

PRESS RELEASE

RISSET Consortium partners contribute to major research findings in Kidney Transplantation

Transplant tolerance 'signature' identified

A team of researchers across Europe have identified a 'full set' of immunological markers in the blood, which could be used to predict whether an individual's kidney transplant will be a long term success or whether it will fail. It is hoped that the research will lead to doctors being able to deliver more personalised care to kidney transplant patients in future, by safely modifying the amount of medication patients take while preventing rejection of the donor organ.

Several sources of funding have allowed this project to be completed: the European Commission through the Indices of Tolerance Consortium (5th Framework Programme) and **RISSET (Reprogramming the Immune System for the Establishment of Tolerance, 6th Framework Programme)**, the Immune Tolerance Network, Medical Research Council, Guy's and St Thomas' Charity, National Institute for Health Research, and Deutsche Forschungsgemeinschaft.

The research, due to be published in the *Journal of Clinical Investigation*, was led by King's College London (KCL) with its MRC Centre for Transplantation and its National Institute for Health comprehensive Biomedical Research Centre, a partnership between KCL and Guy's and St Thomas' NHS Foundation Trust. Seven European institutions collaborated in this multicentre study: King's College London, Imperial College London and Oxford University in the UK, Institut de Transplantation et de Recherche en Transplantation (ITERT) in France, Université Libre de Bruxelles in Belgium, and Charité - Universitätsmedizin Berlin and Miltenyi Biotec in Germany.

The team of European researchers studied kidney transplant tolerance - how accepting the body is of a foreign organ. They studied 11 kidney transplant patients from across Europe who had seemed to develop tolerance of the donor organ naturally, as well as stable transplant patients who were taking varying amounts of immunosuppression (drugs to

control their immune response), patients who were taking such drugs but showing signs of chronically rejecting the donor organ, and a group of healthy volunteers. They carried out a range of detailed laboratory tests to see if they could identify any characteristics in the blood that differentiated the group who were not taking medication and had become tolerant of their transplanted organ.

Dr Maria Hernandez-Fuentes, senior author of the study, at King's College London said: "Astonishingly there are rare individuals who seem to develop tolerance naturally after a kidney transplant. This is usually only revealed when unexpectedly organ rejection does not take place if they have to stop taking their immunosuppressive drugs for some reason. We worked with renal units across Europe to identify this small number of patients and then sought to involve them in our research."

Dr Hernandez-Fuentes and the team were able to demonstrate that these individuals share a 'tolerance fingerprint', a specific 'full set' of immunological markers in the blood. This group displayed an expansion of peripheral blood B and NK lymphocytes, fewer activated CD4+ T cells, absence of donor-specific antibodies, direct-pathway donor-specific hyporesponsiveness and a high ratio of FoxP3/amannosidase gene expression. In addition, microarray analysis revealed tolerant recipients have a B cell bias in differentially expressed genes and their associated molecular pathways.

These findings were subsequently validated by a 'test set' of kidney transplant recipients recruited by the Immune Tolerance Network in the United States, in whom similar tests were conducted.

Every year, approximately 3,500 organ transplants take place in the UK, 1,550 of these are kidney transplants. The average lifespan of a transplanted kidney is 12 years, rising to around 20 years in some cases if the kidney is from a living donor.

Dr Rachel Hilton, a renal consultant at Guy's Hospital, home to the UK's second largest kidney transplant service, and co-author in the study said: "Recipients of kidney transplants take immunosuppression drugs for the rest of their lives to prevent their own immune systems from rejecting the transplanted organ, even though these drugs may also bring serious health complications. The findings of this study are really exciting, and we hope now that they have been validated, we will be able to screen patients for these markers, and perhaps identify small numbers who can safely withdraw or reduce their use of immunosuppressants. It is vitally important though, that transplant recipients do not stop taking their immunosuppression on the back of these research findings, as any reduction in medication needs to be very carefully managed and clinically monitored."

