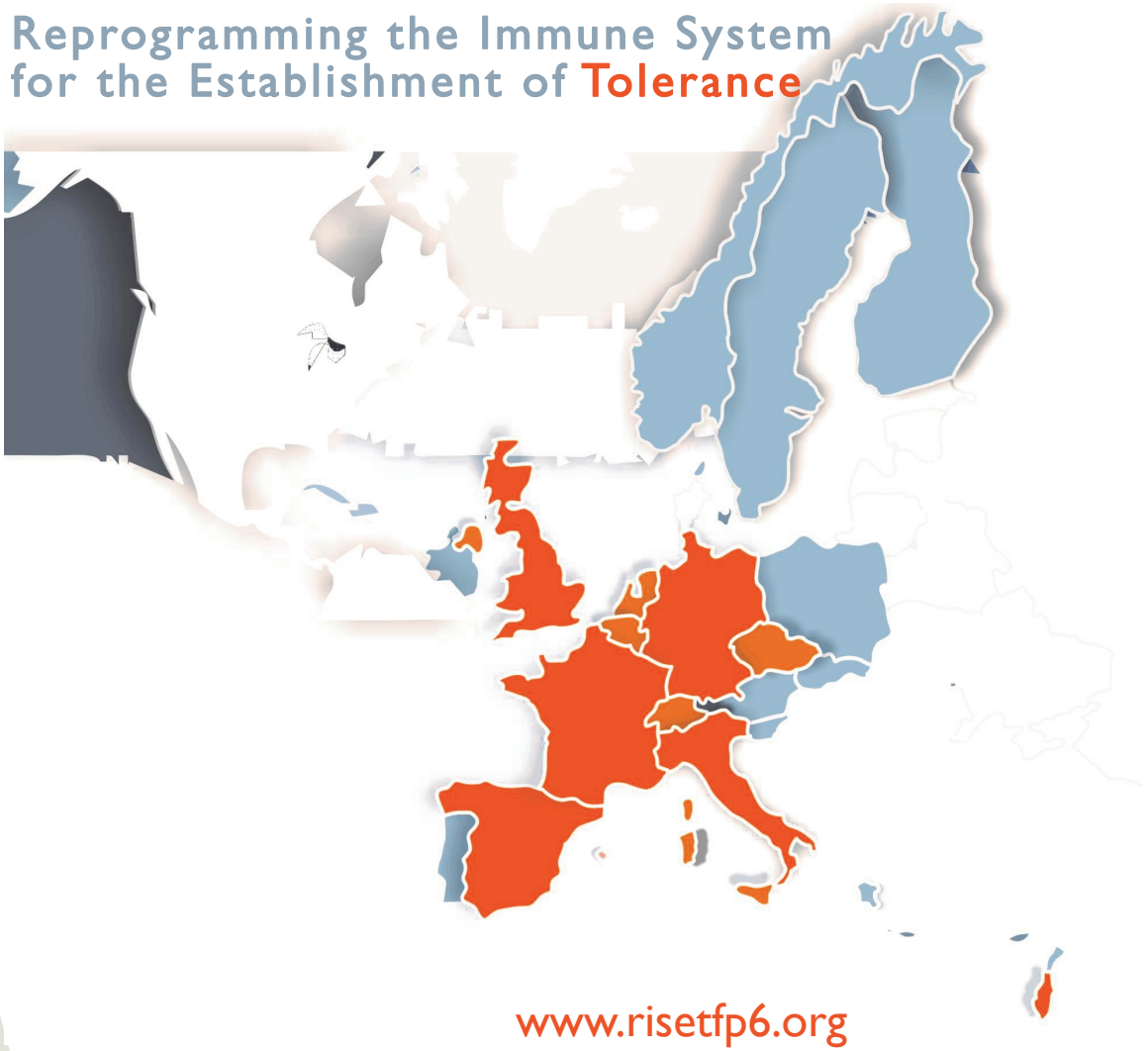
2008 Newsletter

Reprogramming the Immune System for the Establishment of Tolerance



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CONSEQUENCES OF IMMUNOSUPPRESSION: REASONS FOR THE URGENT NEED FOR IMMUNE TOLERANCE IN TRANSPLANT RECIPIENTS.

