Transplant International ISSN 0934-0874

SPECIAL ARTICLE

European research on cell and organ transplantation: towards novel opportunities?

Michel Goldman[1] and Kathryn Wood[2]

1 Institute For Medical Immunology, Université Libre de Bruxelles, Gosselies, Belgium
2 Transplantation Research Immunology Group, Nuffield Department of Surgery, University of Oxford, Oxford, UK

Keywords
biomarker, immunosuppression, tolerance, transplantation.

Correspondence
Michel Goldman MD, PhD, Institute for Medical Immunology, Université Libre de Bruxelles (U.L.B.), 8 rue Adrienne Bolland, B-6041 Gosselies, Belgium. Tel.: +32 2 650 95 60; fax: +32 2 650 95 63; e-mail: mgoldman@ulb.ac.be

Received: 11 April 2007
Revision requested: 30 April 2007
Accepted: 16 August 2007

doi:10.1111/j.1432-2277.2007.00554.x

Summary

Recent developments in basic and translational immunology open new exciting perspectives for clinical cell and organ transplantation, including the development of novel immunosuppressive agents, new diagnostic tools and validation of biomarkers for the prediction of rejection as well as the induction of tolerance. With respect to tolerance, a number of hurdles still need to be overcome before immunosuppressive drugs can be safely minimized or withdrawn in solid organ transplant recipients. Indeed, the human immune system appears more resistant to tolerance induction than expected from experimental studies in animals. Furthermore, the basic ethical principle '*primum non-nocere*' prevents the implementation of clinical protocols endowed with a significant risk for graft and/or patient survival. With this background, the European Commission recently launched several initiatives to tackle unmet needs in transplantation medicine. Herein, we focus attention on the ongoing collaborative effort across the European Union aiming at identifying the current priorities requiring better integration of resources dedicated to transplantation research.

The numbers of patients undergoing organ or cell transplantation has increased steadily over the years and around 250 000 individuals are now living in Europe with a transplanted organ. The immunosuppressive drugs that are currently used in the clinical practice are efficient in preventing or controlling early acute rejection episodes or graft versus host disease and allow for the excellent results of organ transplantation in the short term. However, the long-term outcome of organ and cell transplantation is by far less successful [1,2].

Indeed, current immunosuppression does not efficiently prevent the chronic process that progressively damages the transplant over the years, eventually leading to its loss. In organ transplantation, this situation contributes to the increasing gap between the numbers of patients in need of a transplant and the numbers of organs available for transplantation. About 45 000 patients are currently on renal transplant waiting lists in Europe and depending on the countries considered, 15–30% of candidates for liver or heart transplantation die before a life-saving transplant becomes available to them. Decreasing the number of patients in need of a second transplant is therefore considered a priority to reduce the burden caused by the shortage of organs available for transplantation [3].

Furthermore, the immunosuppressive drugs that are currently used induce a global depression of immune responses and increase the risk of late cancer development [4]. Immunosuppressive drugs create additional problems by exerting significant side effects outside the immune system. As a matter of fact, it is estimated that the costs of immunosuppressive drugs and the management of their adverse effects represent a total amount of at least 2 billions € per year in the European Union [5].

Taken together, these figures indicate that the next significant advances in transplantation medicine will depend on the development of new therapeutic modalities avoiding or minimizing long-term exposure to immunosuppressive drugs. Over the last 10 years, The EU Commission launched several programs related to

transplantation medicine both in terms of biomedical science and public health policy. From these joint European efforts, two complementary strategic approaches emerge as priorities for the future:

(1) To tailor immunosuppression according to the reactivity of the transplant recipient toward donor alloantigens as assessed by reliable and validated biomarkers.

(2) To design novel therapeutic tools to regulate immune events damaging the transplant.

Herein, we suggest that the seventh framework research programme recently launched by the European Commission offers a unique opportunity to implement a new vision of transplantation research requiring a high level of integration within multidisciplinary teams.

