



Major breakthrough in transplantation immunity

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Australian scientists have made a discovery that may one day remove the need for a lifetime of toxic immunosuppressive drugs after organ transplants.

Professor Jonathan Sprent and Dr Kylie Webster from Sydney's Garvan Institute of Medical Research, in collaboration with colleagues, Dr Shane Grey and Stacey Walters, have successfully tested a method, in experimental mice, of adjusting the immune system for just long enough to receive a tissue transplant and accept it as 'self'. At no stage, during or after the procedure, is there any need for immunosuppressive drugs.

The results are now online in the current edition of the prestigious *Journal of Experimental Medicine*.

"Under normal circumstances, the body would attack a transplanted organ unless immunosuppressive drugs such as cyclosporin were given," said Sprent. "In this project, mice were given a substance, or 'complex', that altered their immune systems, so that they accepted transplanted cells as their own."

Sprent developed the 'complex' with Professor Charles Surh from California's Scripps Research Institute and Dr Onur Boyman, physician and Head of the Basic Immunology Unit at the University Hospital of Lausanne in Switzerland.

The complex combines a molecule, interleukin-2 (IL-2), with an antibody in order to stimulate immune cells known as T regulatory cells.

"In broad terms, IL-2 is a growth factor for T cells," explained Sprent. "My colleague Onur Boyman discovered that by combining IL-2 with different antibodies you can control its action, boosting specific populations of T cells, while subduing others. For this project we needed to boost the numbers of T regulatory cells."

"T regulatory cells quiet the immune system, subduing the body's killer T cells when it's time to stop fighting an infection."

"The other side of the coin is that a superabundance of T regulatory cells prevents killer T cells from functioning. And you wouldn't want to be without killer T cells for long because they fight infections and cancers."

"For this project, we boosted T regulatory cells temporarily, in a procedure that we believe might be very useful clinically, particularly for preventing rejection."

It was the task of postdoctoral researcher Kylie Webster, working with Stacey Walters, to see if she could make the T regulatory cell response work in a clinically realistic setting.

"We took normal, healthy mice, injected them for three consecutive days with the complex, then transplanted insulin-producing cells on the fourth day," said Kylie. "By the time of transplant there were huge numbers of T regulatory cells in their systems, making graft-destroying T cells ineffective."

"The numbers of T regulatory cells dropped over time, and the immune systems returned to normal in about two weeks. By that time 80% of the mice had accepted the grafts of insulin producing cells as their own."

"This acceptance rate is very high for transplantation, with mice normally rejecting grafts within 2-3 weeks."

"A graft is considered accepted if it's tolerated after 100 days. We took some mice out to 200-300 days, and not one of them rejected."

While cautious, Professor Sprent is very encouraged by the results.

“We have yet to determine exactly how the complex works. Once we do, I believe a clinical trial of this very non-toxic agent would be worthwhile.”

“Our approach works well with pancreatic islets, or insulin-producing cells, but we have yet to try other clinically-relevant grafts such as kidneys and hearts, which are technically very difficult in mice,” he said.

“I am also aware that effective approaches in mice do not necessarily give good results in humans because of subtle differences in the immune systems of mouse and man.”

“Those provisos given, if we were able to duplicate this experiment in humans, it would fulfil the dream of everyone in the transplant field.”

ABOUT GARVAN

The Garvan Institute of Medical Research was founded in 1963. Initially a research department of St Vincent's Hospital in Sydney, it is now one of Australia's largest medical research institutions with nearly 500 scientists, students and support staff. Garvan's main research programs are: Cancer, Diabetes & Obesity, Immunology and Inflammation, Osteoporosis and Bone Biology, and Neuroscience. The Garvan's mission is to make significant contributions to medical science that will change the directions of science and medicine and have major impacts on human health. The outcome of Garvan's discoveries is the development of better methods of diagnosis, treatment, and ultimately, prevention of disease.

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