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Team develops nanotechnology-based immunotherapy promoting transplant acceptance

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Mount Sinai researchers have developed a novel type of immunotherapy based on innovative nanotechnology that induces long-term organ transplant acceptance in mice. Their study, published in the November 6 online issue of *Immunity*, could transform patient care and help to overcome barriers that prevent successful long-term transplant outcomes.

"Our findings and the development of a novel nano-immunotherapy platform represent a revolutionary approach to prevent organ transplant rejection," said co-lead investigator Jordi Ochando, Ph.D., Assistant Professor of Medicine, Oncological Sciences, Pathology, and Immunology at the Icahn School of Medicine at Mount Sinai. "If this can be successfully translated to the clinic, this may eliminate the need for lifelong, continuous immunosuppressive medication and provide a promising solution for successful organ transplantation."

The body rejects transplants because of innate immune cells known as myeloid cells, which initiate the immune response by activating T-cells that attack the transplanted organ. To suppress this immune response, organ recipients must take medication that suppresses the T-cells activity. But these drugs break down the patients' immune systems, putting them at risk of infection and cancer. Also, organ recipients must take more than a dozen pills daily for the rest of their lives.

A team of researchers from Mount Sinai's Translational and Molecular Imaging Institute (TMII) and investigators from across the world identified trained immunity (an activation state of myeloid cells) as playing an important role in organ rejection.

The Mount Sinai researchers then developed a nano-immunotherapy that directly targets myeloid cells without affecting T-cells, and inhibits trained immunity. When the transplant takes place, the nano-immunotherapy immediately prevents myeloid cells from being activated. That eliminates the triggering of T-cells, so they cannot attack the transplanted organ and cause organ rejection and results in the preservation of T-cell function. Normal T-cell function is important for the body's defense against infections and cancer.

"Instead of suppressing the effects of organ transplantation (activated T-cells), we are preventing the cause (myeloid cell activation) in a highly specific yet short-term fashion. It's a completely different approach that can be employed to other conditions that are characterized by maladaptive trained immunity, such as autoimmune and cardiovascular diseases," said co-lead investigator Willem J.M. Mulder, Ph.D., Professor of Radiology and Oncological Sciences at the Icahn School of Medicine at Mount Sinai, and Director of the Nanomedicine Program at TMII. "We hope in time this could be the standard care for organ transplant recipients, eliminating the need for medication and further treatment. It may increase the success rate of organ transplantation and makes it safer and easier process for patients."

Investigators tested this nano-immunotherapy on mice undergoing heart transplants using a very short-term regimen, and did not give these mice standard anti-rejection drugs. The researchers compared those mice with different groups, including mice that underwent heart transplants and were given no nano-immunotherapy or common anti-rejection drugs, and mice that had heart transplants without nano-immunotherapy, but

with consistent anti-rejection medication long-term. One hundred days after the procedure, 75 percent of mice in the first group (with nano-immumotherapy but no standard anti-rejection drugs) accepted the heart transplant. All animals that received no nano-immunotherapy treatment or standard anti-rejection medication rejected the transplant before day 10. All mice with only the standard anti-rejection therapy rejected the transplant within 50 days.

Mount Sinai investigators are evaluating similar nano-immunotherapy approaches in different cardiovascular disease models and initial results are very promising.

"For the past two years, we have been working very intensively towards developing a program for clinical translation of our nano-immunotherapy. With the strong support of the Mount Sinai leadership and Mount Sinai Innovation Partners, we hope to achieve our goal of patient trials within five years," said Zahi Fayad, Ph.D., Director, TMII, Professor, Medical Imaging and Bioengineering, Radiology, and Medicine (Cardiology), Icahn School of Medicine at Mount Sinai.

Provided by The Mount Sinai Hospital

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