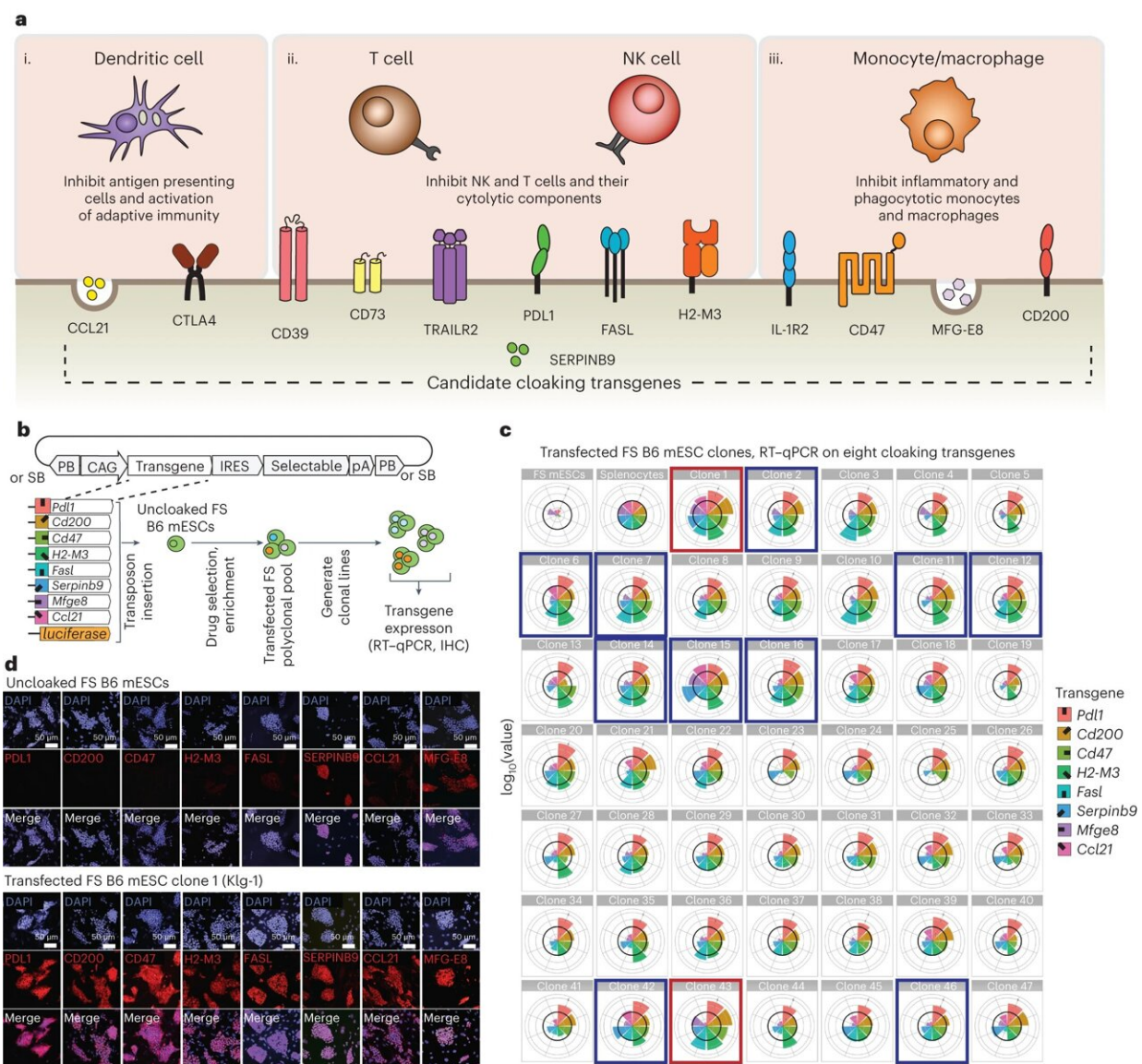


# Scientists create 'cloaked' donor cell and tissue grafts that escape rejection by the immune system

November 29 2023, by Jovana Drinjakovic



**a**, Candidate immunomodulatory factors and their roles in the innate and adaptive immune pathways involved in rejection of non-self. The underlined factors were selected to generate transgene-containing vectors. **b**, Schema showing the generation of clonal B6 mESCs that express the selected eight immunomodulatory transgenes via insertion with piggyBac (PB) and Sleeping Beauty (SB) transposon expression vectors. **c**, Expression level of each inserted transgene by RT-qPCR. Values are shown relative to the corresponding expressions in splenocytes (thick black line on each radial graph) from B6 mice stimulated ex vivo with  $\alpha$ CD3 $\epsilon$  and  $\alpha$ CD28 antibodies. Concentric circles show  $\log_{10}$  scale. Untransfected (FS) mESCs (parental line) are shown in upper left corner. Clones outlined in red and blue boxes were later screened for acceptance in allogeneic hosts. Red boxes, clones accepted in allogeneic hosts (clones 1 and 43, renamed Klg-1 and Klg-2, respectively). Blue boxes, clones rejected. **d**, In vitro antibody staining of all transgene-encoded factors in Klg-1 mESCs. Credit: *Nature Biomedical Engineering* (2023). DOI: 10.1038/s41551-023-01133-y

In a preclinical breakthrough that could transform cell therapies for incurable diseases, researchers at Sinai Health and the University of Toronto have developed a technology that may one day eliminate the need for immunosuppressive drugs in transplant patients.

Through genetic modification of donor cells, the researchers successfully created transplants that persisted long-term in mice without the need for [immune suppression](#). The findings raise hopes that a similar strategy could be employed in [human patients](#), potentially making transplantation safer and more widely available.

"Our work paves the way for an 'off-the-shelf' supply of cells for therapies that could be safely given to many patients," said Andras Nagy, a senior investigator at Sinai Health's Lunenfeld-Tanenbaum Research Institute (LTRI) and professor at U of T's Temerty Faculty of Medicine, who led the research.

