the children's hospital at Westmead
media release

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AUSTRALIA JOINS LARGEST GENETIC STUDY EVER TO RESEARCH ORGAN TRANSPLANT OUTCOMES

The revolutionary study group, involving more than 35 centres in 25 different countries, hopes to dramatically improve the success of organ transplants worldwide.

A number of Australian researchers, including Professor Stephen Alexander from The Children's Hospital at Westmead, will be actively involved in the initiative called the International Genetics & Translational Research in Transplantation Network (iGeneTRAIN).

"These opportunities to study transplants across the world offer new hope to our transplant patients," says Professor Alexander.

Australian leaders of international studies on transplant genetics are also excited about the immense opportunities.

"We've already made discoveries with Australian patients that we think are extremely important and know that further findings will come from working internationally," says Professor Philip O'Connell of The University of Sydney's Millennium Institute.

Details of the study, co-led by researchers from the Perelman School of Medicine at the University of Pennsylvania, have been published today for the first time in a pair of papers in *Genomic Medicine* and the *Transplantation* journal.

"We expect to gain many new insights into the biology of transplant rejection, tolerance and side-effects of immunosuppression drugs," says Dr Brendan Keating, Assistant Professor of Surgery at the University of Pennsylvania.

"That should enable us to make better matches of donors and recipients, to treat and monitor patients more effectively after their transplants, and ultimately develop better drug dosing to prevent transplant complications and failures."

Thousands of organ transplants are performed in Australia every year and routinely extend lives, but the success rate of these procedures continue to be limited by immunological rejection and other complications. It is the opportunity to solve these issues which has Australian researchers eager to be involved.

"We're excited to be part of an international consortium like iGeneTRAIN but also to be involved with leading Australian researchers in the field of transplant genomics. To be able to apply our experience in high-throughput genome sequencing technology and analysis tools to the important challenge of transplantation genomics

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is truly exciting," says David Miller, Team Leader of Genome Sequencing at the Garvan Institute of Medical Research in Sydney.

The Australian Genome Research Facility will also be participating.

"We are delighted to support this innovative initiative that brings together global efforts to harness the power of genomics to address the significant problem of transplant rejection," says Dr Kirby Siemering, AGRF Director.

Researchers say data gathered during the study will likely detect genetic factors, in a donor or recipient, which lead to an acute rejection of a transplant.

FOR MORE INFORMATION:

Go to http://igenetrain.org/ or watch https://vimeo.com/137983688.

BACKGROUND:

Scientists have known for decades that a particular set of proteins, the human leukocyte antigen (HLA) complex, provides a signature that identifies to the immune system the body's cells as belonging to oneself. Studies have shown though that rejection of transplanted organs can occur even when HLA genes appear well matched between donor and recipient, which points to the existence of additional transplant-relevant genes in other parts of the human genome. These other genes are now known to include those encoding so-called killer-cell immunoglobulin-like receptors (KIR) on "natural killer" immune cells, which are well established to interact with HLA molecules and for which some studies suggest take part in self-recognition and impact rejection of a grafted organ, if donor and recipient KIRs are mismatched. Genes that influence the body's metabolism of immunosuppressive drugs are also now recognized as likely factors in transplant failures.

So far there have been, for transplantation, hardly any published genome-wide association studies like those used to link gene variants to other common diseases such as Type 2 Diabetes and myocardial infarction. Moreover, the genome-wide transplantation studies that have been performed to date have only used a few hundred individuals. This project will use our large number of patients to focus initially on kidney, liver, heart and lung transplant outcomes.

The studies by iGeneTRAIN collaborators are looking for links between gene variants and five common outcomes: survival of the transplanted organ, acute organ rejection, side-effects caused in part by immunosuppressive drugs (including new-onset diabetes after transplant and increased cholesterol and blood pressure), adverse events due to chronic immunosuppressive therapy such as infections and malignancies, and delayed function of the transplanted organ. The iGeneTRAIN studies are also examining, for each donor/recipient pair, a uniform set of DNA locations, including *HLA* and *KIR* regions as well as discovery of additional genetic variants across the whole genome, where gene variants relating to transplant outcomes are likeliest to be found. Keating and colleagues, in the paper published in

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Genome Medicine have described their specialized genetic array comprising tests for nearly 780,000 genetic variants across each of the human genomes analysed.

The project has grown rapidly in scale since its inception in 2012 and now includes over 35 participating institutions, whose separate studies around the globe - ongoing and completed - have already generated genomics and outcome data for over 32,000 organ donors and recipients.

*Background source***:** *University of Pennsylvania*

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