Cellular xenotransplantation

To the editor—Concerns have been raised about the possibility that endogenous retroviruses present in xenogeneic tissue, as described in porcine cells, could infect human cells and lead to new, transmissible human diseases[1]. These concerns led to calls for moratoria in the USA and several European countries[2,3] and spurred the US Food and Drug Administration to issue guidelines that, in effect, temporarily halted clinical protocols using grafts derived from non-human primates[4,5]. This blanket approach of regulating all xenotransplantation procedures under the same terms is inappropriate, given the different risks involved.

The hazards of xenotransplantation are influenced not only by the origin of the donor animal, but also by the type of cells and their processing. Cellular transplantation not only holds the greatest clinical promise but offers possibilities for modulating the risks of xenoosis. It is also important to realize that although the field of organ xenotransplantation is still in its pre-clinical developmental stage, cellular transplantation has already reached the clinic.

Several phase I clinical studies have demonstrated the long-term survival of primary xenogeneic cells in human recipients, as evidenced by the transplantation of fetal pig nerve cells to the brain of patients with Parkinson disease[6] and the transplantation of pancreatic fetal beta cells into diabetics[7]. In regard to biosafety, these approaches are similar to organ transplants, as it is impossible to fully screen every donor animal between the time it is killed and the time of transplantation. Moreover, the costs of biosafety tests for each donor animal would be prohibitive.

In contrast, cell lines can be grown in culture and expanded into cell banks from clonal origin, ensuring a high reproducibility from patient to patient. Cell lines can also be cryopreserved pending the completion of safety evaluations. Typically, each cell bank can be tested for the absence of pathogens following the guidelines of the FDA applied for the production of recombinant proteins or vaccines. Most importantly, cell lines can be selected for the absence of shedded amphotropic retroviruses. Various clinical trials involving xenogeneic cell lines are already underway. In a phase III study, patients suffering from brain tumors received a mouse cell line genetically engineered to release a viral vector containing the 'suicide' gene thymidine kinase[8,9] and in a phase I/II study, xenogeneic primate-derived cells genetically modified to secrete interleukin-2 were reported to induce a regression of tumor cells in patients[10].

To further improve biosafety, xenogeneic cells can be encapsulated in a semipermeable membrane with a controlled pore size, allowing the inward diffusion of nutrients and the outward diffusion of the secreted bioactive therapeutic agent. Not only does this eliminate cell-to-cell contact between the donor and host cells while minimizing the entry of immunocompetent molecules, but also the pore size of the membrane can be selected to prevent the potential diffusion of infective viruses. Examples of clinical trials using this approach include encapsulated primary porcine hepatocytes to bridge the gap between fulminant hepatic failure and the transplantation of an allogeneic liver (phase II–III trials)[11], the treatment of intractable terminal cancer pain with primary bovine chromaffin cells secreting analgesic substances (phase II trial)[12] and hamster cells genetically modified to secrete ciliary neurotrophic factor, a candidate for the treatment of amyotrophic lateral sclerosis (phase I trial)[13].

Guidelines on xenotransplantation should take into account the specificity of cell transplantation. They should differentiate between primary cells, cell lines and the possibility of encapsulating transplanted cells. Broader guidelines that attempt to regulate all xenotransplantation procedures will impede the development of promising cell-based treatments.

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Serum amyloid P component (not Serum Amyloid Protein)

To the editor—We enjoyed reading the June issue *News & Views* article[1] by Paul and Carroll that accompanied our paper[2] reporting the development of antinuclear autoimmunity in mice with targeted deletion of the gene for serum amyloid P component (abbreviated as SAP, according to the World Health Organization–International Union of Immunological Societies nomenclature of disease). It is, however, important to identify this protein correctly. There is no such thing as "serum amyloid protein," which appears on the cover of the journal and in the article by Paul and Carroll. This is not a trivial point, as most of the proteins in amyloid deposits are serum proteins. It is also important to recognize that far from just suffering 'guilt by association' with amyloid deposits, SAP contributes to the pathogenesis of amyloidosis *in vivo*[3,4].

Although it is tempting to link our findings in the SAP knockout mice to the human disease of systemic lupus erythematosus (SLE), as Paul and Carroll sought to do, SLE patients do not have SAP deficiency and there is no robust evidence for structural polymorphism of the human SAP gene, protein or glycan. A genetic polymorphism linked to, but not within, the human SAP gene has no effect on the structure, function or *in vivo* metabolism of SAP (ref. 5). Human SAP has one of the most invariant glycans of any known gly-