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New research gives clues to kidney transplant tolerance

25 May 2010

A Medical Research Council (MRC) supported study has 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 to prevent rejection of the donor organ.

The research, due to be published in the *Journal of Clinical Investigation*, was carried out at King's College London (KCL) in conjunction with the MRC Centre for Transplantation and its National Institute for Health Research Comprehensive Biomedical Research Centre, a collaboration between KCL and Guy's and St Thomas' NHS Foundation Trust.

Researchers studied 11 kidney transplant patients from across Europe who appeared to have developed a natural tolerance of the donor organ, alongside stable transplant patients who were taking drugs to control their immune response. They also studied patients who were taking immunosuppressant 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 try to identify any characteristics in the blood that differentiated the group who were not taking medication and had become tolerant of their transplanted organ. Researchers were able to demonstrate that these individuals share a 'tolerance fingerprint', a specific 'full set' of immunological markers in the blood.

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."

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: α mannosidase gene expression. In addition, microarray analysis revealed tolerant recipients have a B cell bias in differentially expressed genes and their associated molecular pathways.

Prof Doreen Cantrell, transplant funding expert at the Medical Research Council said: "We know the human immune system works hard to protect the body throughout our lives and can provide innate resilience to disease and degeneration. Understanding this- and how resilience breaks down with age or disease –is critical for developing and improving treatments, particularly for transplantation. This very exciting collaborative study demonstrates the importance of research into our natural resilience to disease and will make a huge difference to kidney transplant patients"

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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 drugs (immunosuppression) 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."

The research was funded by grants from the EU Indices of Tolerance Consortium and Immune Tolerance Network, Riset (Reprogramming the Immune System for the Establishment of Tolerance), Medical Research Council, Guy's and St Thomas' Charity, National Institute for Health Research, and Deutsche Forschungsgemeinschaft.

Six European institutions collaborated in this multicentre study: 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.

Ends

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*.

1. 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.

2. 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 .

3. 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

4. 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

5. 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