The added value of research integration

The need to gather samples from rare patients such as drug-free transplant recipients with functional grafts, the search for new biomarkers of tolerance and the implementation of new clinical protocols involving experimental therapeutic products require major collaborative efforts and a high degree of research integration. Indeed, it is clear that such activities cannot be developed successfully in an isolated manner at the level of single states.

The *Immune Tolerance Network* launched by the National Institutes of Health in the United States pioneered this collaborative approach by implementing clinical protocols and biological assays for the purpose of inducing, maintaining and monitoring transplant tolerance. In its fifth and sixth framework research programmes, the European Commission launched three closely connected programmes (*Indices of Tolerance*, *RISET* and *ALLOSTEM*) with related objectives. These networks have already led to the design of new tools for the follow-up of transplant recipients (immunological markers or genetic signatures to identify patients at lower risk of allograft failure) and the development of new therapies combining cell and organ transplantation. Further information about ongoing projects can be found at the following URLs: http://www.risetfp6.org; http://www.allostem.org). The challenge now is to translate these advances into clinical practice for the benefit of the largest numbers of transplanted patients.

Development of biomarkers predictive of transplant tolerance or 'near-tolerance'

The development and validation of reliable tests to predict tolerance are mandatory steps for the implementation of large-scale clinical trials. Indeed, these tests based on immunological measurements as well as genomic or proteomic assays are needed to lower as much as possible the risk of rejection during immunosuppression minimization or after withdrawal. The new tests and molecular signatures, which recently emerged, need to be validated with the aim to use them as immune monitoring tools in clinical trials and to make them acceptable as surrogate markers of graft acceptance by regulatory agencies. Validation of new biomarkers will operate at three levels. First, these tests will be applied to relevant preclinical models where tolerance is reproducibly induced. Secondly, they will be applied in current industry-sponsored trials aiming at minimizing immunosuppression. Thirdly, they will be applied in new clinical trials for tolerance induction. The main tests which are currently considered as potential useful biomarkers to monitor transplant recipients are listed in Table 1.

Table 1. Biomarkers in transplantation medicine.

Anti-HLA antibodies
Genetic markers assessed in peripheral blood (DNA polymorphism, mRNA expression of relevant genes)
Levels of relevant proteins/genes in biological fluids (e.g. IP-10 & FOXP3 mRNA in urine…)
Donor-specific T-cell responses (pCTLs, IFN-γ ELISPOT, …)
Graft imaging (invasive and noninvasive)

Special attention must be paid to translation of biomarkers into surrogate end-points. Indeed, according to a definition adopted during a NIH workshop, a biomarker is simply a characteristic measured and evaluated as indicator of a biological process, a pathogenic process or a pharmacological response to a therapeutic intervention [6]. To substitute for clinical end-points and be accepted as such by regulatory bodies, biomarkers must qualify as surrogate end-points on the basis of scientific/medical evidence [6]. It is only when this step is reached that the biomarker can be used on a large scale for the benefit of transplant recipients. The AlloMap test^{R} (XDx, Brisbane, CA, USA) which consists of a 20-gene, real-time, quantitative polymerase chain reaction assay performed on peripheral blood samples of heart transplant recipients might indeed represent the first example of a new generation of commercial products developed for this purpose although results of additional ongoing studies will be necessary for definitive qualification of this assay for the detection of cardiac transplant recipients with low risk of acute cellular rejection [7]. Clearly, partnerships between academic teams and private companies are necessary to move this field forward efficiently [8].

Although current efforts are mostly focused on analyses of peripheral blood samples, it is likely that monitoring of events occurring *in situ* (i.e. within the graft) will be necessary for a reliable assessment of the transplant status. Histological examination has obvious limitations in terms

of sampling and repetition of biopsy procedures. However, new imaging methods based on positron emission tomography, magnetic resonance, ultrasound, and optical imaging could be used in the future to provide relevant information on molecules and cells present in transplanted tissues [9].

Implementation of new approaches for tolerance induction

Although one might hope that the existing basic knowledge of tolerance might be sufficient for successful clinical development, the strategies envisaged might require further improvement. For this reason, experimental studies in relevant animal models still need to be conducted in parallel with human investigations. Besides their usefulness for the development of new biomarkers, experimental studies will hopefully lead to identification of new genes and molecules relevant for the induction of transplantation tolerance.