José Martinez Olmos
Ministry of Health

Spain

GOBIERNO DE ESPAÑA
MINISTERIO DE SANIDAD Y CONSUMO

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The Nobel Prize winner Joseph Murray was the first to report a successful kidney transplant in 1954. The peculiarity of this first successful transplantation was based on the fact that it was performed between identical twins, avoiding the immunological barrier that must usually be faced when using an organ from a donor who is not genetically identical to the recipient. Since then, organ transplantation has progressively become a well-established therapy of absolute importance, representing the best and frequently the only therapeutic alternative for patients with end stage organ failure. Graft and patient survival rates after solid organ transplantation are excellent and significant advantages can be observed in relation to the quality of life after transplantation. Experience, advances in surgical techniques and, without a doubt, the availability of new immunosuppressive drugs have resulted in progressively improved results in organ transplantation.

However, while immunosuppression has been one of the leading factors contributing to advances in organ transplantation, the need for its life-long administration in transplanted patients should be taken into consideration. Transplant recipients, unless receiving an organ from an identical twin, react against the transplanted organ. For this reason, transplanted patients receive a life-long treatment of immunosuppressants, since at any moment, even in the long-term, clinical or subclinical rejection may occur, leading to the damage of the graft and eventually to its loss.

In the early days of transplantation, steroids and azathioprine were the only available immunosuppressants. Adverse reactions were frequent and severe, while the efficacy of the regimens was low, with a marked rate of acute rejection and graft losses. In the 1980s, the discovery and subsequent commercialisation of Cyclosporine A was a revolution in transplantation.

The rate of acute rejection decreased and the results greatly improved. Since then, new drugs have been incorporated into this specific field, such as mycophenolic acid, tacrolimus, mTOR inhibitors and a set of monoclonal antibodies that have been allowing the development of a progressively more tailored immunosuppression, suited to the characteristics of the donor, the recipients and the eventual complications developed by the latter after transplantation. This new situation has obviously helped to improve results of transplantations, with less toxic regimens that contribute to a better outcome for transplant recipients. However, even in this situation there are a wide range of problems related to the use of immunosuppressive drugs in the short and long-term.

Problems related to immunosuppression may be classified as general or specific. The depression of the immune system makes it difficult for the organism to react properly against micro-organisms and cells suffering from a neoplasic transformation. As a result, patients with a compromised immune system are chronically in danger of developing infectious diseases and tumours, with a higher frequency than that observed in the general population. Furthermore, the infections are generally caused by micro-organisms that do not generally cause diseases in people with fully functioning immune systems and the types of tumours developed by transplant recipients are very specific types, many of which are of infectious origin. As a result, survival of transplant recipients may be limited by the development of these conditions. It is not by chance that infections and neoplasias are one of the leading causes of death in organ transplant recipients.

Additionally, immunosuppressive drugs are related to a wide variety of specific adverse reactions, depending on the type of drug. Two important problems related to immunosuppression that I would like to mention are the negative impact of many of these drugs on the cardiovascular risk profile and nephrotoxicity. Regarding the former, most of the immunosuppressive drugs used in transplantation have a negative impact on blood pressure control, lipid profile and glucose metabolism. The worsening of the cardiovascular risk profile after transplantation may increase the incidence of morbidity and mortality due to cardiovascular pathology. For instance, cardiovascular disease has become the main cause of death among transplant recipients in the long-term. On the other hand, nephrotoxicity is one of the main concerns related to the life-long use of immunosuppressants. Regarding kidney transplantation, the loss of function of the transplanted kidney may be closely related to the life-long administration of some of these drugs. In non kidney-transplant recipients, a high frequency of chronic renal failure, which may even result in patients needing dialysis therapy and a kidney transplant, has been observed. Once again, the chronic use of specific immunosuppressants has been involved in the development of such a significant complication.

Therefore, while absolutely necessary for the functioning of grafts in the short and long-term, immunosuppressants carry with them, a set of consequences for patients that limit their quality of life and survival expectancies. The development of immune tolerance is therefore one of the most important challenges facing organ transplantation today. The objective would be to find the mechanisms to completely eradicate the immune reaction against the transplanted organ, therefore minimising or avoiding the use of immunosuppressive drugs after transplantation, and causing no increase in the risk of acute rejection. The most important foreseen benefits of immune tolerance would be a decrease in related adverse reactions, a better quality of life and an increased life-span for transplant recipients. Besides this, many social and health-care benefits may result from gaining immune tolerance. Firstly, the economic savings resulting from a decrease in the use of immunosuppressants, as well as from the decrease of related adverse reactions, in terms of concomitant medication and hospital stays. Secondly, avoiding nephrotoxicity would increase the survival rate of kidney grafts, with a decreased necessity for re-transplantation in the long run. In this context, immune tolerance would help to decrease the number of patients re-entering the waiting lists, therefore contributing to solving the universal and significant problem posed by the shortage of organs for transplantation.

