

HIGHLIGHT

Vascularized Endocrine Constructs Offer New Hope for Scalable Insulin Delivery

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In DM type 1, insulin-producing β -cells are destroyed by autoimmunity. However, the glucose-responsive activity of native pancreatic islets cannot be fully mimicked by insulin therapy [1]. Insulin independence can be achieved in selected patients, and glycemic control can be improved with clinical islet transplantation [2]. The clinical use is, however, restricted due to limited donors, the requirement for lifelong anti-rejection medications, early-stage graft inflammatory damage, and limited graft survival. Despite the liver being the first organ to receive the islets (clinical islet infusion), it is a suboptimal microenvironment due to an immediate blood-mediated inflammatory reaction (IBMIR), loss of matrix, inadequate revascularization, and oxidative stress. These events diminish early engraftment and long-term function. Hence, alternative extrahepatic sites, such as omentum and subcutaneous space, have

attracted great interest as more desirable and accessible alternatives [3]. Bellofatto et al. [4] developed Amniogel, a scalable insulin delivery system based on blood outgrowth endothelial cells (BOECs), pancreatic islets, and GMP-compliant amniotic membrane-derived hydrogel (AMH) (Fig. 1). This platform will promote a more supportive extracellular matrix and vascularization, resulting in better islet engraftment and function after extrahepatic transplantation.

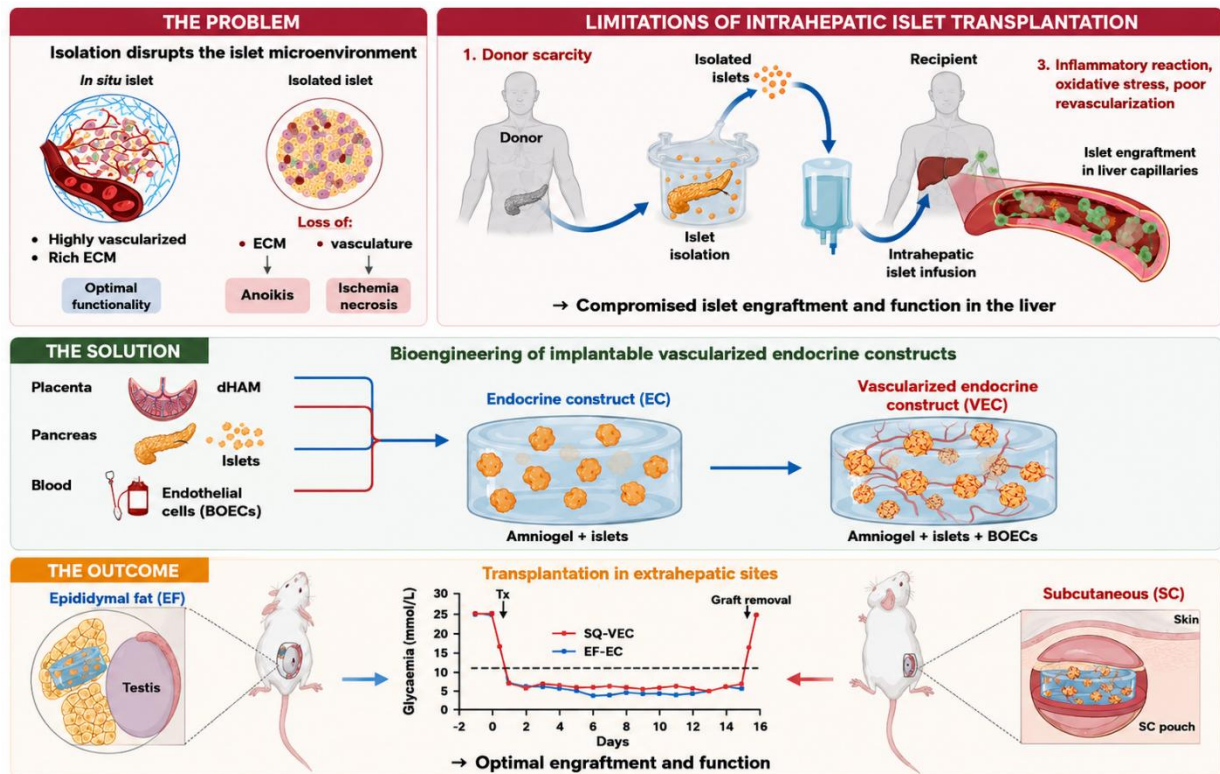


Figure 1. An illustration of an insulin-delivery, vascularized, implantable endocrine platform.

