Reprogramming the Immune System for the Establishment of Tolerance

Riset newsletter 2007

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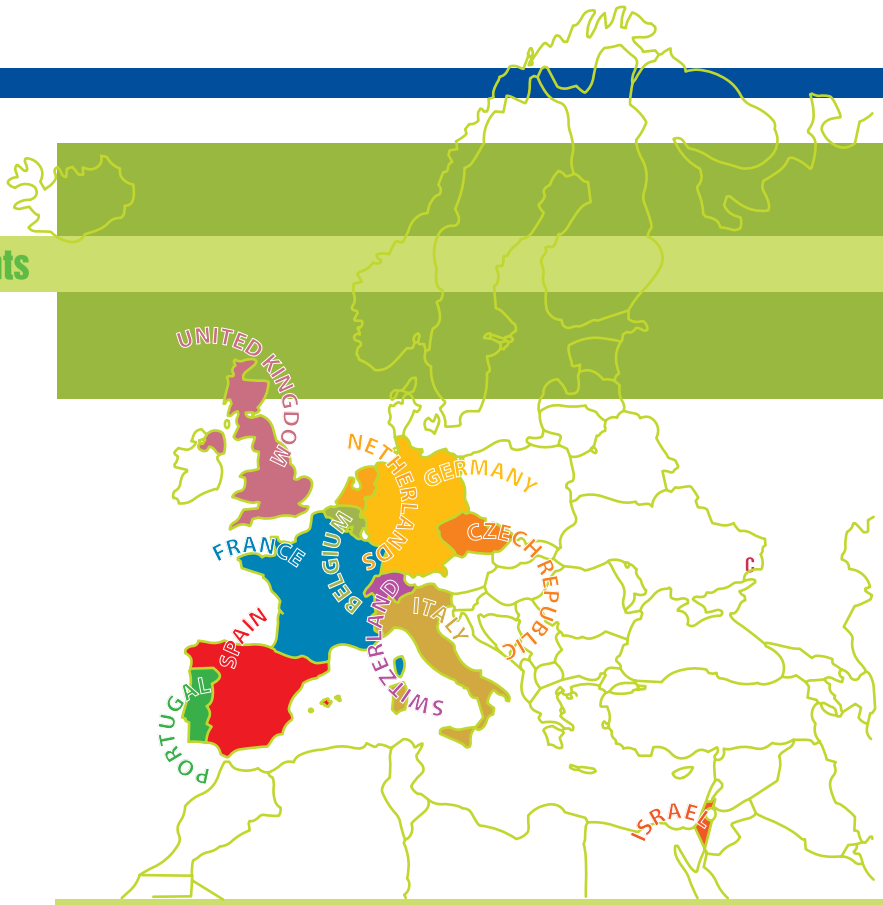
Participants



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INTEGRATED RESEARCH IN IMMUNE TOLERANCE IN EUROPE: A NEED TO IMPROVE RESULTS FOR TRANSPLANTED PATIENTS

Organ and cell transplantation has dramatically improved the survival and quality of life of patients with end-stage organ failure. However, many problems remain to be solved in the field of transplantation. At the present moment, treatment with immunosuppressive drugs is required permanently to avoid the rejection of the organ. While these drugs have been crucial for the achievement of the extraordinary results obtained so far in transplantation, their chronic use is related to a decrease in longevity and quality of life of transplanted patients. In general terms, immunosuppression increases the risk of developing infections and malignancies, and their use in the long-term is related to other adverse events, such as an increase in the risk of cardiovascular disease. In fact, nowadays, cardiovascular disease is one of the first causes of death among transplanted patients. Therefore, one of the most challenging areas in transplantation is finding a way of minimizing and ideally withdrawing immunosuppression in transplanted patients, without the risk of organ rejection.

One of the aims of the **RISET** Project (Reprogramming the Immune System for the Establishment of Tolerance) is to develop efficient diagnostic tools to test for the development of transplantation tolerance. Operational transplantation tolerance occurs when only that part of the immune system which fights against the transplant is inhibited. The development of operational transplantation tolerance should avoid the deleterious effects of the long term use of any immunosuppression. To reach this ambitious objective the **RISET** project, financed by the European Commission, started in March 2005. At present 21 research teams organized into 4 workpackages (WP) are active participants in **RISET**.

