Published in final edited form as:

Curr Opin Organ Transplant. 2014 April ; 19(2): 131–132. doi:10.1097/MOT.0000000000000056.

Underpinnings of cellular organ replacement therapies

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Dialysis as a therapy for end-stage kidney failure is life preserving but replaces only a small fraction of normal kidney function and has and considerable morbidity. Kidney transplantation provides a higher level of renal function and a less constrained lifestyle. However, it is limited by the numbers of human organs available. Use of oral hypoglycemic drugs and insulin are cornerstones of treatment for diabetes mellitus. However, adequate control of glucose levels cannot be attained by most patients, and intensive insulin therapy leads to hypoglycemia. In contrast, whole pancreas or islet transplantation can normalize glucose control. Unfortunately, a major limitation to the use of either is the insufficient supply of human organs. Furthermore each requires the use of immune suppression that, in effect, trades one set of morbidities (associated with diabetes and its medical treatment) for another (associated with immune suppression) [1].

Cell therapies offer an alternative to whole organ replacement. This issue of Current Opinion in Organ Transplantation, organogenesis and organ regeneration and repair after transplantation focuses on novel cell therapies under development for kidney disease and diabetes mellitus and the some of the scientific underpinnings that will enable their use.

The first contribution, Classic and current opinion in embryonic organ transplantation [2] represents an exercise of the section editor's prerogative to summarize his investigations into the use of embryonic kidney or pancreas transplantation as an organ replacement therapy. Historical (classic) precedents for the use of embryonic primordia as donor organs are reviewed as are important antecedent investigations, one [3] from a contributing author for this issue [4]. An important key point is, on the basis of the author's experience and that of others, it is impossible to know what will happen after an embryonic organ is transplanted to an ectopic site until one does the experiment.

In the second contribution, Drs. Patricia Murray and Adrian Woolf update the journal's readership on the use of stem and progenitor cells to recapitulate kidney function [4]. Within this field, the authors highlight recent research papers focusing on mesenchymal stem cells (MSCs), embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs) and kidney-derived stem/progenitor cells (KSPCs). In preclinical studies, MSCs ameliorate varied acute and chronic kidney diseases. Their efficacy depends on immunomodulatory and paracrine properties. MSCs do not differentiate into functional kidney epithelia. iPSCs can be derived

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Conflicts of Interest: None

from healthy individuals or from patients with kidney disease by forced expression of precursor genes. Like ESCs, iPSCs are pluripotent and theoretically have the potential to form functional kidney epithelia when used therapeutically. KSPCs, existing as cell subsets within adult and developing kidneys, constitute attractive future therapeutic agents. Molecular, morphological and functional characterization of 'kidney cells' generated from ESCs, iPSCs, KSPCs have not been exhaustive, and long-term safety associated with their use has yet to be established.

Next, Drs. Luis Tapias and Harald Ott summarize recent investigations employing the use of decellularized scaffolds to bioengineer functional organs including heart, lung, and liver [5]. In addition, Dr. Ott's own elegant work describing regeneration and experimental orthotopic transplantation of a bioengineered kidney occupies a deservedly prominent place in the review [6]. Decellularized whole-organ scaffolds can be obtained from virtually any organ in the body. The scaffolds retain the specific microarchitecture of the extracellular matrix preserving the organ's three dimensional blueprint. The use of human pluripotent stem cells extracted from a patient requiring organ replacement holds great promise to repopulate decellularized scaffolds. Bioengineered organs have been successfully created in the laboratory and transplanted in small animal models. However, thus far the regenerated organs have shown only rudimentary function [5].

A review highlighting current insights into the renal collecting system is next. Drs. Kevin Bush, Gleb Martovetsky and Sanjay Nigam explain why the ureteric bud can be considered an iterative tip-stalk generator (ITSG), how its morphogenesis can be recapitulated *ex vivo*, and how cultured ureteric bud retains inductive competence and can incorporate appropriately into engineered kidney like tissues. The authors propose that the inherent ability of the ureteric bud to branch can be exploited to generate the scaffold around which to build a renal structure *ex vivo*, as happens during kidney development.

This issue concludes with a manuscript from Drs Ricardo Calafiore, Pia Montanucci and Guiseppe Basta that outlines strategies for stimulating endogenous pancreatic progenitor cells or for using of exogenous stem cells for the treatment of diabetes mellitus [8] and one from Drs. Aaron DeWard, Junji Komori and Eric Lagasse entitled, Ectopic Transplantation sites for cell-based therapy [9]. Drs. DeWard, Komori and Lagasse opine that a major reason why hematopoietic stem cell transplantation has been superior to alternative cell therapies is the ability to adequately address what they term the four S's: source, surveillance, safety, and site. Their review briefly discusses each of these components, with the main focus on the site of transplantation as a major factor to achieve clinical success. The authors consider potential benefits and limitations of ectopic transplantation sites used in rodent studies that could be employed in patients. The sites include the sub-renal capsular, subcutaneous, intra peritoneal or intra venous spaces, and the spleen or muscle. They point out that the ideal transplantation site needs to be relatively accessible, provide sufficient space, offer access to vasculature, and support long-term engraftment, suggest that the lymph node meets these criteria better than other commonly used sites, and envision the lymph node acting as an *in vivo* bioreactor to support ectopic tissue function [9]. Interestingly, members of this group have described engraftment of functional hepatocytes in lymph nodes following intra

peritoneal injection [10], similar to engraftment of beta cells originating from embryonic pig pancreas after mesenteric implantation [2].

The contributions included herein reflect the section editor's interest in using cell based therapies to replace renal or endocrine pancreatic function. Each of the authors is recognized for innovative approaches directed towards this end, and each has defined his or her own work within the context of the scientific literature at large. As is customary for Current Opinion in Organ Transplantation, most of the citations are very current and those of particular interest are annotated. However, some of the cited literature is classic reflecting what is a longstanding quest to develop novel treatments for human disease using 'replacement' cells. The outcome of the quest, like the endeavors of those involved in it, remains a work in progress.

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