Islet Transplantation - perspective from Poland

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**Keywords:** Islet transplantation, Poland, Regulation.

### ABSTRACT

**The article describes impact of advanced research in the USA and collaborative approach of US scientists and clinicians on development of the field of islet transplantation in Poland and all over the world. At the same time, it presents negative consequences of islet regulation by FDA as a biological drug leading to decline and extinction of the field in the US, while it is on the rise worldwide.**

We have read the article by Ricordi and Japour in STATNEWS with great interest. It is difficult to believe that the USA, the country, which developed the islet transplantation procedure, optimized the islet isolation technique, and proved its safety and efficacy, still after 19 years of research and clinical experience cannot offer it as a standard of care to patients in need. The primary obstacle has been the regulation of allogeneic islets as a biological drug in the USA based on the premise from decades ago that the biological characteristics of islets may change (re-differentiation, growth, etc.) during 72 hours of incubation in culture media, when in fact the islets are only preserved in a steady state for logistical reasons prior to transplantation.

Of note, autologous islets isolated in the same GMP facility in the way with the same reagents as allogeneic islets but without short incubation, have not been regulated as a drug by FDA.

Based on the results of the US-based Collaborative Islet Transplantation trial, it has been clear that the biological properties and *in vivo* function of human islets are not significantly affected by this short incubation period. Therefore, there is no need to regulate allogeneic human islets as restrictively

as a biological drug (Advanced Therapy Medicinal Product)<sup>1</sup>. The regulatory agency of the European Union, the European Medicines Agency (EMA), has already taken this approach.

The first islet allotransplantation procedure in Poland was performed at the Medical University of Warsaw in June of 2008<sup>2</sup>. However, the path to this achievement was long and tortuous. Following the first description of the isolation of pancreatic islets in 1965 by a Polish scientist<sup>3</sup>, the islet isolation technique was further developed by research teams in the US and Canada, who pioneered clinical islet transplantation by introducing the procedure into the clinic<sup>4,5</sup>. Paul Lacy, David Sutherland, Camillo Ricordi, and James Shapiro, respectively, performed the first transplantation that resulted in insulin-independence, developed automated methods for islet isolation<sup>6</sup>, and implemented a revolutionary program of immunosuppressive treatment to prevent graft rejection<sup>7</sup>. Following decades of research and clinical development, the effectiveness of islet transplantation as a treatment was evaluated in the multicenter Clinical Islet Transplantation (CIT) trial sponsored by the NIH and JDRF. The CIT trial, which incorporated multiple centers, proved that the procedure can be safely and effectively replicated and inspired the development of an islet transplant program in Poland.

After the success of islet transplantation in North America, the leaders of the transplantation community in Poland received funding from the Ministry of Health to construct the first clinical islet isolation and cell processing facility in Warsaw. Polish teams received generous contributions of knowledge, experience, and resources by islet leaders from US-based centers, who provided advanced training, optimized islet cell processing and

clinical protocols, and key supplies including media, reagents, and equipment manufactured in the US. Physicians from Warsaw, supported by funding from the Polish Transplantation Society, were trained in islet transplant centers in Minnesota, Texas, and Milan. This collaboration with leaders in the field from the US culminated in the first clinical islet allotransplantation in Poland in 2008.

Further successful development of the program was possible due to European and Polish regulations classifying islets not as a biological drug (Advance Therapy Medicinal Products) but as a “tissue or organ for transplantation” under the authority of Poltransplant, the agency responsible for human organ and tissue sharing for clinical transplantation (the Polish equivalent of UNOS in the US), and the National Center of Tissue and Cell Banking (NCTCB) (Krajowe Centrum Bankowania Tkanek i Komórek). The regulation of human cadaveric islets as a “tissue for transplantation” enabled more rapid clinical development while maintaining the quality of the islet product and the efficacy of the procedure. In 2011, based on clinical data from the USA, Canada, and the first few cases in Poland, the Ministry of Health approved islet transplantation as an alternative to pancreas transplantation, a standard-of-care procedure fully reimbursed by the Polish National Health Fund. While islet cell processing centers are required to obtain an accreditation from the NCTCB, islet transplantation centers must be accredited by the National Council for Transplantation under the Ministry of Health. Current policy allows for and financially covers islet allo- and auto-transplantation not only into the liver via portal vein infusion, but also into the peritoneal and submucosal spaces, if intraportal access is not feasible or safe<sup>8,9</sup>.

