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  Rafael Matesanz. Organización Nacional de Trasplantes, Spain.

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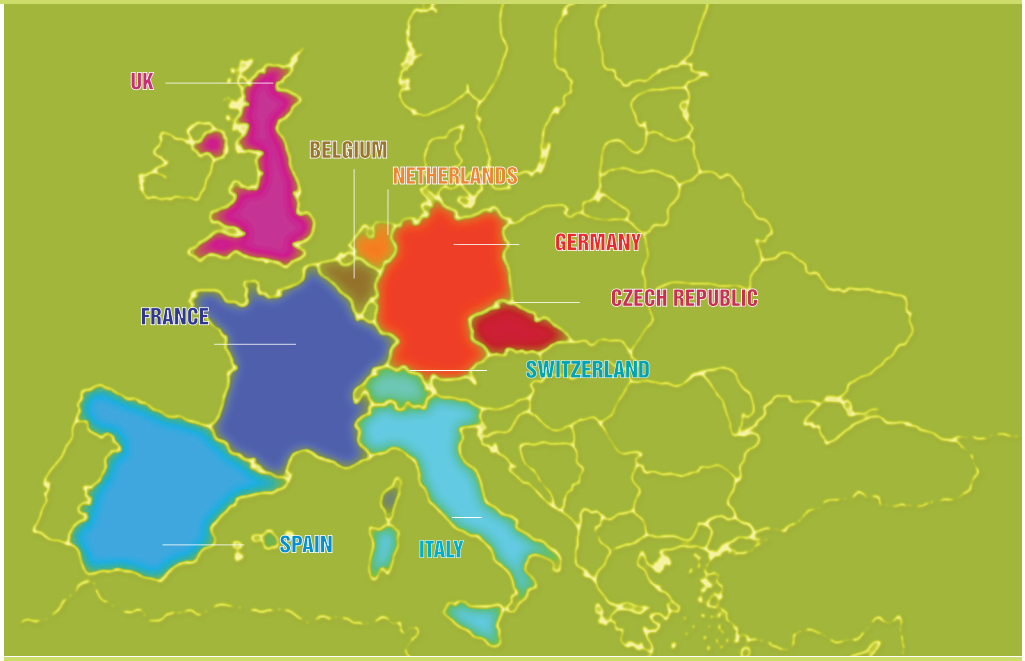

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INTEGRATING EUROPEAN RESEARCH ON IMMUNE TOLERANCE: A KEY STEP TO BUILD A BETTER FUTURE FOR TRANSPLANTED PATIENTS

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Transplantation of organs, cells or tissues treats and in some cases cures chronic, degenerative, autoimmune diseases as well as cancer. Conditions that can be treated or cured by transplantation include heart and kidney failure, lung and intestinal diseases as well as haematological malignancies and diabetes. Indeed, the numbers of patients undergoing organ or cell transplantation has increased steadily over the years and around 250,000 individuals are living nowadays in Europe with a transplanted organ.

The survival of transplanted organs or cells and often of the patients themselves depends on the efficient prevention and treatment of graft rejection. Rejection occurs when the immune system of the transplant recipient recognises and attacks the foreign tissue from the organ donor. This is the reason why most transplant recipients are treated permanently with medications that inhibit the functioning of the immune system. The immunosuppressive drugs that are currently used in clinical practice are efficient at preventing or controlling early acute rejection episodes and allow for the excellent results of organ transplantation in the short term. However, the long-term outcome of organ transplantation is less successful.

The unmet needs in transplantation medicine

Current immunosuppression does not efficiently prevent the process of chronic rejection which progressively damages the transplant over the years, eventually leading to its loss. This situation contributes to an increase in the gap between the numbers of patients in need of a transplant and the numbers of organs available for transplantation a gap which is continually increasing. About 45,000 patients are currently on renal transplant waiting lists in Europe and "depending on the countries considered" 15 to 30% of candidates for liver or heart transplantation die before a life-saving transplant becomes available to them. Decreasing the numbers of patients in need of a second transplant is therefore considered as a priority to reduce the burden caused by the shortage of organs available for transplantation.

Furthermore, the immunosuppressive drugs that are currently used induce a global depression of immune responses and increase the risk of cancer development and infection.

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.

Taken together, these figures indicate that the next significant advances in transplantation medicine will depend on the development of new therapeutic approaches avoiding long-term exposure to immunosuppressive drugs. It is the goal of the RISET Integrated Project to design novel tools to induce and ascertain transplantation tolerance, a state in which immunosuppressive drugs are not needed and global functions of the immune system are preserved.