The work is being developed through the following multi-step approach:

- Development of tests or biomarkers predictive of transplant tolerance or "near-tolerance".
- Identification of new molecular targets for tolerance induction in pre-clinical models.
- Implementation and evaluation of new approaches for tolerance induction in man.
- Establishment of ethical guidelines for the use of tolerance induction protocols and educational programs on tolerance induction for patients and their families.

The first and most important step in the **RISET** project is the establishment of immunological and molecular tests that can be used to predict the success or failure of tolerance induction. The development of this task needs the identification of molecular signatures that correlate with the development of tolerance. Once developed, each of the new tests will be validated rigorously. Finally the test will be applied in clinical trials for tolerance induction.

Because of the cutting edge nature of this research, special attention will be paid to the ethical aspects and to the development of educational programs. Based on the experience obtained within **RISET** recommendations for the development of ethical guidelines that can be used for the development of tolerance studies in the future will be established tol provide a reference framework for local ethics committees and for consideration by the European regulatory body.

Educational programs explaining the benefits but also the potential risks of tolerance induction protocols will be developed for patients and their families, as well as programs suitable for medical and paramedical practitioners involved in transplantation research. A key tool in the dissemination of information to all parties is the **RISET** Web site: http://www.risetfp6.org/.

The website is being developed continuously and provides relevant information for clinicians, scientists, partners and the general public about the **RISET** programme.

Workpackages

WP5 Project Coordination

General Objectives:

* To coordinate and management partners efforts to achieve project objectives and expected results.

Michel Goldman.
Coordinator
Université Libre de Bruxelles- IMI.
Gosselies. Belgium.

WP2 Inducing Allograft Tolerance

General Objectives:

* To gain insight into mechanisms of immune regulation and tolerance to design pre-clinical protocols.

Marie-Christina Cuturi.
WP2 Leader
Centre Hospitalier Universitaire.
Nantes. France.

WP3 Pilot Clinical Studies

General Objectives:

* 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 generalised immunosuppression.

Lucienne Chatenoud.
WP3 Leader
Université René Descartes.
Paris. France.

WP1 Diagnostic test for transplantation tolerance

General Objectives:

* 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.
WP1 Leader
Charité-Universite Medicine Berlin.
Germany.

WP4 Dissemination, Dialogue, Ethical and Societal Issues

General Objectives:

* To identify key issues and any potential problems or obstacles to the translation of the results and developments obtained in the frame of this project in terms of benefits 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.
* To establish a Transplantation Industry Platform (TRIP).

Kathryn Wood.
WP4 Leader
Oxford University.
United Kingdom.

BIOMARKERS AND DIAGNOSTIC TESTS: A NECESSARY TOOL TO ADVANCE IMMUNETOLERANCE

In order to successfully implement tolerance protocols in the clinical setting, it is necessary to develop diagnostic tests to identify those patients in whom tolerance can be achieved successfully, without the risk of developing rejection while immunosuppression is weaned or stopped. Even in well-defined experimental models, tolerance induction has been rarely 100% successful, suggesting that some people may be more susceptible to the development of tolerance than others. Working out tests to define the precise characteristics of the immune response to the transplant and thus which patients may become tolerant to their transplants vs which patients require continuous immunosuppression is very important.

One example of a situation when it might be difficult to induce tolerance is the following: The high microbiological load in the environment that we live in means that some people may have a high number of so-called memory T cells. If this is the case there is a strong chance that these cells might contribute to the immune response made to the donor antigen after transplantation increasing the probability of rejection.

It follows that tolerogenic protocols which try to wean immunosuppression might be more difficult in patients with enhanced frequencies of donor-reactive memory T cells. Issues such as this have meant that trials trying to withdraw or avoid the use of calcineurin inhibitors (CNI), basic immunosuppressants in the last few years, have only been successful in some patients, but not in all.