RISET is a project funded by the European Commission that exclusively deals with the induction of immune tolerance in organ transplant recipients by identifying the procedures that will help to transmit the knowledge "from the bench to the bedside". Clinical pilot findings within RISET represent a key step in making immune tolerance an achievable goal. In this challenging scenario, I can only welcome this innovative initiative that will help to provide a better quality of life and a longer life-span for our transplant recipients.

Hans Dieter Volk.

WP1 Leader

Immune Monitoring Tools in Clinical Trials.

Charité- Universite Medicine. Berlin. Germany

One significant component of the RISET project is the development of reliable tests or biomarkers, which are able to act as immune monitoring tools in clinical trials.

Several tests have been established since the start of the project. They have almost all been methodically validated. Two types of Standard Operating Procedures (SOPs) have been developed for this purpose: One SOP referring to the sampling and a second SOP referring to the assay itself.

Whereas the first SOP contains a step-by-step description of how to collect the necessary amount of samples of a clearly defined source and how to handle, store and transport these samples, the second SOP contains an equally detailed description of how to perform the assay, a preceding statement of its purpose, duration time and indications concerning the pre-analytics. In order to minimise assay variation, both SOPs additionally include lists of the complete range of the required materials and technical equipment.

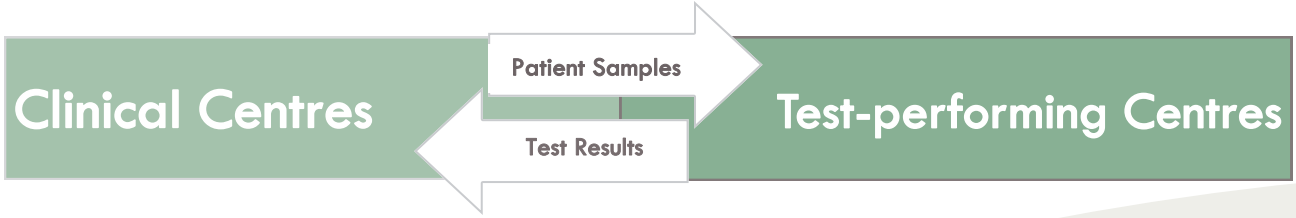
The SOPs have been evaluated and approved by InPuT; a unit of the Steinbeis GmbH founded by the Federal State of Baden-Würtemberg, that develops, adapts and validates *in vitro* and *ex vivo* test systems of animal and human origin. InPuT also evaluates and approves the validation data (reproducibility, sensitivity, specificity) that is generated and documented, once the operational procedure of each assay has been concluded.

Theoretical standardisation of the assays obtained by the development, evaluation and approbation of the above-mentioned documents is completed by on-site audits to ensure that standardisation is in practice and will be maintained. All in all, a very complex procedure is employed to obtain and control quality.

We selected the most promising candidate tests and defined a pool of assays to include in the study protocols of all clinical trials run by RISET.

Our selection includes safety and tolerance markers (EBV/CMV/Polyoma viral load, HLA-DR expression on monocytes, CMV/EBV spec. T-cells; gene expression profiling by real-time RT-PCR/Agilent Microarray), as well as tests to characterise humoral and cellular sensitisations (screening of HLA alloantibodies, IFN-gamma ELISPOT, Multiplex cytokine and CTLp assay) or particular expansions and response states (TcLandscape; HMOX-1 polymorphism). The additional subdivision into obligatory and optional tests guarantees availability of blood, serum, PBMC and urine to analyse the feasibility and clinical applicability of the tests on which we decided to focus our attention.

There is a need for a large quantity of clinical samples provided in sets (serial of samples of one single patient taken at different time intervals). Only some of the assays are performed by the clinical centres themselves. Most of the assays are centralised in "core units" to be performed by the experienced companies/university groups. The transfer of samples is therefore organised in semi-annual sample shipments with centralised monitoring.



ANALYSIS OF EBV/CMV/BKV BY REAL TIME PCR

Due to the aforementioned sample transfer, it has been possible to determine the EBV/CMV/Polyoma viral load of about 15 sets of blood as well as serum samples and 6 sets of urine samples.

Increased viral load is closely associated with "over-immunosuppression" and indicative of clinical complications.

GENE EXPRESSION PROFILING BY REAL TIME PCR / MICROARRAY

Gene expression profiling by real -time PCR and/or Microarray could be performed on about 25 sets of blood samples to date.

Real-time PCR technology allows a precise and highly sensitive quantification of gene expression, while Microarrays offer the possibility to detect patterns of differentially expressed genes among hundreds or thousands of genes.

