

Interim IXA recommendations for clinical islet xenograft trials

2/17/08

IXA has developed an interim consensus statement on preclinical efficacy and safety milestones that we believe should be met before initiation of a clinical islet xenotransplant trial. This document is intended as a guide for academic and corporate programs and regulatory agencies until a formal consultative process on clinical islet xenotransplant trial recommendations is completed.

The infectious risks associated with xenotransplantation trials are borne not only by study participants but by society at large. For this reason IXA strongly recommends that preclinical efficacy should be demonstrated in non-human primates as a prerequisite to justify clinical trials. The results of primate studies should suggest that the chances of success for the human subjects are sufficiently high to balance predictable risks, while keeping in mind that there may be additional unknown risks.

With respect to efficacy in preclinical studies, IXA would support a clinical trial if at least 5 of 10 consecutive primate recipients of islet xenografts are normoglycemic and exogenous insulin-free for 6 months post-transplant, and if at least 2 remain insulin independent for 12 months on a clinically applicable immunotherapeutic protocol. For the example of porcine islet grafts in primates, islet function should be documented at least weekly by 1) demonstration of circulating PORCINE insulin or C-peptide with pig-specific tests (by specific ELISA or HPLC), 2) demonstration of minimal or absent PRIMATE insulin or C-peptide (by specific ELISA or HPLC) both under fasting conditions and in response to glucose challenge, and 3) glycosylated hemoglobin (HgbA1c) <7.5%. Insulin-free survival can be achieved in primates after porcine islet cell transplantation (1-3). While less stringent evidence might prove acceptable as the basis for approval of a clinical islet xenograft trial in the context of thorough peer-review and informed public consideration, the IXA strongly recommends that efficacy sufficient to proceed to clinical investigation should be defined as primate survival dependent on the islet xenograft, without requirement of exogenous insulin.

The definition of a “clinically applicable” immunotherapeutic protocol will differ according to the clinical situation of the intended patient population. Such a regimen must balance the risks of the treatment regimen against the likely benefit for that subject. For example, an immunosuppressive regimen highly similar in intensity and composition to that currently employed for organ or islet allograft recipients would be considered clinically applicable, especially if the intended subject would already receive that chronic immunosuppressive regimen for another reason, such as a prior or concurrent renal allograft. Where ever possible, immunosuppression should be minimized, based on islet modification by genetic engineering of source animals and/or islet encapsulation. Subject age, health status, and predicted life span with and without islet transplant should be considered in assessing clinical applicability.

Any proposed clinical trial should be conducted in keeping with published IXA ethics guidance (4). Oversight of xenotransplantation trials by a national health authority should include specific regulations for animal husbandry and recipient monitoring. The specific safety studies will largely depend on the islet product and the proposed immunotherapeutic strategy. At a minimum, blood and tissues from the source animal

Interim IXA recommendations for clinical islet xenograft trials

2/17/08

and recipient serum collected before and at regular intervals after transplant should be archived for future investigation of unexpected or untoward events.

- 1) Hering BJ, Wijkstrom M, Graham ML, et al. Prolonged diabetes reversal after intraportal xenotransplantation of wild-type porcine islets in immunosuppressed nonhuman primates. *Nat Med* 2006; 12(3): 301-3.
- 2) Cardona K, Korbitt GS, Milas Z, et al. Long-term survival of neonatal porcine islets in nonhuman primates by targeting costimulation pathways. *Nat Med* 2006; 12(3): 304-6.
- 3) Rood PP, Cooper DK. Islet xenotransplantation: are we really ready for clinical trials? *Am J Transplant* 2006; 6(6): 1269-74.
- 4) Sykes M, d'Apice A, Sandrin M; IXA Ethics Committee. Position paper of the Ethics Committee of the International Xenotransplantation Association. *Transplantation* 2004; 78(8): 1101-7. Bloom ET. Xenotransplantation--federal regulatory considerations. *Curr Top Microbiol Immunol* 2003; 278: 239-51.
- 5) Bloom ET. National policies for xenotransplantation in the USA. *Xenotransplantation* 2007; 14(4): 345-6.
- 6) Bloom ET. New FDA xenotransplantation documents: a proposed rule and a draft guidance. *Xenotransplantation* 2001; 8(3):153-4.

The proceedings of the June 2007 Stockholm Summit on Pig-to-Human Islet Xenotransplantation are in press in Xenotransplantation. A confidential draft of this document might be obtained by contacting the editor of the Journal, Professor Carl Groth.