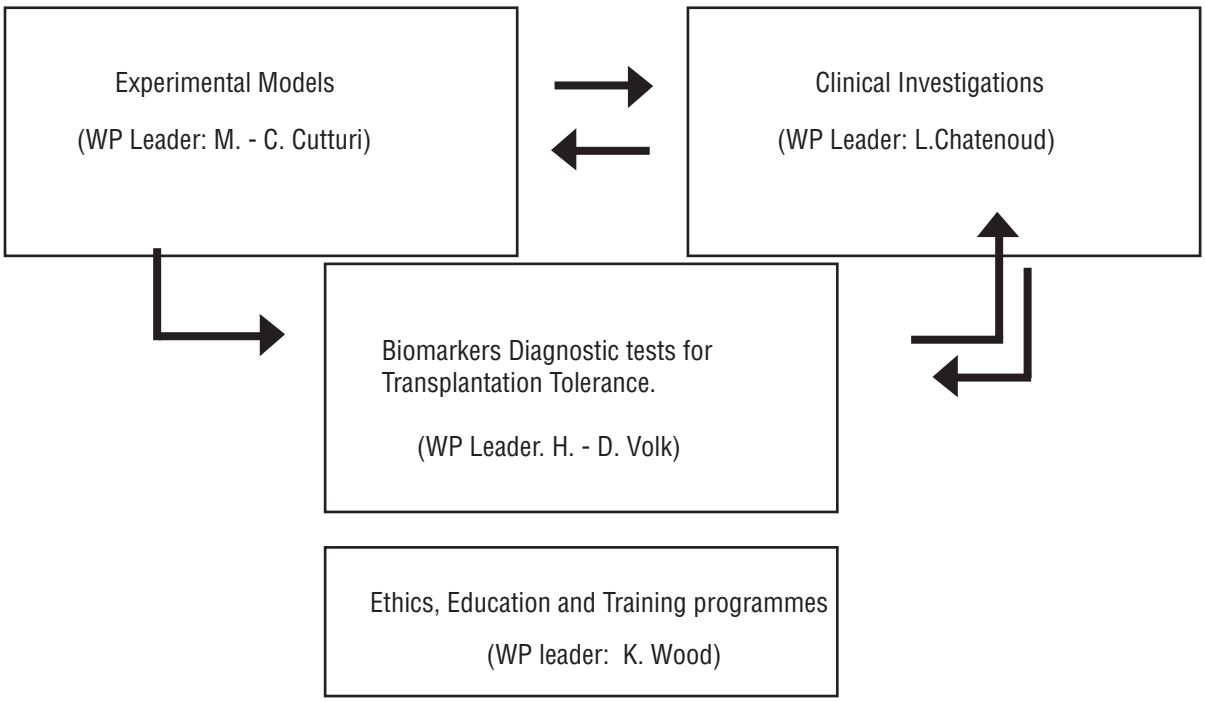
The RISET Workprogramme at a glance

The ambitious goal of translating transplantation tolerance in clinical practice can only been achieved in the long-term through a multi-step approach. For this purpose, a roadmap was designed with intermediate milestones that could reasonably be reached by 2010. The objectives and the strategy will be updated at regular intervals with the assistance of an external advisory board composed of Sir Peter MORRIS, Pr. Josep GRINYO, Pr. Jeffrey BLUESTONE and Dr. Werner WOLFF.

The RISET Workprogramme is organized in to 4 workpackages (WP) led by WP leaders, as described below.

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

The development of reliable tests to predict tolerance is a mandatory step for the implementation of large-scale clinical trials. Indeed, these tests based on immunological measurements as well as genomics or proteomics assays are needed to lower as much as possible the risk of rejection after immunosuppression withdrawal. The new tests that will emerge from this



and other projects such as the Demonstration Project "Indices of Tolerance" (www.transplant -tolerance.org.uk) will be validated in order to use them as immune monitoring tools in clinical trials.

Validation of new biomarkers will operate at three levels. First, these tests will be applied to relevant preclinical models where tolerance is reproducibly induced. Second, they will be applied in current industry-sponsored trials aiming at minimizing immunosuppression. Third, they will be applied in new clinical trials for tolerance induction.

Identification of new molecular targets for tolerance induction in preclinical models

Although one might hope that the existing basic knowledge on tolerance might be sufficient for successful clinical development, envisaged strategies might require further improvement. For this reason, experimental studies in relevant animal models will be conducted in parallel with human investigations. Beside 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.

Implementation and evaluation of new approaches for tolerance induction in man

A major goal of the project is to assess clinically and biologically the outcome of patients enrolled in current or future pilot clinical investigations aiming at complete withdrawal of immunosuppression. In a first phase, the effort will be focused on clinical studies based on novel cell therapies applied to different types of transplanted patients. These trials were approved by local committees and patients are already enrolled. The added value of the RISET Integrated Project will be to provide new knowledge from the integration of the results of a thorough evaluation of the immunological status of the patients.

Establishment of ethical guidelines for tolerance induction protocols and educational programs on tolerance induction for patients and their families

Thorough consideration of ethical questions and efficient collaboration with patients and their families is essential for the implementation of clinical research on new diagnostic and therapeutic tools in the field of transplantation tolerance. Special attention will be paid to these issues at two levels. First, ethicists with a scientific background in the field will analyse in depth the societal and ethical aspects of the research conducted within the consortium. The output of this analysis will be the establishment of guidelines providing a reference framework for local ethical committees and for a possible European regulatory body. Second, educational programs explaining the rationale, the benefits but also the potential risks of tolerance induction protocols will be set up for patients with end-stage organ failure, transplanted patients and their families. A major educational effort will also be made to provide relevant information to medical and paramedical practitioners involved in transplantation research.

The added value of research integration: the RISET consortium

The multidisciplinary nature of the RISET workprogramme, the need to gather samples from rare patients such as drug-free transplant recipients with functional grafts, 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 successfully developed in an isolated manner at the level of single EU member states.

A large research network involving academic scientists as well as industrial partners was therefore established. This network is open to new partners interested in developing innovative approaches for tolerance induction in the clinic. These new partners will be selected following a call for proposals to be released in 2006-2007.

The success of the RISET initiative will depend for a large part on the capacity of the partners to share their most promising knowledge through privileged communications, exchange of scientists and joint research activities. The principles governing the modus operandi of RISET including intellectual property management are recorded in a consortium agreement to which all partners are bound. It will be the responsibility of the Steering Committee of RISET consisting of the coordinator and the WP leaders assisted by WP managers to translate these principles into reality.

The RISET consortium

Steering Committee

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S. YOU	Université René Descartes Paris (WP3 manager)	Paris, FR
K. WOOD	Oxford University (WP4 leader)	Oxford, UK
M. DOLTON	Oxford University (WP4 manager)	Oxford, UK
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R. BACCHETTA	San Raffaele Telethon Institute for Gene Therapy	Milan, IT
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Perspectives beyond RISET

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 ten 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. It is our hope that RISET will represent the platform on which the European Union will be able to build in order to regain a strong position in this important field of modern medicine. The next step will then be to join our forces with those of our US colleagues engaged in the *Immune Tolerance Network* initiative launched by the National Institutes of Health and to establish fruitful partnerships with major charity organisations such as the *Juvenile Diabetes Research Foundation*, for the ultimate benefit of our transplanted patients.

THE VII[TH] FRAMEWORK RESEARCH PROGRAMME. EUROPEAN COMMISSION

Octavi QUINTANA
European Commission

The European Union is something new and innovative -there is no history of anything similar, and therefore, no comparison. The EU has evolved very fast in some fields, while in others there is great resistance from some of the member states.

The principle of subsidiarity guides the activities and intervention of the European Union. It means that EU interventions are only justifiable if the expected results are better when all member states work together than when they work separately.

The framework is the instrument with which the EU supports scientific research and its aim to finance research that is better done at a cross- European level as compared with Regional or National level.