The RISET project includes a custom designed Tolerance-Microarray for the analysis of mouse, rat and human samples. Two different data sources are used for the configuration of this RISET Agilent microarray platform (about 4200 genes represented in triplicates):

- knowledge-based data extracted from literature and/or provided by RISET partners
- experimental data extracted from RISET Microarray experiments

The most promising candidate genes detected by Microarray will be confirmed by RT– PCR.

HLA ANTIBODY SCREENING

Circa 15 sets of serum samples could be screened for HLA antibodies.

The induction of antibodies is considered to be a risk factor for rejection.

CTLP ANALYSIS

The frequency of donor-specific cytotoxic T-cells that might be indicative of rejection could be determined in approximately 12 sets of blood samples (PBMC).

HMOXX-1 POLYMORHISM ANALYSIS

6 sets of blood samples could be analyzed to distinguish the individual alleles of the human gene hemooxygenase 1 (HMOX-1) that influences graft survival and acute rejection incidence.

IP-10 ANALYSIS

The IP-10 level could be determined in 6 sets of urine samples.

The chemokine IP-10 is an interesting candidate to uncover ongoing immune processes within the graft (specific for kidney transplantation).

Most of the sets consisted of two to three samples, some of more than four samples. The results of the analyses have all been transmitted to the clinical partners for clinical validation.

In addition, several optional tests were running.

More precisely, in 3 sets of blood samples (PBMC) the frequency of donor-reactive IFN-gamma producing memory T-cells could be counted by using ELISPOT technology.

Donor reactive memory T-cells pose the major challenge for transplantation tolerance.

Even with ELISPOT technology, it has been possible to monitor the CMV/EBV specific anti-viral response in the T-cells of 8 sets of blood samples (PBMC).

CMV and EBV is strictly T-cell dependent. They are the most critical viruses in immunosuppressed patients.

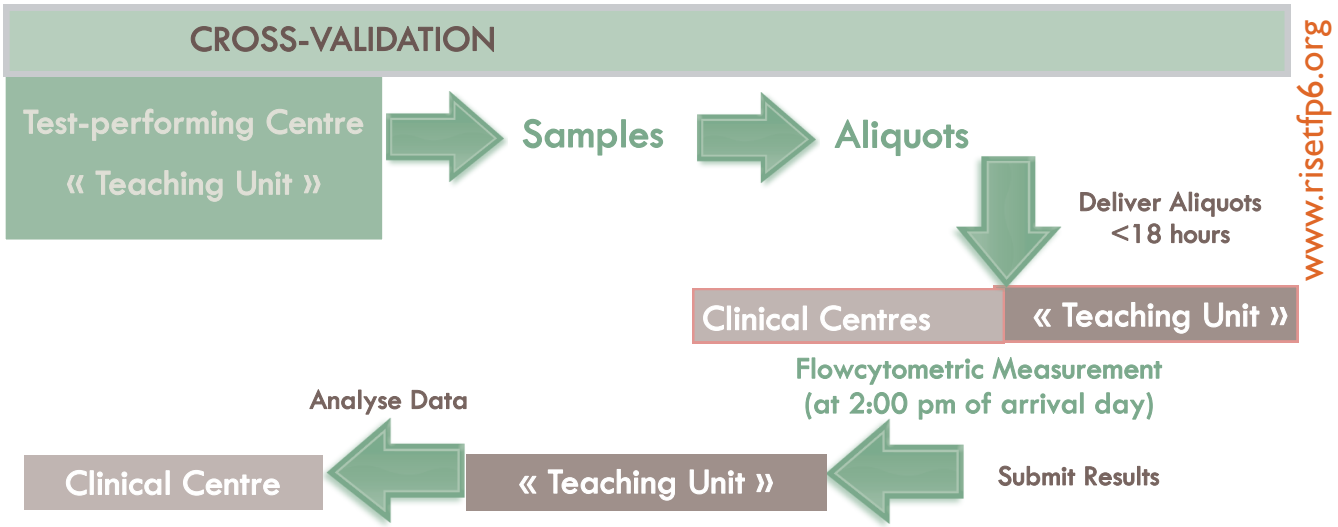
The TcLandscape analysis, which makes it possible to show on the same graph the whole T-cell immune system of an individual at a given time, could be performed on about 17 sets of blood samples (PBMC).

And the Multiplex Cytokine analysis - an analysis of donor-specific cytokine profiles that may serve as n indication of donor-specific (un) responsiveness in the case of solid organ transplantation - could be performed on 6 sets of blood samples (PBMC).

Decrease of HLA-DR on monocytes is a good "biomarker" of general immunosuppression. A dramatic decrease to <10.000 molecules/cell is associated with an enhanced risk of severe bacterial/fungal infection.

