Transplantation: from tolerance to rejection

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"'Transplantation: from tolerance to rejection' is focused on organ transplant immunobiology and immunosuppression and aims to address some of the hot topics of modern transplantation."

As the appointed Guest Editors, we are delighted to introduce this special focus issue of *Expert Review of Clinical Immunology*. "Transplantation: from tolerance to rejection" is focused on organ-transplant immunobiology and immunosuppression and aims to address some of the hot topics of modern transplantation. It has been conceived and implemented as a paradigm of high-quality continued postgraduate training for transplant operators and as a valuable update for clinicians and researchers working in and around this rapidly changing field.

In the first paper, Tisone's group at the Tor Vergata University of Rome, Italy, illustrates the impact of an immunosuppression-free status on the natural history of HCV infection and disease-recurrence after liver transplantation [1]. His group has pioneered immunosuppression-weaning investigations in this category of liver transplant patients [2–5]. Based on the evidence that the magnitude of impairment of the host immune system is among the main determinants of the severity of the progression of HCV recurrence after the transplant, he hypothesized that the full resumption of the host immune-competence following the complete withdrawal of immunosuppression would improve the natural history of HCV recurrence in the graft. Short-term [5], mid-term [4] and long-term (Manzia *et al.*, Unpublished data) results have confirmed the working hypothesis. Importantly, the Tor Vergata's experience represents the background rationale of a large, multicenter, randomized, prospective trial sponsored by the NIH immune tolerance network [101], which aims to confirm such hypothesis in a larger and more heterogeneous patient population.

In their paper on the minimization of immunosuppression after hand transplantation, Brandacher, Lee and Schneeberger from John Hopkins University School of Medicine (MD, USA) describe the state-of-the-art immunosuppression management in the setting in question [6]. After concisely describing the unique immunological and biological aspects of vascularized composite allografts, the authors provide evidence that the implementation of immunosuppression minimization strategies is both possible and safe. Furthermore, they clearly outline the most recent investigations aiming to achieve tolerance in translational animal studies and they anticipate the results of the first clinical trials in reconstructive transplantation.

Significant progress has been made in clinical organ transplantation toward an improvement in allograft survival and function with the application of efficient immunosuppressive medicine. However, long-term allograft function is still limited by the development of chronic allograft rejection and recurrent diseases, which have consequently received great attention. In their review, entitled "Chronic rejection: a significant role for Th17-mediated autoimmune responses to self-antigens," Subramanian and Mohanakumar (Washington University School of Medicine, MO, USA) emphasize the important role of alloimmune responses to donor-specific antigens and autoimmune responses to tissue-restricted self antigens in the immunopathogenesis of chronic graft rejection [7]. In particular, they discuss the role of Th17 autoimmunity and the cross-talk between autoimmune- and alloimmune-responses.

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Efficient and accurate diagnosis for the pathological alteration of allografts is critical for clinical treatment in organ-transplanted patients. In their review entitled "Post-transplant liver biopsy and the immune response: lessons for the clinician," Shetty, Adams and Hubscher (University of Birmingham, UK) systematically discuss the contribution of long-term immunosuppression, recurrent disease and liver graft-inflammation including *de novo* autoimmune disease and idiopathic post-transplant hepatitis to the complex and atypical features on biopsy specimens [8]. Thus, they speculate that genetic and immune profiling in liver biopsy may be predictive for the identification of patients in whom immunosuppression can be safely withdrawn.

Insufficiency of allogeneic donor organs is still a great limitation for clinical organ transplantation. In their review entitled "Immunobiology of liver xenotransplantation," Ekser *et al.* excellently discuss the progress and obstacles for the potential clinical application of xenogeneic pig liver [9]. They point out that the immediate development of thrombocytopenia is very limiting for pig liver xenotransplantation, even when used as a 'bridge' to clinical allo-liver transplantation. Thus, they emphasize that the aim of current studies is to understand the immunobiology of platelet activation, aggregation and phagocytosis after xenogeneic pig liver transplantation.

In an interview titled "Minimization of immunosuppression in liver transplantation: steps from 'how' to 'now,' Lerut from UCL Brussels, Belgium, discusses how he came to be involved in research in this area and the rationale and required steps for steroid-free immunosuppression [10]. Giving his opinion on recent research and the protocol implemented at his institute, he outlines his thoughts on the next 5 years for research in this field.