There is no doubt that in the field of Health a European Programme has many advantages. Health research benefits from large amounts of evidence stored on an efficient database together with large biological sample banks which often do not exist in a single country. Health research is " nowadays" always multidisciplinary and in the case of clinical research, multicentre clinical trials are the norm.

Furthermore, the best acces to high quality research, both in projects and teams, is available at a European level.

There is a long standing tradition of researchers working with foreign colleagues, and health researchers are clearly pro-transnational cooperation. Hence, the development of a European Framework does not meet with much resistance.
However, we cannot deny that some weaknesses exist at European level. At this point, I must underline two subjects of major concern. One is the lack of enough financing, the other is fragmentation.

Europe receives 2% of GDP for research. This is a long way from the USA (2.9%) or Japan (3.3%). India and China will reach the European level at the end of this decade. There was a compromise of the European leaders during a meeting in Barcelona in 2002 where they agreed on the objective of reaching 3%, but some weeks ago they decreased this previously agreed figure to 2.7% by the year 2010. It must be said that this figure is still probably too optimistic.

In fact, political reasoning, which is clearly favorable to research, is not followed by corresponding economic translation. The Commission did ask for an increase of the Framework budget from 4,500 million € to 10,000 million € / annually, but the agreement was to increase the budget by only 30%. Among the activities proposed by the Commission most of them are delayed, some of them are reduced and some (a lesser number) deleted. If we look at the new projects that can be found in the VIIth Framework Programme and we compare them with the VIth one, there is practically no increase for the first 4 years.

Fragmentation issues are the same as those in the Sixth Programme: The average number of participants per consortium was 4 in the IInd Framework Programme and 14 in the VIth one. The average budget was 1 million € per project and now is about 5 million €.

Furthermore, the integrating projects (ERANET) that are supporting the coordination of existing National programmes will be reinforced for the VIIth Programme, including the possibility of promoting open calls for all member states to participate.

Traditionally it has been difficult to cover the requisites of the Framework Programmes. Basically there are two reasons for that:
a) The administrative rules are very complex (in order to give enough security to the contracts)

b) The increasing number of participants increases not only the scientific complexity but also the management difficulties.

There is a firm decision of the Commission to simplify the procedures both for the proposals and for the follow up of the projects. It maybe impossible to reduce the complexity of big projects but it is possible to facilitate the administrative work of the researcher.

Health

The Health Programme is divided into different subjects. The most important is Health, but there are others like food & safety, environment, nanotechnology, information systems, etc. The Health Programme has as its main objectives:

* To improve the level of health of European citizens.

* To improve the competitiveness of European companies.

* Improve research into diseases related to poverty. Although, for the EU, the main incidence of disease takes place in developing countries, Europe has an important responsibility in the search

for solutions to this problem.

A key point in the VIth Programme was genomics. In the VIIth Programme it will be Translational Medicine. We want to underline the importance of the relationship between basic research and clinical application. This interaction is bidirectional: basic research must be followed by the necessary clinical research and therapeutic application, but also clinical practice must be the starting point for developing questions for the basic researchers.

Research will be focused on:

1. Biotechnology for Health

* High field research -Development of technologies for modern biology: Genomics, Proteomics.

* Diagnostics, detection and follow up: Biochemistry, chemical practice, image techniques.

* Innovative therapeutics: Cellular therapy, genetic therapy, regenerative medicine, transplant, immunotherapy, vaccines.

* Methods to predict safety an efficacy of new treatments. Facilitation of drug development including the early discard of those substances that are not safe or efficient enough.

2. Translational Medicine

The objective of this area is to improve knowledge of biological processes, and in what way they improve healht or contribute to disease.

* Integration of biological data and processes: Development of data bases with enough information to be able to understand gene function or gene interaction and to facilitate multidisciplinary research.

* Research into the brain and its associated diseases, from childhood to the elderly. The Brain is the only organ that will have a specific programme that will allow research on its normal function. Less is known about this organ due to its enormous complexity.

* Infectious diseases: Infectious diseases that were under control 20 years ago, still continue to be a problem due to: Antimicrobial agents resistance and diseases related to poverty, specifically, AIDS, Malaria and Tuberculosis. For basic and clinical research into these three diseases there are specific budgets, provided that the research is done in Africa (EDCCTP: European Developing Countries Clinical Trial Partnership) Furthermore, there are the emergent diseases: SARS and Avian Flu.

Highly prevalent diseases like cancer, cardiovascular problems, diabetes etc. wil be an important part of the Programme. Whilst rare diseases are at mid programme level as they cannot be investigated at a National level.

3. Improving the level of health of European citizens

This as a research area that has never been covered by the Research Framework Programme. The reason that it is now included is because this field has an important impact on health policies. Europe has a clear advantage in that we can compare different health systems. Activities will be divided into two areas:

a) Promotion of Health and Prevention of Disease. We want to determine the best methods for public health assessment, covering lifestyles and all types of intervention that may have an impact on health determinants.

b) Clinical Research application on clinical practice. The rationale for the use of drugs, patients' safety, organizational aspects etc will be covered.

4. Quality, solidarity and sustainability

The study of the adaptation of health systems to demographic changes without losing universal access and solidarity as basic piers. The inclusion of this third pillar of sustainability, in the context of a reduction in budgets has caused important resistance among basic researchers, who see how the possibilities are being restricted due to the acceptance of something that for them is not "science".

5. International cooperation

Research outside the European Union, specially in developing countries, is focused on three basic activities: Diseases related to poverty (besides the above mentioned infectious diseases: AIDS, Tuberculosis and Malaria), Health systems in developing countries and cooperation with the so called: objectives of development of the century.

The entire Programme places the emphasis on the need to analyse problems that affect particularly childhood and the elderly. There is a specific budget that can be used for unpredictable needs: public health problems that may merit specific attention at a given time (SARS, Creutzfeldt Jacob, …for example).

Conclusions

* The VIIth Framework Programme follows the line of the VIth Programme. The areas and subjects covered by the VIth Programme continue to be financed in the VIIth.

* The emphasis on genomics that was characteristic of the VIth Programme has been transformed into the emphasis on transnational research.

* The important area of research into public health problems and the application of the results of clinical research into clinical practice is opened up. Hence, giving the Programme a new dimension on public health.