A "core unit" cannot perform the assay, as the pre-analytic part is time-/temperature-sensitive. Therefore, this marker is an optional RISET assay only.

Because of its high diagnostic value, several clinical centers were interested in employing the technique in-house. Assay transfer became necessary and is controlled by cross-validation (see diagram).

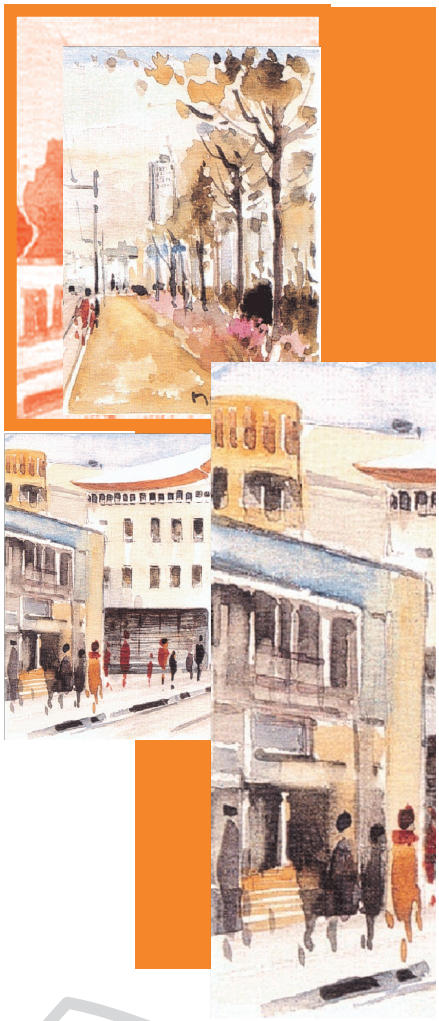


Mª Christina Cuturi

WP2 Leader.

Inducing Allograft Tolerance

Centre Hospitalier Universitaire



The overall objective of work package (WP) 2 is to design a clinical protocol of allograft tolerance based on the collective knowledge of RISET partners. To do this, we will examine the basic mechanisms of immune regulation, allograft rejection and tolerance (cell-therapy strategy and monoclonal antibodies). We are studying different models of tolerance and regulation at the cellular and molecular level and have started to identify biomarkers that could represent tools to diagnose or induce tolerance (in collaboration with WP1 and WP3).

According to European Commission announcements, the leading committee has decided to decrease the WP2 budget and to strongly support collaborative projects that could be applicable to clinical studies. The commission also asked for a reduction in the use of animal models. In order to therefore decrease animal models and focus our efforts and collaborations, we have decided to concentrate our work on preclinical models in mice and studies with human cells.

To strengthen the collaborative efforts and discuss the results in depth, we organised a WP2 meeting in Paris on 26th January 2007. Decisions have been made on the collaborative projects and we have compiled a precise list of genes to be studied by the different partners of the consortium on DC, T-cells or tolerance models. According to the results obtained so far, we have selected candidate molecules, which are upregulated in regulatory T-cells, immature DC or tolerated allografts and have started to develop tools to analyse their function and their potential for tolerance of immunotherapy (antibodies, KO mice). We will use the findings to define suitable markers of tolerance (WP1) and translate them to appropriate clinical studies (WP3). Moreover, other genes identified by WP1 will be tested in experimental models

In addition, different Treg markers have been identified and the preliminary data demonstrated in humanised mouse models shows an attenuation of transplant arteriosclerosis by human CD4+CD127 low cells expanded *ex vivo*.

Moreover, we will determine whether *per se* the "ideal" "tolerogenic" DCs are sufficient in inducing graft acceptance or whether in combination with Tregs they can be more effective in inducing tolerance. The possibility that other DC subtypes need to be targeted *in vivo* to induce allograft acceptance is under investigation.

The validation of a good pre-clinical model for testing anti-CD3 or CD52 antibodies in the autoimmune setting and the transplantation setting is ongoing. This would lead to a proposal of protocols aiming at inducing allospecific, long-term tolerance that could be applied in the clinic.

Anne Cambon-Thomsen, Virginie Commin.