Orlando *et al.* illustrate in their review how regenerative medicine may meet those needs of organ transplantation that so far have been addressed through a traditional immunological approach [11]. The authors are affiliated to the School of Medicine of the Wake Forest University (NC, USA), and their research is focused on organ bioengineering and pancreatic islet isolation [12–18]. The manuscript briefly describes the two main regenerative medicine-based strategies that are currently being developed to allow transplantation of different organs without any immunosuppression, namely encapsulation and immunocloacking. The manuscript reaffirms the potential that regenerative medicine holds to the transplant field.

In summary, we are delighted to introduce the present special issue of *Expert Review of Clinical Immunology* focusing on organ transplantation. We believe that the reader will enjoy it and will find interesting and stimulating information on how the field of organ transplantation is evolving in the coming decades.

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References

1 Tisone G, Manzia TM, Angelico R, *et al.* HCV recurrence and immunosuppression-free state after liver transplantation. *Expert Rev. Clin. Immunol.* 8(7), 635–644 (2012).

2 Orlando G. Finding the right time for weaning off immunosuppression in solid organ transplant recipients. *Expert Rev. Clin. Immunol.* 6(6), 879–892 (2010).

3 Orlando G, Soker S, Wood K. Operational tolerance after liver transplantation. *J. Hepatol.* 50(6), 1247–1257 (2009).

4 Orlando G, Manzia T, Baiocchi L *et al.* The Tor Vergata weaning off immunosuppression protocol in stable HCV liver transplant patients: the updated follow up at 78 months. *Transpl. Immunol.* 20, 43–47 (2008).

5 Tisone G, Orlando G, Cardillo A *et al.* Complete weaning off immunosuppression reduces the progression rate of fibrosis in HCV liver transplant patients with recurrence of disease: mid-term results. *J. Hepatol.* 44, 702–709 (2006).

6 Brandacher J, Lee WPA, Schneeberger S. Minimizing immunosuppression in hand transplantation. *Expert Rev. Clin. Immunol.* 8(7), 673–684 (2012).

7 Mohanakumar T, Subramanian V. Chronic rejection: a significant role for Th17-mediated autoimmune responses to self-antigens. *Expert Rev. Clin. Immunol.* 8(7), 635–672 (2012).

8 Shetty S, Adams DH, Hubscher SG. Post-transplant liver biopsy and the immune response: lessons for the clinician. *Expert Rev. Clin. Immunol.* 8(7), 645–661 (2012).

9 Ekser B, Burlak C, Waldman JP *et al.* Immunobiology of liver xenotransplantation. *Expert Rev. Clin. Immunol.* 8(7), 621–634 (2012).

10 Lerut J. Minimalization of immunosuppression in liver transplantation: steps from 'how' to 'now'. *Expert Rev. Clin. Immunol.* 8(7), 605–607 (2012).

11 Pareta R, Sanders B, Babbar P *et al.* Immunoisolation: where regenerative medicine meets solid organ transplantation. *Expert Rev. Clin. Immunol.* 8(7), 685–692 (2012).

12 Orlando G, García-Arrarás JE, Soker T *et al.* Regeneration and bioengineering of the gastrointestinal tract: current status and future perspectives. *Dig. Liver Dis.* (2012).

13 Orlando G, Bendala JD, Shupe T *et al.* Cell and organ bioengineering technology as applied to gastrointestinal diseases. *Gut* (2012) doi: 10.1136/gutjnl-2011-301111 (Epub ahead of print).

14 Orlando G, Wood KJ, De Coppi P *et al.* Regenerative medicine as applied to general surgery. *Ann. Surg.* 255(5), 867–880 (2012).

15 Orlando G. Immunosuppression-free transplantation reconsidered from a regenerative medicine perspective. *Expert Rev. Clin. Immunol.* 8(2), 179–187 (2012).

16 Orlando G, Wood KJ, Soker S, Stratta RJ. How regenerative medicine may contribute to the achievement of an immunosuppression-free state. *Transplantation* 92(8), e36–e8; author reply e39 (2011).

17 Orlando G. Transplantation as a subfield of regenerative medicine: an interview by Lauren Constable. *Exp. Rev. Clin. Immunol.* 7, 137–141 (2011).

18 Orlando G, Baptista P, Birchall M *et al.* Regenerative medicine as applied to solid organ transplantation: current status and future development. *Transpl. Int.* 24, 223–232 (2011).

Website

101 Immune tolerance network. Gradual Withdrawal of Immunosuppression in Patients Receiving a Liver Transplant (AWISH). www.immunetolerance.org/studies/gradual-withdrawal-immunosuppression-patients-receiving-liver-transplant-awish