* Improvements in flexibility an efficiency hope to answer both the demands of researchers and of society.

CLINICAL INVESTIGATIONS

Lucienne CHATENOUD
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Organ and bone marrow transplantation represent the only therapeutic possibility for a wide variety of life-threatening conditions. It is important to counteract the immune system's response so that the transplant can survive in the recipient. Otherwise, the immune response progresses inevitably towards the destruction of the transplanted organ, that is, rejection. The mechanisms which the immune system uses to destroy the transplant are now well known. They consist of a response essentially involving a category of white blood cells called T lymphocytes which interact with other immune cells by making use of a complex network of receptor membranes and soluble molecules.

Current therapeutic approaches to tackle the rejection process are essentially based on the combined use of drugs that are immunosuppressants, a number of which are non-specific, in other words unrelated to the foreign structures or antigens presented by the grafted organ or cells. The mainstay drugs of such non-specific immunosupression are small molecules (corticosteroids, azathioprine, cyclosporin and its derivatives, mycophenolate mofetil), whose activities are targeted to intracellular processes. Their major drawback is their relative inefficiency over the long term with the likely risk of recurrence of the pathogenic immune process once the drug is withdrawn, so necessitating indefinite drug administration with the attendant problems of recurrent infection and drug toxicity.

The main aim of RISET is to discover ways in which the immune system can be selectively inhibited just to those antigens unique to the target tissue, so avoiding the hazards of long-term non-specific immunosuppression. In this way, the transplant recipient's immune system will not aggressively react to the transplanted organ while still retaining the ability to react normally against foreign infectious agents to defend the host satisfactorily. This situation is defined as "operational transplant tolerance".

To better respond to the need for interdisciplinary studies that such a goal demands, the consortium has brought together both laboratories and clinics. The laboratories are interested in the most fundamental aspects of immune mechanisms which underlie operational tolerance, as well as the means (in terms of laboratory tests) which can be used to detect such tolerance in patients and monitor it over time. On their side the clinical centers have fixed their sights on implementing pilot trials that would be able to evaluate the efficiency of new therapeutic strategies in inducing operational transplant tolerance. Within RISET, we propose to transfer to the clinic pre-defined strategies that have been proven effective in inducing transplant tolerance in the experimental setting. These are essentially based on the use of cell therapy approaches and the administration of novel drugs derived from biotechnology, such as monoclonal antibodies recognizing specific receptors on T lymphocytes. Several members of the consortium have developed in-depth, well-recognized expertise in both these types of approaches over the past few years.

Combining pilot clinical investigations with the predetermined aim of completely stopping immunosuppression with trials based on reducing or "minimizing" immunosuppression as much as possible is a totally original approach. The reason for such a deliberate choice is that being able to completely stop immunosuppression while retaining a well-functioning organ or bone marrow transplant is presently the only way to really prove that "robust" long-term operational immune tolerance has been achieved.

At present, RISET is running four protocols in different clinical transplant situations which have the complete halt of immunosuppression as a major common objective. Three of them are based on cellular therapy approaches. They were approved by local ethical committees and were selected based on their sound scientific rationale, the previous experience of the investigators, and the possibility for immediate implementation. These protocols include recipients of bone marrow, liver, and kidney transplants. The implantation of the bone marrow or organ transplants is preceded or followed by the infusion of well-characterized cellular preparations endowed with tolerogenic potential. The tolerogenic cellular preparations in the three protocols are distinct, and include either lymphocytes recovered from the blood of the recipients and cultured in vitro under suitable "tolerizing" conditions prior to reinfusion, immature bone marrow stem cells of donor origin, or monocytes, a subset of white blood cells with important immune functions recovered from the blood of the recipients and cultured in vitro under adequate conditions prior to reinfusion.

The tolerogenic cellular preparations, as well as the modalities of their in vitro isolation and expansion, have been established as a result of many years of work by the participating investigators, well-known experts in the field.

There is compelling evidence derived from pre-clinical experimental models to show the significant tolerogenic potential of all three cell therapy tools presented.

The fourth protocol (starting in 2007) is based on the use of a combination of two T cell-directed monoclonal antibodies coupled to a toxin, ricin, which recognizes functionally relevant receptors on two T lymphocytes termed CD3 and CD7. This study will be performed in bone marrow transplant recipients to allow successful long-term engraftment of the bone marrow.

All these pilot clinical trials comprise a limited number of patients (10 patients per protocol) for whom enrollment can be completed and clinical and biological read-outs can be made available within the time frame of the project.

These clinical studies should be able to provide the "proof of concept" that tolerance induction strategies, established and proven effective in the experimental setting, can be transferred to the clinic in order to promote, in human recipients, long-term acceptance of well-functioning organ or bone marrow allografts without the need for continued administration of immunosuppressive drugs. The participating partners' expertise in the field constitutes the basis of this joint effort. It will provide the tools to guarantee the feasibility of the investigations undertaken, whose design is, once again, the direct continuation of the experimental work the researchers have developed over the past few years. As a part of this goal, clinical pilot studies will also be conducted to better adapt or refine the use of some of the strategies in order to overcome potentially significant side effects.

In addition to this, to make this clinical effort effective in bringing added value to the development of future trials it is essential that the patients be very closely monitored in order to detect (if the therapeutic strategies used are effective) what the meaningful biological indications for tolerance are. This is in fact the only way to ensure that these new therapeutic approaches may be reproduced and implemented in the most beneficial way possible. Therefore the laboratories involved in RISET will carefully monitor the functional capacity of immune cells recovered from the patients included in the trials in order to establish validated tests that correlate with the induction of transplant tolerance in humans, or safe use of the minimum amount of drugs needed to maintain the graft while preserving the immune responses of the host from foreign agents. Linked to this and taking advantage of the expertise within RISET in the use of the molecular and genomic tools available, a major effort will be devoted to translating the cellular immune mechanisms that are identified as having a key role in tolerance induction and maintenance into reliable molecular surrogate markers of tolerance.

This consortium will then disseminate these validated surrogate markers for tolerance as more generally applicable tests for the monitoring of transplanted patients included in tolerance induction trials. In addition to this, it is expected that these markers will guide the rationale and design of future trials to be conducted in the context of RISET aimed at a programmed minimization of immunosuppression and importantly individually adapted to each recipient on a patient-to-patient basis.

