HHS Public Access

Author manuscript

Kidney Int. Author manuscript; available in PMC 2016 May 01.

Published in final edited form as:

Kidney Int. 2015 November ; 88(5): 1196–1197. doi:10.1038/ki.2015.262.

Cell-based immunosuppression in kidney transplantation: the value of non-human primate studies

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To the Editor

In their review, Hutchinson and Geissler[1] present a well-argued case for testing immunoregulatory cell-based immunosuppression in early-phase (phase I/II) clinical trials in renal transplantation. Extensive rodent studies have documented the potential of innate and adaptive regulatory immune cells to prolong allograft survival and induce transplant tolerance. Limited reports have demonstrated the feasibility of delivering such regulatory cells in human hematopoietic stem cell or organ transplantation. The significant barriers faced when translating these approaches to the clinic can be addressed in outbred non-human primates (NHP) that have immune systems and histories of immune exposures similar to humans. These models have allowed rigorous pre-clinical assessment of the most promising tolerogenic strategies[2] (eg donor bone marrow-induced mixed chimerism[3]) that have been applied in clinical renal transplantation.

Three recent NHP studies demonstrate the safety and efficacy of regulatory immune cell-based therapy in renal transplantation. Thus, ex-vivo expanded, donor antigen-specific regulatory T cells prolong MHC-mismatched kidney allograft survival in monkeys when combined with ATG and low dose sirolimus[4]. Renal transplant rejection can also be safely prevented in cyclosporine and cyclophosphamide-treated monkeys and donor-specific tolerance induced by a single post-transplant (day 13) infusion of anergic (regulatory) T cells.[5] Furthermore, infusion of (donor-derived) regulatory dendritic cells to prospective renal allograft recipients a week before transplant, together with costimulation blockade and sirolimus, safely prolongs graft survival, without evidence of host sensitization.[6]

These NHP studies underscore the potential safety and efficacy of innate or adaptive regulatory immune cell therapy in robust pre-clinical models and provide additional justification for testing these cell products in phase I/II trials in kidney transplantation.

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Acknowledgments

The authors' work is supported by National Institutes of Health (NIH) research grants as part of the NIH NHP Transplantation Tolerance Cooperative Study Group sponsored by the NIAID and NIDDK.

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