This study is part of a exciting and wide ranging programme of liver, kidney and bone marrow transplantation research taking place across King's Health Partners (*see note 4 at end), one of the country's first Academic Health Sciences Centres.

Professor Robert Lechler, Executive Director of King's Health Partners and also a senior author of the study said: "At King's Health Partners we are at the leading-edge of transplant research internationally, with a strong focus on translational research. We are studying a number of areas, ranging from ways to improve the matching of patients to donor organs to improve the lifespan of donated organs, ways to better predict transplant outcomes, and to personalise the amount of immunosuppression individual transplant patients need to take. This translational research will bring real benefits to our patients and others more further afield."

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Note to editors:

The paper: Development of a crossplatform biomarker signature to detect renal transplant tolerance in humans, will be published in the 1 June issue of the Journal of Clinical Investigation.

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2. King's College London is one of the top 25 universities in the world (Times Higher Education 2009) and the fourth oldest in England. A research-led university based in the heart of London, King's has more than 21,000 students from nearly 140 countries, and more than 5,700 employees. King's is in the second phase of a £1 billion redevelopment programme which is transforming its estate.
3. Guy's and St Thomas' provides around 850,000 patient contacts in acute and specialist hospital services every year. As one of the biggest NHS Trusts in the UK, it employs around 10,000 staff. The Trust works in partnership with the Schools of Medicine, Dentistry, Nursing and Biomedical Sciences of King's College London and other Higher Education Institutes to deliver high quality education and research. Website: www.guysandstthomas.nhs.uk.
4. Guy's and St Thomas' is part of King's Health Partners Academic Health Sciences Centre (AHSC), a pioneering collaboration between King's College London, and Guy's and St Thomas', King's College Hospital and South London and Maudsley NHS Foundation Trusts.

King's Health Partners is one of only five AHSCs in the UK and brings together an unrivalled range and depth of clinical and research expertise, spanning both physical and mental health. Our combined strengths will drive improvements in care for patients,

allowing them to benefit from breakthroughs in medical science and receive leading edge treatment at the earliest possible opportunity.

For more information, visit www.kingshealthpartners.org

5. The comprehensive Biomedical Research Centre at Guy's and St Thomas' NHS Foundation Trust and King's College London, is one of five National Institute for Health Research (NIHR) comprehensive Biomedical Research Centres in England. With its strong focus on 'translational research' across seven research themes and a number of cross-cutting disciplines, it aims to take advances in basic medical research out of the laboratory and into the clinical setting to benefit patients at the earliest opportunity. Access to the uniquely diverse patient population of London and the south east enables it to drive forward research into a wide range of diseases and medical conditions. Website: www.biomedicalresearchcentre.org
6. The National Institute for Health Research (NIHR) provides the framework through which the research staff and research infrastructure of the NHS in England is positioned, maintained and managed as a national research facility. The NIHR provides the NHS with the support and infrastructure it needs to conduct first-class research funded by the Government and its partners alongside high-quality patient care, education and training. Its aim is to support outstanding individuals (both leaders and collaborators), working in world-class facilities (both NHS and university), conducting leading-edge research focused on the needs of patients. www.nihr.ac.uk
7. For almost 100 years the Medical Research Council has improved the health of people in the UK and around the world by supporting the highest quality science. The MRC invests in world-class scientists. It has produced 29 Nobel Prize winners and sustains a flourishing environment for internationally recognised research. The MRC focuses on making an impact and provides the financial muscle and scientific expertise behind medical breakthroughs, including the first antibiotic penicillin, the structure of DNA and the lethal link between smoking and cancer. Today MRC funded scientists tackle research into the major health challenges of the 21st century. www.mrc.ac.uk
8. Guy's and St Thomas' Charity invests in improvements to the NHS in Lambeth and Southwark. The Charity's funding helps support new services and innovations in the health services, and fund research infrastructure as well as the translation of laboratory research into clinical practice. Find out more on the Charity's website: www.gsttcharity.org.uk.