BIOMARKERS AND DIAGNOSTIC TESTS FOR TRANSPLANTATION TOLERANCE

Hans-Dieter VOLK , Petra REINKE
Charité- Université Medicine Berlin

Background, objectives and overall strategy

In order to implement novel drug weaning and tolerance induction protocols in the clinical arena, we need to develop diagnostic tests able to identify in a retrospective or prospective manner those patients in whom tolerance can be or has been successfully induced. Even in well-defined experimental models, tolerance induction is rarely successful in 100% of the animals. In non-human primates the success rate decreases even further. In humans, the extended immunological experience of transplant recipients already before transplantation is a major challenge for drug weaning or even tolerance protocols. In contrast to animals that live in very clean housing conditions, human beings are exposed to high microbial load in their environment that results in enhanced memory immune responsiveness. The more memory T cells the higher the probability of heterologous immunity, that means the occurrence of donor-reactive memory T cells before transplantation. As memory T cells are less susceptible to immunosuppressive protocols and more difficult to tolerize, drug weaning and tolerance induction protocols in patients with enhanced frequencies of donor-reactive memory T cells should be quite difficult (Fig.1). In addition, the frequent use of pre-injured organs from elderly and brain-dead donors (resulting in enhanced immunogenicity and incidence of chronic rejection), and the development of post-transplant infections all influence the risk of acute and chronic transplant rejection and probably also the threshold for drug weaning strategies and tolerance induction. Recent trials addressing calcineurin-inhibitor (CNI) withdrawal or avoidance protocols have shown that this is possible without problems in some patients but in others it is associated with graft injury and need for conversion back to CNI. These data show the medical need for tests to minimise the risk of novel drug weaning and tolerance inducing principles during clinical trials. The main objectives of this workpackage are therefore:

1. Development of assays for the:

* Definition of immunological pre-transplant constellations identifying patients that are not suitable for a particular drug weaning / tolerance induction protocol *(definition of high-risk patients before transplantation that should be excluded at the moment from drug weaning/tolerance protocols)*.

* Early identification of failure of drug weaning / tolerance induction, possibly before graft deterioration occurs *(definition of negative predictors early after transplantation to guide drug weaning/tolerance induction protocols)*.

* Early demonstration of tolerance after induction therapy *(definition of early positive predictors of successful drug weaning / tolerance induction protocols after transplantation)*.

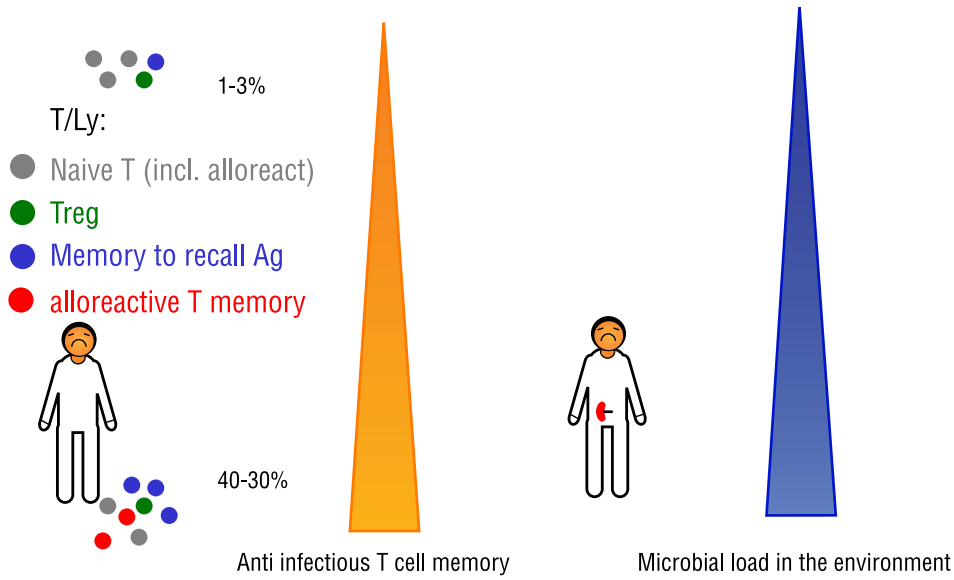


Fig 1. We are living in a “”dangerous” environment making tolerant response more difficult.

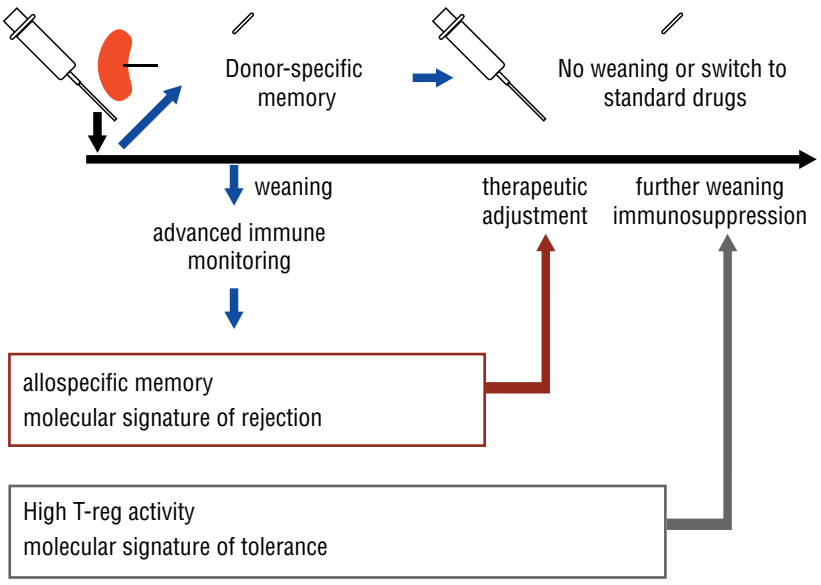


Fig 2. Strategy of immune monitoring for drug weaning trials.

* measurement of harmful injury/ tolerisation of the anti-microbial immune response *(definition of safety markers to identify patients at high risk for infectious complications)*.