European Regulation On Transplantation And Related Therapies: Recent Developments At The European Level And Interactions With The Riset Consortium

Inserm U 558, Faculty of Medicine, Toulouse, France

RISET work on reprogramming the immune system to establish tolerance in transplantation covers aspects from fundamental research to pilot clinical assays involving cell therapy, whithin the context of transplantation. The regulatory framework of such a wide scope is evolving quickly and is regularly scrutinised in order to update the consortium on new relevant texts at legal, regulatory and ethical levels. Schematically there are a number of institutional levels to consider both for transplantation and for cell therapy ; Table I and Figure I illustrate the most important documents that apply to the work performed in RISET at the Council of Europe and European Commission level. Such updates cannot only increase the awareness of the consortium on these aspects, but they also allow the RISET consortium members to interact with the relevant Agencies of the European Commission and working groups promoting interaction between professionals at the forefront of research and regulatory bodies to generate the new regulations or foster their implementation. RISET has also planned an educational session on such aspects, entitled "European regulatory framework for organ and cell transplantation and clinical assays" in the context of the 22nd European Immunogenetics and Histocompatibility Conference, which will be held in Toulouse on April 2-5, 2008.

In 2007 specific attention has been paid to relevant recommendations given by EMEA: the European Medicine Agency, http://www.emea.europa.eu/. EMEA works in the area of protection and promotion of public & animal health, and its main tasks are:

1. Safety of medicines through constant monitoring by a pharmacovigilance network within the European Union
2. Scientific advice for the development of new medicinal products.

EMEA has different committees in the various areas it covers. The CHMP (Committee on Human Medicinal Products) is relevant in part for RISET. The assessments conducted by the CHMP are based on purely scientific criteria and determine whether or not the products concerned meet the necessary quality, safety and efficacy requirements (in accordance with EU legislation). These processes ensure that medicinal products have a positive risk-benefit balance in favour of patients/users of these products once they reach the marketplace. The documents are drafted by working groups of EMEA Committees and, later presented for public consultation. Such a mechanism allows not only the Commission services but also all interested organizations to express their views and possibly impact on the final version of the documents produced by EMEA.

Two sets of recommendations were specifically analysed in 2007 as they were of direct relevance for the RISET project. One is the *Guideline on human cell-based medicinal products*[1], and the other is the *Guideline on clinical investigation of immunosuppressants* [2] *for solid organ transplantation*, prepared by a working group of the CHMP. We aim here to summarize the scope of these regulations and to indicate on which aspects the RISET consortium has commented and made suggestions.

[1] http://www.emea.europa.eu/pdfs/human/cpwp/41086906en.pdf

[2] http://www.emea.europa.eu/pdfs/human/

Guideline on human cell-based medicinal products:

Its scope is the development, manufacturing and quality control as well as non-clinical and clinical development of cell-based medicinal products. It covers especially viable human cell of allogeneic or autologous origin undergoing a manufacturing process, with or without genetic modification. Its relevance is in accordance with EU TISSUE Directive (Directive 2004 / 23/ EC) on quality/ security standards for cells procured, stored and used for application on human being; it concerns: Risk analysis, Quality and manufacturing aspects, Traceability and biovigilance, Comparability and Clinical development. The document was very positively received in the **RISET** consortium as a useful, reasonable and well documented set of guidelines; the consultation process allowed physicians and scientists from **RISET** directly involved in the relevant clinical field to insist on the importance of the reproducibility among different samples and propose to fully test the final sample cell preparation product, while limiting the tests done in intermediate stages for each single patient preparation, to propose measures in order to avoid that the amount of product dedicated to pharmacological testing and quality controls becomes bigger than that needed for the treatment itself, to insist on the fact that tumourigenicity is an important aspect of cellular therapy and could be more clearly underlined in the set of recommendations. Finally the risk analysis chapter was found to be most useful also as a reference for research ethics committees. The consultation process ended in July 2007 and the guidelines will be completed by **EMEA** in 2008.

Guideline on clinical investigation of immunosuppressants for solid organ transplantation:

It was open for consultation until end of January 2008 and the **RISET** consortium was also submitting comments. Its scope is defining treatment goals, study designs, outcome measures and data analysis for new immunosuppressive products/ protocols developed to prevent and treat solid organ allograft rejection. The **RISET** comments relate to underlining more strongly the importance of issues related to quality of life of patients, to specificities of living donors and their follow-up and to specific aspects in patients with cancers.

