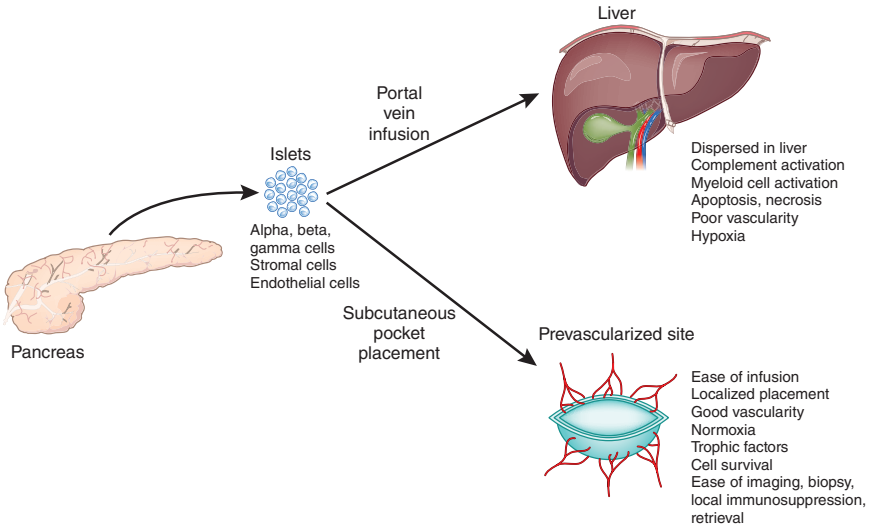


Marina Corral Spence/Nature Publishing Group

**Figure 1** Islet preparation and sites for implantation. Relative advantages and disadvantages of portal and subcutaneous implantation sites.

and fibrosis. They reasoned that short-term device implantation would create a prevascularized space to accept and support islets. They also reasoned that once established, the catheter could be removed, obviating catheter-related complications of infection and pathologic inflammation. Their results convincingly demonstrate that 4-week implantation of a clinically approved nylon catheter creates a vascularized space. The site supports syngeneic islets that survive and cure diabetes almost as well as islets transplanted to the more conventional kidney subcapsular space. Transplantation is effective for at least 100 days, for different strains of mice, for mice made diabetic for several weeks before transplant, for allogeneic islets and for human islets in a xenogeneic model. In contrast, transplantation to unmodified dermis or skin resulted in almost immediate islet death.

This is an early study and many parameters remain to be refined, such as biomaterial selection and geometry, timing of implantation, and interval between implant removal and transplant. It was assumed that neovascularization was critical but was not formally proved; and if this proves to be true, the nature of the 'best' vasculature is unknown. The cytokines, chemokines and growth factors induced by the catheter were assumed to be important for the success of the site but remain to be investigated for their effects on islet biology. The subcutaneous site was not as effective as the kidney subcapsular site, and the reasons for this are unknown, but may relate to vascularity, survival or growth. The durability of islet function beyond 100 days is not known. It will be important to determine if the exuberant fibrosis seen around the islets (Figs. 2 and 6 in ref. 1) is stable or progresses, and whether this new site is able to support the self-renewing functions of beta cells. Another group used a similar approach in rats but with more novel, unapproved agents to establish a seemingly immune-privileged subcutaneous site[8].

The findings here are exciting because if similar results can be achieved in other species, and if enough subcutaneous space can be constructed for scalability to larger animals and humans, then islet transplantation may become a procedure that can be delivered far more readily. Without the large initial cell death accompanying portal infusion, this site may be more durable and preserve beta-cell renewal capacity. Other challenges remain. Implantation into the skin engages a different immune environment compared to the liver. In humans, transplant of liver is the easiest to tolerate immunologically and requires less immunosuppression than transplants of other organs, although this does not seem to protect portal-implanted islets[9]. In contrast, it has been challenging with composite tissue allografts, which comprise skin and its supporting structures, to provide safe levels of maintenance immunosuppression without frequent rejections or drug toxicities, suggesting that it may be more difficult to suppress alloimmunity in this location[10]. An important implication of the results is that transplantation of beta stem and progenitor cells becomes far more realistic as the cells can not only be imaged and biopsied, but also retrieved should they develop unregulated insulin output or neoplastic characteristics. Lastly, it is important to acknowledge that islets compete with closed-loop technologies for glucose sensing and insulin delivery[11]. Ultimately, durability, reliability, long-term outcomes, patient characteristics, and the cost of procedures, drugs and technology will determine which treatments prevail.

COMPETING FINANCIAL INTERESTS
The author declares no competing financial interests.

1. Pepper, A.R. *et al. Nat. Biotechnol.* **33**, 518–523 (2015).
2. Shapiro, A.M. *et al. N. Engl. J. Med.* **343**, 230–238 (2000).
3. Ryan, E.A. *et al. Diabetes* **54**, 2060–2069 (2005).
4. Harlan, D.M., Kenyon, N.S., Korsgren, O. & Roep, B.O. *Diabetes* **58**, 2175–2184 (2009).
5. Hlavaty, K.A. *et al. Am. J. Transplant.* **14**, 1523–1532 (2014).
6. Tomei, A.A. *et al. Proc. Natl. Acad. Sci. USA* **111**, 10514–10519 (2014).
7. Maffi, P. *et al. Diabetes* **62**, 3523–3531 (2013).
8. Luan, N.M. & Iwata, H. *Am. J. Transplant.* **14**, 1533–1542 (2014).
9. Feng, S. *et al. J. Am. Med. Assoc.* **307**, 283–293 (2012).
10. Schneeberger, S. *et al. Transpl. Int.* **24**, 760–769 (2011).
11. Russell, S.J. *et al. N. Engl. J. Med.* **371**, 313–325 (2014).

## Research Highlights

*Papers from the literature selected by the Nature Biotechnology editors. (Follow us on Twitter, @NatureBiotech #nbtHighlight)*

**Genome-wide CRISPR screen in a mouse model of tumor growth and metastasis**
Chen, S. *et al. Cell* **160**, 1246–1260 (2015)

**The genetic architecture of the human immune system: a bioresource for autoimmunity and disease pathogenesis**
Roederer, M. *et al. Cell* **161**, 387–403 (2015)

**Identification of a large set of rare complete human knockouts**
Sulem, P. *et al. Nat. Genet.* doi:10.1038/ng.3243 (25 March 2015)

**Structural imprints *in vivo* decode RNA regulatory mechanisms**
Spitale, R.C. *et al. Nature* **519**, 486–490 (2015)

**The mutagenic chain reaction: a method for converting heterozygous to homozygous mutations**
Gantz, V. *et al. Science*, doi:10.1126/science.aaa5945 (19 March 2015)

**Soft, curved electrode systems capable of integration on the auricle as a persistent brain–computer interface**
Norton, J.J.S. *et al. PNAS* **112**, 3920–3925 (2015)