2. Standardization and commercialization of the assays:

The involvement of Biotech companies and organizations with extended experiences in translational medicine (e.g. Memorec, TC-Land, ProImmune, InPut) in the WP1 of RISET will facilitate the standardization of the tests and their subsequent commercialization.

Implementation schedule

The **RISET** consortium has powerful start conditions that make "... it likely that this part of the project will be a success". The partners have i) several well established experimental tolerance models, including that mimic clinical situations more closely (e.g. long ischemic time, old donors, enhanced memory T cell pool) ii) extensive preliminary work in the specific field of "search for tolerance markers", iii) a broad technology basis, iv) extensive experiences in immune monitoring programs of transplant and other patients, v) involvement of well-recognized companies to guarantee high-quality standards and fast translation of knowledge into assay development.

We will use different biological systems (samples from patients and from experimental animal models, different kinds of transplants) and different read-out systems for characterization of immune responsiveness (see above) under the umbrella of various immunosuppression minimization / tolerance induction protocols.

We have three categories of assays:

i) set-1 "ready-to-go" tests: already established and methodically validated assays.

ii)set-2 "almost ready-to-go" tests: established assays/markers that need final methodical validation (Standard operation procedures for collecting material are almost ready).

iii) set-3 tests that have to be developed.

The assays will be validated in several clinical trials – drug weaning protocols (WP 1) and tolerance induction protocols (WP 3) – regarding their robustness, reproducibility, and clinical predictive value.

Based on the validated assays we want to adapt our therapeutic protocols (Fig. 2):

* to exclude patients at high risk for drug weaning / tolerance induction protocols

* to identify failure of our immunosuppressive minimization protocols before graft injury to adjust therapy.

* to identify successful drug weaning / tolerance induction for further weaning.

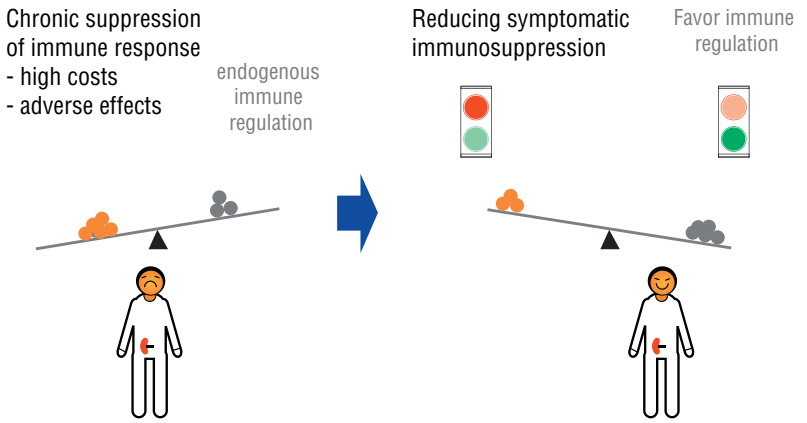


Fig 3. Shifting the chronic immunosppressive therapy towards Reprogramming the Immune System The Establishment of Tolerance.

NOVEL THERAPEUTICS FOR NEXT GENERATION OF CLINICAL INVESTIGATION: ALLOGRAFT TOLERANCE

Marie-Christina CUTURI, Elise CHIFFOLEAU
Centre Hospitalier Universitaire de Nantes.

This work package (WP2) was designed to generate novel therapeutic strategies; new concepts, methods and collective know-how for the prevention of transplant rejection to be tested in pre-clinical models.

The main aim of this collaborative effort is to discover and test new ways in which the immune system can be selectively immunosuppressed just to those antigens unique to the target tissue, so avoiding the hazards of long term non-specific immunosuppression. Operationally, this means the establishment of immunological tolerance in a mature immune system, that is, a state of durable antigen specific unresponsiveness in the absence of generalized immunosuppression. The field of tolerance research has recently undergone a major rejuvenation with advances coming from many avenues of fundamental research. Some derive from groups working on basic mechanisms of transplant rejection and tolerance in humans, in normal mice or mice transgenic for defined T-cell receptors to particular "transplantation" antigens and led to the identification of subsets of immune cells accumulating preferentially within long-term accepted/tolerant allograft and genes dominantly expressed by tolerant immune cells. Some derive from empirical yet successful attempts to induce tolerance with biological agents that selectively interfere with precise events in triggering and/or maintaining the activation of effectors T lymphocytes such as the mode presentation of the alloantigens by antigen presenting cells, the delivery of costimulatory signals (signal 2) and the availability of regulatory T cells. Such models lend themselves to the study of the mechanisms by which tolerance can be induced and maintained. It is from this conjunction of pre- and post-genomic approaches that the phenomenology of tolerance processes is becoming increasingly understandable and for this reason we have brought together groups with different expertise that might pool their knowledge and resources to tackle the common goal of achieving tolerance therapeutically. That balance is achieved by the inclusion of laboratories with expertise in the identification of novel therapeutic strategies, of novel genes and in the development reagents and therapeutic tools to probe the systems.

The European partners forming part of this consortium have recognized international experience in studying the mechanisms of allograft rejection and tolerance in animal models.

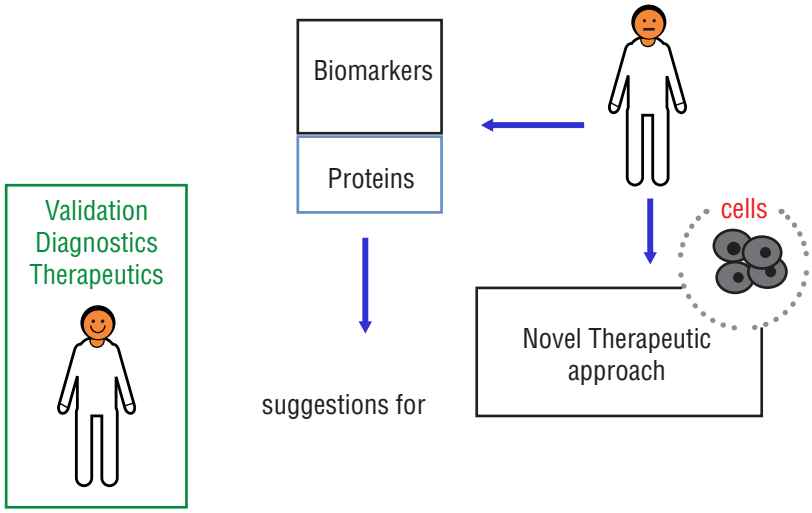
The project aims to identify common checkpoints of the immune pathways leading to peripheral transplant tolerance in terms of both cellular and molecular mediators. During the first 18 month period we will concentrate our effort in two points:

1. Characterization and ex-vivo generation of allospecific regulatory T cells. (K. Wood, R. Lechler, B. Arnold, Y Reisner, H. Waldmann) and of tolerogenic dendritic cells.(C. Van Kooten and M.C. Cuturi).