Physicians involved in haematopoietic stem cell transplantation and solid organ transplantation share a number of concerns regarding long-term immunosuppression and consider similar strategies to achieve allograft tolerance. For example, infusions of regulatory T cells or mesenchymal stem cells are currently considered as adjunct therapies to limit pathogenic alloimmune responses in both settings. Thus, it is now time to bridge the fields of cell and solid organ transplants, an objective which depends on the implementation of innovative training programmes. Thorough consideration of ethical questions and efficient collaboration with patients and their families will also be essential. Indeed, a reference framework for local ethical committees and regulatory bodies are clearly needed for the safe development of innovative cell therapies in transplantation.

The TRIE project: towards a rationale agenda for transplantation research in the European Union

European physicians have made major contributions in transplantation science and the European pharmaceutical industry has been instrumental in developing immunosuppressive drugs. However, over the last 10 years, the brain drain of scientists and delocalization of R&D departments of the pharmaceutical industry have significantly weakened the position of Europe in transplantation. Being convinced that further integration of existing and novel research programmes in transplantation are key for the future of transplantation medicine in Europe, we and others currently conduct with the support of the EU Commission a specific effort to identify priorities for joint research activities in Europe. This project named TRIE (*Transplantation Research Integration across Europe*) should allow a rationale agenda to promote and integrate research and training on transplantation in each member state of the European Union within the seventh EU framework programme to be established.

How to get involved?

At this time, the overall aim of TRIE is to identify priorities in the field of transplantation research, focusing on themes common to cell and solid organ transplantation for which joint efforts and integrated programs across Europe would represent an added value. The success of TRIE will very much depend on the mobilization of the whole transplant community, which is invited to express its view via a dedicated website (http://www.transplantation-research.eu). Following this consultation process with the wider transplantation community, TRIE will proceed to make recommendations to the EC regarding the next actions, which need to be taken to move forward on the implementation of research in these priority topics.

For further information on TRIE, or to participate in the transplantation stakeholder consultation process, please contact: eutransplantintegration@nds.ox.ac.uk or register online at: http://www.transplantation-research.eu.

Acknowledgements

Michel Goldman is overall coordinator and Kathryn Wood is president of the scientific council of the TRIE project supported by the European Commission as a Specific Support Action of the sixth Framework Programme. Parts of this article were previously published in the Newsletter of the RISET Integrated Project launched by the European Commission.

References

1. Tantravahi J, Womer KL, Kaplan B. Why hasn't eliminating acute rejection improved graft survival? *Annu Rev Med* 2007; **58**: 369.
2. Ferry C, Gemayel G, Rocha V, *et al.* Long-term outcomes after allogeneic stem cell transplantation for children with hematological malignancies. *Bone Marrow Transplant* 2007; **40**: 219.
3. Langone AJ, Helderman JH. Disparity between solid-organ supply and demand. *N Engl J Med* 2003; **349**: 704.

4. Penn I. Overview of the problem of cancer in organ transplant recipients. *Ann Transplant* 1997; **2**: 5.
5. Veenstra DL, Best JH, Hornberger J, Sullivan SD, Hricik DE. Incidence and long-term cost of steroid-related side effects after renal transplantation. *Am J Kidney Dis* 1999; **33**: 829.
6. Biomarkers Definition Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clin Pharmacol Ther* 2001; **69**: 89.
7. Deng MC, Eisen HJ, Mehra MR, *et al.* Noninvasive discrimination of rejection in cardiac allograft recipients using gene expression profiling. *Am J Transplant* 2006; **6**: 150.
8. Editorial. The time is now. *Nat Rev Drug Discov* 2005; **4**: 613.
9. George AJ, Bhakoo KK, Haskard DO, Larkman DJ, Reynolds PR. Imaging molecular and cellular events in transplantation. *Transplantation* 2006; **82**: 1124.