Any clinical study on immune tolerance should be on the basis of ensuring the protection of the organ against rejection. Therefore, in order to develop suitable studies on drug weaning and tolerance induction, it is important to develop specific assays that help us to avoid as much risk for the patient as possible. Among the objectives of the **RISET** program, we aim to identify these tests or **BIOMARKERS** in order to help us to develop safe and effective clinical studies on immune tolerance while protecting the transplant, and most importantly the patient. Specifically, biomarkers will help us to:

1. Identify patients that are not suitable for a particular drug weaning / tolerance induction protocol. These patients would be considered high-risk patients and should be excluded at the moment from drug weaning/tolerance protocols.

2. Provide early identification of the failure of drug weaning / tolerance induction, ideally before graft deterioration occurs. We would have then negative predictors to guide drug weaning/tolerance induction protocols, offering the chance of early adjusting immunesuppression when failure of the protocol has been detected. Therefore we would ensure that the graft is protected.

3. Provide early demonstration of tolerance after induction therapy. These biomarkers would be considered as early positive predictors of successful drug weaning / tolerance induction protocols, allowing us to further wean immunosupression.

4. Measure harmful injury/tolerisation of the anti-microbial immune response. We would define safety markers to identify patients at high risk for infectious complications.

Biotech companies and organizations with extended experiences in translational medicine (e.g. Memorec, TC-Land, Pro-Immune, InPut) are involved with **RISET** and will facilitate the standardization of these tests and their subsequent commercialization, after their proper and strict validation in clinical trials of drug weaning/tolerance induction. **BIOMARKERS** are considered by the **RISET** consortium to be a necessary tool for the advancement of immunetolerance research.

OTHER EUROPEAN RESEARCH PROJECTS IN TRANSPLANTATION EUROPEAN PROJECTS

RESCUE

From stem cell technology to functional restoration after spinal cord injury. This program will be achieved in three steps: Harvesting of adult and/or foetal stem cells; grafting in the injured cord; monitoring of the grafted cells with in vivo imaging and assessing their effects using functional studies. Coordinator: Institut National De La Santé Et De La Recherche Médic.
http://cordis.europa.eu/fetch?CALLER=FP6_PROJ&ACTION=D&DOC=11&CAT=PROJ&QUERY=1173092868555&RCN=78767

ALLIANCE-0

European Group for Coordination of National Research Programmes on Organ Donation and Transplantation. ThisGreffes.
http://allianceo.free.fr

GENOSTEM

Adult mesenchymal stem cells engineering for connective tissue disorders. From the bench to the bed side. The objective of this project is to establish a European international scientific leadership for stem cell regenerative medicine in the field of connective tissue disorders. Coordinator: Institut National De La Sante Et De La Recherche Medicale.
https://www.rdb.ethz.ch/projects/project.php?proj_id=10897

ALEA JACTA EST

Shaping the Future of a New Generation of Hybrid Human Resources for the Tissue Engineering of Connective Tissues. The aim is to create a multi-site PhD training program for multidisciplinary researchers. Coordinator: Universidade Do Minho.
http://www.aleajactaest.org/

TRANS-NET

Identification of genomic and biological markers as predictive/diagnostic/therapeutic tools for use in allogeneic stem cell transplantation: Translational research towards individualised patient medicine. Coordinator: University Of Newcastle-Upon-Tyne.
http://www.uni-goettingen.de/de/sh/36531.html

RISET

Reprogramming the immune System for the Establishment of Tolerance.
http://www.risetfp6.org/cgi-bin/WebObjects/Awo3.woa

BARP+

Development of a bioartificial pancreas for type I diabetes therapy. Coordinator: Centre Europeen D'etudes Du Diabete.
http://cordis.europa.eu/lifescihealth/major/diabetes-eu-funding.htm

DOPKI

Improving the Knowledge and Practices in Organ Donation. The project aims to develop applicable methodology that could be used to the potential for organ donation and its outcome, as well as to define the limits for organ's safety and quality. Coordinator: Organización Nacional de Trasplantes.
http://www.dopki.eu