In conclusion,

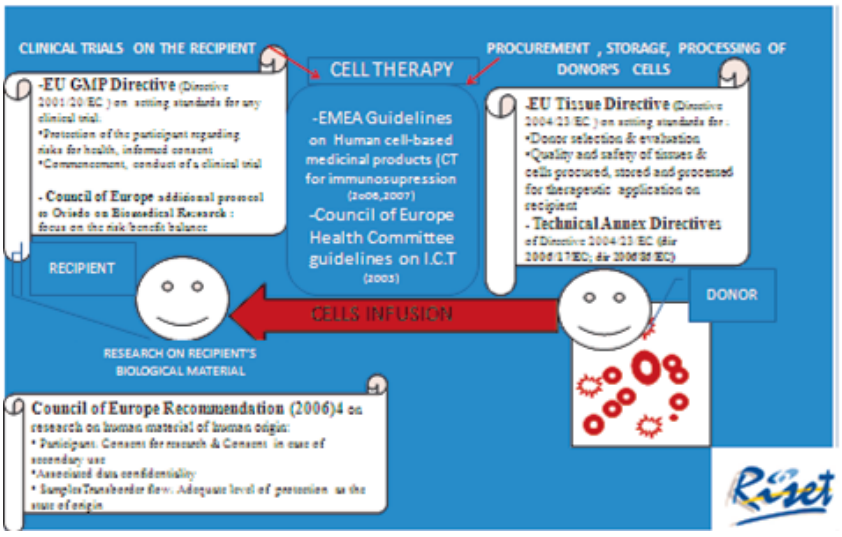
it is important to include in the activities of a scientific EU consortium such as **RISET,** to plan proactively both education and reactivity regarding the preparation of regulatory texts that can only be improved if the concerned professionals take the responsibility to comment during their preparation.

Table 1: Overview on European regulation in transplantation

- **Source:**
  Council of Europe, Additional Protocol to Convention on Human rights and Biomedecine, on Transplantation of Organs and Tissues of Human origin (2002)
- **Scope:**
  Organ and tissue (cells) removal from living/deceased persons for therapeutical transplantation purposes
- **Main provisions:**
  - Donor's Informed consent when living; Organ procurement organized by national law when donor deceased
  - No financial gain, no organ trafficking
  - Health and security requirements (risk evaluation for donor and recipient)
- **Juridic force:**
  Binding if it is ratified after Oviedo convention ratification since it is enclosed into Oviedo Convention

  Despite no ratification by most of **RISET** partners countries (except Spain and Czech Republic) the Oviedo Convention and its additional protocols
  - Are mandatory in EU funded projects
  - Have a very strong moral authority across Europe .

Figure 1: Schematic representation of regulations that apply in the domain covered in Riset pilot clinical assays involving cell therapy.



Germany

Regensburg University Medical Center

Project Summary: The main objective of this RISET project is the development of tolerance promoting immunosuppressive regimens for liver transplant recipients. For this purpose a novel anti-thymocyte globulin (ATG) and sirolimus containing immunosuppressive regimen will be established and compared to standard immunosuppression. Using the functional assays provided by the RISET partners as well as through clinical and histological examinations, the safety and tolerogenicity of this strategy will be evaluated. Ultimately, this immunosuppressive protocol will serve as a platform for the adoptive transfer of *in vitro* expanded CD4+CD25+FOXP3+ regulatory T cells for the prevention of allograft rejection and the promotion of mutual tolerance.

Prof. Edward K. Geissler, PhD.

Head of Experimental Surgery

Professor Geissler is engaged in transplantation immunology research with a focus on tolerance induction after organ transplantation. In addition, he studies cancer development after organ transplantation, as cancer has emerged as one of the most common causes of death in transplant recipients. The influence of different immunosuppressants on tumor development and progression are main areas of his interest. He is actively engaged in translational studies aimed at bringing preclinical concepts into clinical practice.

PD Dr. Matthias Edinger.

Dept. of Hemotology & Oncology

Dr. Edinger heads a research group focused on the pathophysiology of graft-versus-host disease after allogeneic stem cell transplantation (SCT). His group explores the role of donor CD4+CD25+FOXP3+ regulatory T cells after SCT in animal models and in phase I clinical trials.

Spain

Project Summary: The goal of this project is to find biomarkers capable of identifying liver transplant recipients who can safely discontinue immunosuppressive therapy (operational tolerance). For this purpose, peripheral blood and liver tissue samples will be collected in stable liver transplant recipients (> 3 years after transplantation) before and after immunosuppressive drugs are gradually weaned over a 6-month period. Patients who do not undergo rejection over the following 12 months will be considered as operationally tolerant. Gene expression and serological assays will be used to identify biomarkers predictive of successful weaning.

University of Barcelona

Alberto Sánchez-Fueyo, PhD.

Liver Transplant Unit Faculty.

Dr. Sánchez-Fueyo directs a research group focused on the study of the immunological aspects of liver transplantation. Current major lines of research are the characterization of operationally tolerant liver transplant recipients, the search for biomarkers predictive of tolerance development, and the study of anti-hepatitis C virus immune responses in liver transplant recipients.

New Partners in Riset

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Transplantation Research Integration in Europe (TRIE) is a Specific Support Action supported by the 6th EU-RTD Framework Programme and led by a European consortium of renowned scientists of the transplantation field.