The regulation of islets as a “tissue for transplantation” and not as an “Advanced Therapy of Medicinal Products” in Poland allowed for the rapid clinical implementation and introduction of a reimbursement system for the procedure by the National Health Fund. This was a key and critical factor that enabled the islet transplantation program in Poland to serve disadvantaged patients with the life-threatening brittle form of type 1 diabetes.

Last year, a second islet transplantation center emerged in Poland. The Medical University of Gdansk and a second Laboratory for Cell and Tissue Transplantation (CellT) were accredited by the proper authorities and have already performed 5 successful islet isolations and transplantations. Assistance

from the Islet Transplant Center at the University of Chicago in the US was instrumental for the development of this new program. In addition to receiving guidance during the construction of the cell processing facility as well as optimized clinical and islet cell isolation protocols, the team in Gdansk was trained extensively in Chicago and at home in Poland.

Clinical experience from Poland, in addition to that of other countries from around the world, has proven that the regulation of islets as a “tissue for transplantation” without the stringent requirements mandated for highly manipulated cellular therapies (“advanced therapy medicinal products”) is sufficient to reassure patients of the safety and efficacy of this treatment while offering significant advantages including the rapid development and clinical implementation of islet transplantation by limiting time, effort, and funding requirements. We do hope that the FDA will revise the regulation, adjusting it based on current knowledge and experience regarding the risks and benefits for patients. This would allow for the elimination of barriers to clinical islet transplantation in the US while maintaining the safety and efficacy of the procedure via current regulations for tissue and organ transplantation. In fact, human islets are more similar to organs than individual cells, and should be treated as such scientifically and by regulatory agencies. Islets have a consistent and sophisticated structure composed of multiple cell types, distinct and dedicated vasculature providing a blood supply, innervation by both autonomic and sensory nerves, and unique function essential to homeostasis. The structure and function of islets is preserved during transplantation in the same way as for all other solid organs. After procurement from a deceased donor, a whole pancreas is preserved under cold conditions, then islets are separated (isolated) from surrounding tissue, and then preserved in warm, as is often the case for other solid organs such as the liver, or lungs (OCS Lung System, Transmedics, Andover, MA). Islets and solid organs are transplanted as allogenic tissue under the same donor and organ distribution regulations and the same clinical management including immunosuppression therapy. There is no reason not to regulate human islets as any other solid organ in the US. The application of more restrictive standards than to solid organs may be perceived as some by “discrimination” based on size, only because human islets are smaller than solid organs. It is not only unfair but clearly detrimental to patients and the entire field.

## REFERENCES

1. <https://www.ema.europa.eu/en/human-regulatory/overview/advanced-therapy-medicinal-products-overview>
2. Wszola M, Kwiatkowski A, Berman A, Górski Ł, Chmura A. Islet transplantation as a treatment for complications of type I diabetes. *Pol Merkur Lekarski* 2013; 35: 127-132.
3. Moskalewski S. Isolation and culture of the islets of Langerhans of the guinea pig. *Gen Comp Endocrinol* 1965; 5: 342-353.
4. Lacy PE, Kostianovsky M. Method for the isolation of intact islets of Langerhans from the rat pancreas. *Diabetes* 1967; 16: 35-39.
5. Najarian JS, Sutherland DE, Matas AJ, Steffes MW, Simmons RL, Goetz FC. Human islet transplantation: a preliminary report. *Transplant Proc* 1977; 9: 233-236.
6. Ricordi C, Lacy PE, Finke EH, Olack BJ, Scharp DW. Automated method for isolation of human pancreatic islets. *Diabetes* 1988; 37: 413-420.
7. Shapiro AMJ, Lakey JRT, Ryan EA, Korbutt GS, Toth E, Warnock GL, Kneteman NM, Rajotte RV. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. *N Engl J Med* 2000; 343: 230-238.
8. Wszola M, Berman A, Ostaszewska A, Gorski L, Serwanska-Swietek M, Gozdowska J, Bednarska K, Krajewska M, Lipinska A, Chmura A, Kwiatkowski A. Islets allotransplantation into gastric submucosa in a patient with portal hypertension: 4-year follow-up. *Transplant Proc* 2018; 50: 1910-1913.
9. Wszola M, Berman A, Gorski L, Ostaszewska A, Serwanska-Swietek M, Krajewska M, Lipinska A, Chmura A, Kwiatkowski A. Endoscopic islet autotransplantation into gastric submucosa—1000-day follow-up of patients. *Transplant Proc* 2018; 50: 2119-2123.