ALLOSTEM

The Development of Imm
notherapeutic Strategies
Treat Haematological a
Neoplastic diseases on t
Basis of Optimised Al
geneic Stem Cell Tra
plantation. Coordinat
The Anthony Nolan Tru
http://www.allostem.org/dex.html

IN DEVELOPMENT

EUROSTEMCELL
European Consortium for Stem Cell Research. The goal of this project is to develop an advanced technological platform for new cell based therapies and create a foundation for translational research in the stem cell field. Coordinator: University Of Edinburgh. http://www.eurostemcell.org/

ETHICTRANSPLANTATION
Organ transplantation: Ethical Legal and Psychological aspects. Towards a Common European Policy 2007 Conference. The proposal concerns the organization of a European conference on ethical, legal and psychological aspects of organ transplantation to establish a European platform in order to facilitate a common European policy. Coordinator: Erasmus Universitair Medisch Centrum. http://www.elpat.eu/

HEARTREPAIR
Heart Failure and Repair. It addresses four R&D themes: Genes for heart repair and plasticity; diversification of cardiac progenitor cells; cell interaction and cardiac reprogramming; cardiac rejuvenation, to develop techniques to facilitate and speed repair of damaged, not yet necrotic. Coordinator: Academic Medical Centre Amsterdam.
http://www.heartrepair.eu/

CORNEA
Development of an Artificial Cornea for the Human Eye. The CORNEA project will combine the invention of a novel corneal transplant by one SME partner with novel flexible ophthalmic polymers developed by a second, the manufacturing technology of a third, and the surgical instruments and technology of two more SME partners. Coordinator: Coronis Gmbh.
http://www.ibcp.fr/fr/project_presentation.pdf

MYOCARDIAL REPAIR. Clinical Experience with Bone Marrow Cells and Myoblasts Transplantation for Myocardial Repair. This project is dedicated to the clinical applications of autologous stem cells, including bone marrow derived stem cells as well as myoblasts, to the regeneration of heart muscle in irreversibly damaged post-infarction regions. Coordinator: University School Of Medical Sciences.
http://pi.ijs.si/pibrain.exe?Cm=Project&Project=MYOCARDIAL+REPAIR&Reference=511992

PILOT CLINICAL INVESTIGATIONS IN IMMUNETOLERANCE

There are currently 3 pilot clinical investigations being conducted within the **RISET** project.

The centres carrying out these studies are based in Kiel, Germany; Milan, Italy and Brussels, Belgium. A call for new proposals for pilot clinical studies has been issued recently. The response from around Europe has been high with 15 new projects being submitted for consideration by the evaluation panel.

Each pilot clinical study is designed to evaluate the potential of new strategies for preventing the immune response to a transplant carefully and safely. It has taken many years of experimental work in the laboratory to reach the stage where a pilot study involving patients can be considered. The **RISET** project has brought together both scientists and clinicians from different countries in Europe who will work together in an effort to give transplant patients a better quality of life.

Organ and bone marrow transplantation are often the only effective ways to treat a wide variety of life-threatening conditions. However, unless the transplant comes from a genetically identical twin, the body, using the immune system will try to destroy the transplant. White blood cells including cells that are called " T lymphocytes", interact with other immune cells to cause rejection. To stop this happening doctors use drugs called " immunosuppressants" . However, these drugs are not specific to the immune response made against the organ or cells that have been transplanted and may affect other parts of the body. Also, over a long period of time, the drugs become less efficient and if the drugs are stopped, then the body will try to reject the organ again.

This is where the **RISET** project is trying to help: the main aim is to discover ways to stop only the part of the immune system which fights against the organ or cells that have been transplanted. If it was possible to inhibit just the immune response against the transplant – a situation known as "operational transplant tolerance" – this would be a major step towards the ultimate goal of the transplant community - drug free immunosuppression. We are quite a long way from achieving this at the moment, but the information obtained from the **RISET** pilot clinical studies will provide valuable insights into how it might be possible to achieve this in the future.