Trie

aims to develop a coherent strategy for integrating research in transplantation in Europe

Objetives

Identifying priorities in the field of transplantation research, focusing on themes common to cell and solid organ transplantation for which joint efforts and integrated programmes across Europe would represent an added value.

Providing recommendations to the EC regarding priority actions to be implemented. The objective is to implement collaborative projects of a clinical nature which could not be successful at a national level.

Methodology

TRIE has adopted a consultative approach in order to ensure the views of different stakeholder groups are taken into account in recommending research topics and instruments to the EC.

With this view, the following advisory bodies have been established

Stakeholder Forum.

This forum is open to involvement from any organisation or individual with a direct interest in transplantation research e.g. National Societies for Solid Organ, Cell and Bone Marrow Transplantation, political representatives, research agencies and funding bodies, industry (large players and SMEs), patient organisations etc.

The first consultation with the transplantation community on priority research topics started soon over TRIE was officially launched on 1st March 2007. Researchers and scientists as well as patient groups and European associations such as the EBMT and ESOT were among nearly 350 organisations contacted by TRIE to give their initial input on a short list of priority research topics.

The results of this initial consultation process were presented at a meeting of the Scienific Council of TRIE in June 2007, at which a peer group of transplantation scientists agree on 3 priority topics which emerged as the front-runners in terms of priorities for future research.

As part of this background investigation, TRIE aims to build a clear picture of the state of the art in Europe in each of these subject areas. Research projects currently underway at regional, national or European level will be identified before recommendations are made on emerging research gaps and the measures needed to address such gaps in the future.

In line with the other findings of the initial stakeholder consultation, TRIE is also undertaking a comprehensive review of existing training resources in the field of transplantation in Europe.

Scientific Advisory Council

Leading transplant scientists in Europe have been invited to contribute to the work of the Scientific Council of TRIE in identifying and agreeing the details of an integrated research agenda.

Members of this council are:

Dr. F.MUELBACHER, University of Vienna represented by Dr.T.WEKERLE .

Dr.J-P.SOULILLOU, CHU Nantes represented by Dr.R.JOSIEN.

Dr.C.STAVROPOULOS-GIOKAS, General Hospital of Athens .

Dr.G.REMUZ Z I, Mario Negri Institute for Pharmacological Research represented by Dr.N.PERICO .

Dr.M.DURLIK, Transplantation Institute, The Medical University of Warsaw.

Dr.A.SLAVCEV, Medicon .

Dr.B.LOTY, Agence de Biomédecine and Coordinator of ALLIANCE O ERA-Net FP6 project .

Dr.H.EINSELE, Medizinische Klinik und Poliklinik II, Chair EBMT Infectious Disease Working Party.

Dr.R.RIEBEN, University of Bern.

For more details see the recent publication in Transplant International.
Transplant International, 20 (2007) 1016–1019 .
http://www.transplantation-research.eu/cgi-bin/WebObjects/Trie.woa

www.risetfp6.org

Work Packages

Project Coordination.

To coordinate and manage partners efforts to achieve Project objectives and expected results.

Michael Goldman

Coordinator

Université Libre de Bruxelles– INI.

Gosselies, **Belgium**

WP 2 Leader

WP2
Inducing Allograft Tolerance.

To gain insight into mechanism of immune regulation and tolerance design pre-clinical protocols.

Center Hopitalier. Université Nantes,

France

Mº Christina Cuturi.

To conduct hypothesis-driven pilot clinical investigations, based on strategies that proved effective to induce tolerance in the experimental setting, to induce "operational transplant tolerance" in patients defined as a state of lasting antigen specific unresponsiveness in absence of generalize immunosuppression.

Lucienne Chatenoud

Université René Descartes. Paris,

France.

WP 3 Leader

WP3
Pilot Clinical Studies.

WP 1 Leader

WP1
Diagnostic Test for Transplantation Tolerance.

To define immunological and molecular phenotypes of transplantation tolerance success and/ or failure in patients and clinically relevant experimental models for the design of subsequent clinical protocols.

Hans Dieter Volk.

Charité – Université Medicine Berlin,

Germany

To identify key issues and potential problems or obstacles for the translation of the results and developments obtained in the frame of this project in the terms of benefit to patients, the EU society and the EU economy.
To identify solutions to the problems identified
To disseminate the results of the project where needed in order to accelerate the effective translation of findings and developments in terms of social benefits to the patients, the economy and the EU in general.

Kathryn Wood

Oxford University.

United Kigdom

WP 4 Leader

WP4
Dissemination, Dialogue, Ethical and Societal Issues

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Sixth Framework Programme

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