One important aspect of this project is that Amniogel is not just a structural scaffold. It provides extracellular matrix-bound survival signals that help isolated islets recover from the stress of isolation. Islet isolation disrupts the native matrix and the vascular niche, leading to β -cell injury and functional loss [5]. In the study by Bellofatto et al., Amniogel was shown to enhance islet viability, maintain hormone expression, enhance β 1-integrin signaling, reduce apoptotic markers, and increase glucose-stimulated insulin secretion [4]. These results emphasize the value of restoring cell–matrix connections for efficient β -cell replacement.

The second foremost modernization is prevascularization. BOECs self-assembled inside Amniogel and created vascular-like networks around islets. This is essential as vascularization is mandatory for nutrient exchange, glucose sensing, oxygen delivery, and rapid insulin release. Prior tissue-engineering reports have also confirmed that vascular support can enhance islet survival and performance after transplantation [6, 7]. In the Bellofatto et al. study, BOECs deposited a laminin-rich basement membrane around the islets and improved connexin-mediated cell communication. This made a more physiological endocrine niche. In vivo, Amniogel endocrine constructs achieved better glycemic control than islets alone in the well-vascularized epididymal fat pad, whereas non-vascularized constructs were ineffective in the poorly vascularized subcutaneous site. These findings evidently

indicate that matrix support alone is not sufficient when the transplant site lacks sufficient blood supply. When BOECs were added, the vascularized endocrine constructs restored durable normoglycemia after subcutaneous implantation and outperformed nonvascularized controls [4].

The subcutaneous space is clinically attractive because it is accessible, safer to monitor, and easier to retrieve than the liver. However, its poor vascularity has long limited its use for islet transplantation. Bellofatto et al. [4] show that prevascularized Amniogel constructs may help overcome this limitation. This approach could support future modular graft designs, in which multiple small implants are placed across subcutaneous pockets to improve oxygenation and reduce the risk of central necrosis. Computational modeling studies also support thin and distributed graft designs for bioartificial pancreas devices [8]. Another interesting feature of the platform is that Amniogel may have an immune barrier effect. The authors demonstrated that Amniogel significantly inhibited β -cell killing and CD8⁺ cell migration in vitro. This is good news, as immune rejection remains a significant problem with β -cell replacement. An immune-protective effect has been shown in simplified in vitro models, which must be confirmed in allogeneic, immunocompetent, or humanized in vivo models.

The human amniotic membrane (hAM) has been derived appropriately, clinically proven, and

extensively used in wound healing and regenerative medicine, making Ammiogel highly promising for clinical applications [9]. The production protocol was also adapted to GMP standards, further enhancing its translational potential. Nevertheless, some critical issues remain. The construct should be scaled up to clinically relevant islet doses, vascularization should be validated in larger models, and regulatory considerations for combination products of cells and biomaterials should be discussed [10]. Overall, Bellofatto et al. [4] offer impressive proof-of-concept for vascularised endocrine constructs. This platform overcomes major hurdles to successful extrahepatic islet transplantation. It furthers the development of clinically translatable islet insulin delivery platforms by incorporating ECM support, forming vascular networks, and using clinically scalable hydrogel. Future studies should focus on long-term safety, immune protection, compatibility with stem cell-derived β -cells, and scalable manufacturing.

Declaration of Competing Interest

The author declares no competing financial interests.

Authorship contribution statement

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