The main aim of the pilot clinical investigations in the **RISET** project at this stage is to reduce or minimise treatment with immunosuppressive drugs rather than to stop it altogether. Reducing or minimising the immunosuppression would be a significant achievement if the pilot studies are successful as it would reduce the impact and side effects of high dose, long-term immunosuppression.

The three pilot investigations each uses a different approach to reducing or minimising immunosuppression and usually ten patients that are on the waiting list to receive either a bone marrow, liver or kidney transplant are recruited to participate in each study. In each case, the person taking part in the study will be given clear information about what will be involved and will receive an infusion of treated cells which have the capacity to induce tolerance. They will receive this treatment either before or after their transplant takes place.

The different types of treatment being investigated are:

- **Pilot Study 1:** Lymphocytes are taken out of the blood of recipients and cultured to make them tolerant and then replaced into the patient.

- **Pilot Study 2:** Immature bone marrow stem cells from the donor are treated and given to the patient.

- **Pilot Study 3:** part of the white blood cells called monocytes, are taken from the recipient, treated and replaced.

Once the patients have undergone treatment they will be monitored very carefully over the next few years to determine whether or not their transplanted organ (or cells) is able to keep functioning without the need for as much non-specific immunosuppressive drug treatment. The assays that will be used to monitor each patient are also being developed and refined as part of the **RISET** project to ensure that they provide as much information as possible about the immune status of each recipient both before and after transplantation.

The scientists and clinicians involved in these pilot studies will continue to work together to refine and develop each of the strategies being investigated to ensure that patients receive the best possible treatment.

THE PATIENTS VIEW: TITO MORA'S EXPERIENCE

My name is Carlos and my artistic name is Tito Mora. I am a singer and a liver transplant patient.

I was shopping with my wife María one day in 1991 when I suddenly felt dizzy - eventually I went to hospital where it was discovered that I suffered from a very serious hepatic disease. Not having had either minor or major illness before it was very difficult to reconcile myself to this fact.

During this first admission, I received blood transfusions and medical treatment and I quickly recovered, "as a young man", the doctors said. In a short time I was discharged from hospital. I returned home and with the help of the medication, I tried to live life as normally as possible. I could not imagine how brief my improvement was going to be and how quickly I would go back into the hospital. I clearly had not understood the seriousness of my health situation, which soon became apparent because of my exhaustion and the progressive changes in my body and in the colour of my skin.

In October, one month after leaving the hospital, I unexpectedly fainted; it was my first episode of encephalopathy. I was admitted again. This time the diagnosis was more conclusive and severe: "acute hepatic failure". The symptoms were clear: exhaustion, liquid retention, bloated feet and stomach, yellow eyes and skin, extreme slimness, microscopic haemorrhages and as a result, the encephalopathies. When I recovered consciousness at the hospital, I thought the episode had just occurred. María told me it had occurred twenty-four hours before.

After this first episode of encephalopathy, the visits to the hospital were more and more frequent. I had to receive blood transfusions very frequently as a way of charging my batteries and going back home with María. The autumn passed with more transfusions and episodes of encephalopathy. The Spanish writer Pío Baroja said "autumn was the good smell", but I identified that season with the smell of serum.

The 28th of November that year seemed to be just another day. Before going to work María tried to wake me up to remind me not to forget my medication, this meant a list of 30 pills a day. According to María, the scary word "encephalopathy" was again written on my face. During the trip to hospital on that ambulance María's anxiety progressively increased and the doctor confirmed that I had gone into a coma. She tells me now that there were more than 20 hours of anguish for my relatives and they decided to give me extreme unction. At eleven o'clock that night María bent down to give me a kiss. She didn't know if that was going to be the last one. Then, as in a dramatic script, I brought forward my lips with a well known gesture to receive her and recovered consciousness. It seemed a miracle.

My medical records were sent to a Liver Transplant Unit and on the 15th of December 1991, my name was included in the waiting list to receive a liver transplant.