Identification of new strategies to prevent early endothelial cell activation and allograft rejection (R Rieben).

2. Identification of new strategies to improve clinical protocols of transplantation using monoclonal antibody therapy (H. Waldmann, L. Chatenoud).

Several of the participants have direct interest in clinical application, and given the overall structure of the integrated project, they are in a position to translate discoveries into suitable markers of tolerance (WP1) and adapt discoveries to appropriate clinical investigation (WP3).



SOCIAL, ETHICAL AND LEGAL ISSUES

Kathryn WOOD
Oxford University

Communication

As part of the RISET programme we have developed an active communication strategy to ensure that information about RISET (Resetting the immune system for the stablishment of tolerance) is available both in Europe and further afield.

Transplantation issues often attracts media attention and recently there have been many items about transplantation in newspaper and magazine articles, as well as storylines woven into television programmes and soap operas. Talking about transplantation is very important to ensure that as many people as possible throughout Europe know what the issues are and understand why it is so important that families talk to each other about organ, bone marrow or haematopoietic stem cell donation.

RISET plans to launch a number of initiatives to make talking about transplantation easier. We have already launched the RISET website – www.risetfp6.org. The website is designed to provide information and links about transplantation for anyone who is interested. There will be special sections on the website for the general public, for transplant recipients and their families, and particularly for those who are taking part in one of the clinical studies that are being carried out as part of the RISET programme. Ther will also be more technical areas for specialists who work in the field.

RISET has also developed a brochure that explains the key features of the RISET programme. This short publication has been distributed to transplant centres throughout Europe, as well as Members of the European Parliament who take an active interest in transplantation and health issues. The brochure is also available to upload from the website.
RISET will also be holding or participating in a series of meetings for patient organisations and schools to talk about transplantation. These events will be advertised locally and on the RISET website and anyone who is interested is welcome to attend.
Our main objective is to develop a coherent dissemination plan in order to ensure the widest visibility of the Project. The target audience includes professionals, including scientists and clinicians, stakeholders, patientsand donors and the general public. To date, the dissemination plan has included:

* Preparation of a general information brochure.

* Development and maintenance of a web site.

* Preparation of a general newsletter with short but detailed information about the project.

A scientific directory together with one for stakeholder, has been stablished and updated to keep others informed about the evolution of the project.

The plan also includes the preparation of two international workshops, one in the second year of the project and another one at the end, with the aim of presenting preliminary and final results to the scientific community and health care representatives from the European Union Member States.

At the same time, a strategy for informing the mass media of advances in the project is being developed, and from this a communication plan will be implemented. There-after, a communication plan shall be implemented.

However, the main tool for the dissemination of information will be the web site. It is constantly reviewed and updated to provide the latest information available.

Ethical issues and RISET

Transplantation and tolerance as a treatment for people who have established organ or bone marrow failure raises a number of important ethical issues. As part of the RISET programme we will attempt to identify a molecular signature of transplantation tolerance. This will require analysing material taken from transplant recipients in different European Transplant Centres. Therefore, one of the key aspects that will be investigated as part of RISET is the ethical issues associated with the exchange of samples and clinical data and how to ensure appropriate consent and protection of confidentiality throughout the different European countries participating in the RISET project. The aim is to conduct research in accordance with the required high ethical standards, to produce position papers with well balanced views and to set up an open dialogue with relevant stakeholders, among them patient organisations, and ethics committees, in order to propose well founded guidelines for specific ethical aspects where the RISET experience is relevant.

Pilot clinical “proof of principle” studies will be performed as part of the RISET programme. Some of these will involve cellular therapy, for example using engineered stem cells from bone marrow or peripheral blood of the donor. Medical and research practices are rooted in a set of common values in the European Union countries and some of the issues relevant to the use of cellular therapy are regulated by EU Directives. However, variability exists between countries in the way that such common values are translated into practice and how Directives are implemented, the work of RISET will identify any differences that exist and develop recommendations to reduce their impact on studies where transplant centres from more than one European country are involved.

THE NEED FOR COOPERATION IN TRANSPLANTATION RESEARCH

Rafael MATESANZ
Organización Nacional de Trasplantes

Modern research relies more and more on cooperation among the many participants involved in the more complex fields of science. This is especially true for transplantation. There are many examples in medicine, where a number of specialists are required in order to succesfully save a patient an in the case of organ donation, thanks to the generosity of another human being and one of the most exciting technical miracles of modern medicine. Immunologists, all kind of clinicians, surgeons, coordinators, health managers, epidemiologists, experts in law, in bioethics, in economics, in sociology: all have a contribution to make organ transplantation and transplantation research.

Research in the field of transplantation is crucial for the future development of this science.Howecver, one of the main limitations for research is a lack of resources, especially in some countries. Therefore, only by cooperation among countries and with the support of European institutions can we hope to guarantee the opportunity for all European countries to contribute to improving our knowledge in this field.

Translational research, that is, the translation of basic research as applied to patients can be considered as the “gold standard” of research. The limitations on every hospital imposed by the shortage of deceased donors makes joint efforts between institutions and accross countries a priority. Cooperation among different hospitals to include as many cases as possible should be encouraged.

Furthermore, in order to establish centres of excellence in the different aspects of transplantation, this level of cooperation will be vital, especially when competing with more advanced scientific groups from all over the world .

Donor shortage, the never ending problem of rejection, the problems of safety and quality of organ, tissue and cell transplantation, the emerging field of cell therapy and stem cell research and many other topics are attractive issues fro those working in transplantation and exciting reason for working together and learning from each other.

International cooperation between hospitals is desirable in order to find realistic solutions at grassroots level, and this seems especially true for research. European institutions should be encouraged to promote this cooperation by favouring and funding coordinated programs like RISET. This project provides a great opportunity to follow this direction and we be will endeavour to reap the benefits of this.