For several months, I defied the expectations of doctors but a donor did not arrive. My body needed a lot of different medicines every day. I also had to measure the amount of water and food I ingested in order to avoid a new episode of encephalopathy, which would had been fatal in my situation. On the 5th of April, 1992, we decided to go out for lunch; I was desperate and could not stand so much dieting. We returned home immediately because of my exhaustion, and I went to bed. At six in the afternoon we received the long awaited phone call, after three in vain attempts. The phone call was from the liver transplant unit: there was a liver for me. After a very long surgical procedure, from 22h that night until 16h the next day I was finally transplanted.

After my liver transplant, life has gone back to normal and I feel very well. I do have to go to periodic check-ups. I have to keep to a special treatment regime though, receiving immunosuppressive therapy, this means a medication to stop my body rejecting the transplanted organ. After some 14 years, I still have to take this medication. I've never been involved in a clinical trial or a research programme. But, if proposed I would probably have accepted. Research, and progress in medicine, kept me alive. The advances that this and other projects produce have made it possible for the donors to make donations and allowed life to continue. I feel so indebted.

My thanks to the doctors and health personnel who saved my life, to all my family and especially to my wife María, who lived and lives every second of my illness, taking care of me with all her love, but over and over and always overall, my thanks go to my donor and his/her family…

I now dedicate a big part of my life to making people aware of the importance of organ donation, participating in many charity galas and collaborating with different organizations related to donation and transplantation. I have even recorded a CD entitled "I live thanks to you" which contains several songs to make people aware of the necessity of donating their organs to save lives, as somebody did for me once. If something can be done by also participating in the clinical trials, we must, it also becomes our responsibility as patients and beneficiaries of medical progress.

I value everything more now, maybe because I have been very ill. I look at things more quietly and try to enjoy every single moment. We are here for a short period of time, so we have to try to be better people; there is no sense in getting angry so much if you can die at any moment. We never know if our life depends on the generosity of an unknown person, on the solidarity of a stranger, sometimes from a different nationality or culture to ours, who gives us a part of his/her body that they will not need any more. That is why we have to make ourselves aware of the importance of organ donation, being able to give life to other people…

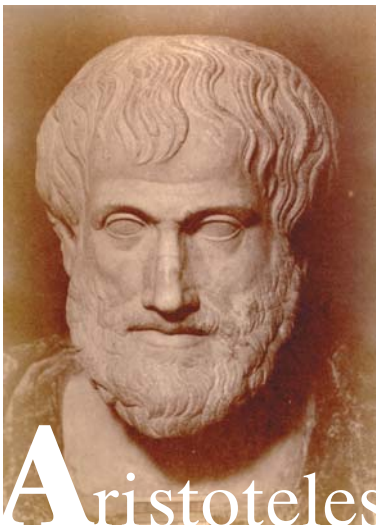
IDENTIFYING ETHICAL, LEGAL AND REGULATORY ISSUES WITHIN THE RISET PROJECT

Alongside the scientific research being undertaken, other research is being carried out to identify issues which may arise within the project which have an ethical, legal or regulatory basis.

Using various methods, researchers are undertaking a comprehensive review of material that has already been developed and assessing its relevance to **RISET**, both with respect to the clinical pilot studies as well as the assay development and experimental programme. The topics being considered are as diverse as; the use of personal data or genetic information, contact with transplant recipients and donors as well as the development of new protocols. Consortium partners have already responded to a questionnaire and taken part in an internal debate.

To date, the consortium has concentrated on the following issues; communication about the objectives of the project, the consent of donors and recipients, specific ethical and legal issues relating to cell therapy (when used as a means of induction of tolerance in the context of transplantation), the exchange of samples across geographical borders and data for research.

Using the various regulatory texts as well as opinions from local and country specific ethics committees which already exist as a starting point, the eventual aim of this aspect of the **RISET** programme is to produce a booklet of recommendations based on the experience of the consortium that can be used by other teams working with cell therapies in the future.



Université Libre de Bruxelles- IMI. Gosselies. Belgique.

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ORGAN DONATION
A GIFT FOR LIFE

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