Transplantation is the only therapy that has the potential to cure patients with certain diseases, not only saving lives but more importantly, transforming the lives of those affected, throughout Europe. From an economic perspective, transplantation also offers a cost effective treatment for patients with some chronic diseases.

The numbers of patients undergoing organ or cell transplantation has increased steadily over the years. During 2003, based on figures made available through the DOPKI project, over 17,000 kidneys, 6,000 livers and 2,000 hearts were transplanted in European countries and currently around 250,000 individuals are thought to be living in Europe with a transplanted organ (Groth, Transplantation 75:1098-1100, 2003). These are undoubtedly very impressive achievements, but unfortunately, the number of people waiting for a transplant continues to rise in all member states. In Europe, more than 50,000 people who could benefit from haematopoietic stem cell transplantation (HSCT) are newly diagnosed with malignant and non-malignant haematological diseases each year and about 45,000 people whose quality of life would be improved with a kidney transplant are currently on waiting lists in different member states. The situation for liver and heart transplants is even more serious, as depending on the countries considered, up to 60% of candidates for liver or heart transplantation die before a life-saving transplant becomes available to them. In 2004, 59% of heart transplantation patients died while on the waiting list in Hungary, whilst in Austria 48% of patients on the liver transplant waiting list died while awaiting a transplant.
The need for organ and cell donors is therefore ever increasing but unfortunately, the number of donors is failing to meet this need by a long way. At present, organ donation rates in Europe are “at best” static but for most organs and cells donation rates are in decline with only around 5000 deceased (brain-dead) donors donating each year. As a result, the number of living donors of organs, such as kidney and liver, and of cells has increased in all member states as individuals who require a transplant are forced to consider identifying a living donor. Even if the number of living donors were to continue to rise, it would not keep pace with the number of people who could benefit from an organ, tissue or cell transplant. This number will increase proportionately with the incorporation of new countries into the EU through the changing demographics of the EU population as well as the increased incidence of chronic diseases such as diabetes over the next 10 years.

After transplantation, the survival of the transplanted organs or cells, and often of the patients themselves, depends on the efficient prevention and treatment of graft rejection and/or graft-versus-host disease. Rejection occurs when the immune system of the transplant recipient recognises and attacks the foreign tissue from the organ donor. In the case of HSCT the situation is reversed, here the curative effect of the transplant is due to immune responses directed against the specific tumour markers or individual-to-individual differences between the donor and the recipient. However, in some recipients this beneficial immune response against recipient cells can be detrimental when so-called graft-versus-host disease (GvHD) occurs. Rejection and GvHD respectively, are the reasons why most transplant recipients are treated with medications that inhibit the detrimental functions of the immune system, sometimes permanently, and why careful and continuous monitoring is required after transplantation.

The immunosuppressive drugs that are currently used in clinical practice are efficient at preventing or controlling early acute rejection episodes and GvHD and allow for excellent results in organ and cell transplantation in the short term. However, the long-term outcome of organ and cell transplantation is less successful by far for several reasons. First, current immunosuppression does not prevent the process of delayed or chronic rejection that progressively damages the transplanted organ over the years, eventually leading to its loss, efficiently. Second, the immunosuppressive drugs that are currently used in the clinic induce a global depression of immune responses and increase the risk of the development of cancer and infection. Third, immunosuppressive drugs often exert significant side effects outside the immune system. Indeed, in HSCT recurrence or progression of the primary tumour is responsible for over 30% of all deaths following transplantation, while GvHD and infection are responsible for 20% of deaths.

Saving health-care costs related to transplantation

The costs of immunosuppressive drugs are high (Best & Sullivan, Transplant Rev 12:34-50, 1998), being around 15,000 per patient per year to which one should add the costs related to the management of the adverse effects of these drugs. In total the costs of immunosuppressive drugs and

the management of their adverse effects represent an amount of at least 2 Billions € per year in the European Union. Therefore, strategies of tolerance induction which allow the weaning off of immunosuppressive treatments would clearly be cost-saving.

It is estimated that at present 3% of health care budgets of member states are dedicated to patients who are waiting for a transplant, a figure that will inevitably increase unless active steps are taken not only to increase the number of organ and cell donors but also to ensure that innovations in immunogenomics, immunotherapy and stem cell technology are introduced to the clinic as rapidly as possible to ensure that the transplants that are performed work for as long as possible.

The economic cost to EU member states of patients who could benefit from a transplant is considerable not only in terms of general health care resources and treatment costs but also in loss of productivity and the impact on society. In this context, the integration of the new member states requires specific efforts to achieve a balanced and fair dissemination of cell and organ transplantation activities throughout the European Union.

Creating a competitive and innovative European task force to translate transplantation tolerance into clinical practice

European physicians have made major contributions in the field of transplantation and the European pharmaceutical industry has been instrumental in developing immunosuppressive drugs. However, over the last ten years, the brain drain of scientists and delocalization of R&D departments of the pharmaceutical industry have significantly weakened the position of Europe in the transplantation field. The development of a coordinated initiative in organ and cell transplantation therapies in Europe will enable Europe to regain pre-eminence in this field and to compete with other countries more effectively.

An integrated, large-scale initiative in transplantation research

The requirement for an integrated, large-scale initiative in transplantation research can be based on the following body of evidence:

1. Urgent needs in the field of organ and cell transplantation are not and cannot be adequately addressed at the level of single national research programmes. Although the excellent success rates in terms of survival and quality of life in transplantation medicine have led during recent years to high levels of demand, organ donor rates and hence transplantation probabilities have remained unchanged. Despite all the advantages many patients cannot benefit from such therapy. An improvement in the number of available organs for transplantation is a permanent challenge for health-care organizations. European cooperation in sharing transplant information will be crucial to define the limits of safety and quality of those organs coming from elderly donors, or donors with rare conditions or diseases, or positive viral markers among other risk factors;

2. The translation of recent advances in basic knowledge into novel clinical practice for the benefit of transplanted patients and society requires the assembling of a critical mass of transdisciplinary competences across Europe.

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Reprogramming the Immune System for the Establishment of Tolerance

www.risetfp6.org