The journal *Nature Biomedical Engineering* [published](#) the research.

Immune rejection poses a significant challenge in donor cell therapy, said Nagy, a stem cell pioneer and Canada Research Chair in Stem Cells and Regeneration. In such cases, the recipient's immune system recognizes the [transplanted cells](#) as foreign invaders and launches an attack, leading to rejection.

"Transplant and cell therapy patients are required to take [immunosuppressive drugs](#), sometimes for the rest of their lives, to prevent their bodies from rejecting the transplant," explained Nagy. The extended use of these drugs can lead to serious health issues, including recurring infections and an elevated cancer risk.

Scientists worldwide have been exploring various solutions, including creating therapeutic cells from the patient's own cells or encapsulating donor cells in inorganic material for protection.

These methods face challenges such as high costs, long preparation times and foreign body [immune response](#), complicating their widespread and cost-effective applications.

Stem cells have the unique ability to divide indefinitely and give rise to specialized cells that form our organs. They make an ideal source for cell therapies as large numbers of cells can be obtained and converted into desired cell types to replace those lost to disease or injury. But there are major safety concerns. In addition to addressing immune-matching, scientists must ensure that no unwanted dividing cells remain in the transplant that could cause cancer in the future.

Nagy, who established Canada's first human embryonic stem cell line in 2005, has dedicated his life's work to engineering safeguards for future cell therapies. In 2018, his team published a landmark paper in *Nature*

about a drug-inducible "kill-switch" called [FailSafe](#) that protects from cancer by eliminating unwanted proliferating cells in transplants.

For the current study, postdoctoral fellow Jeff Harding and Ph.D. student Kristina Vintersten-Nagy combined the kill-switch technology with a strategy they called "immune cloaking."

Nag's team selected eight key genes related to immune function—Pdl1, Cd200, Cd47, H2-M3, FasL, Serpinb9, CCl21, and Mfge8—that regulate how the immune system responds to threats, including foreign cells. Forced overexpression of these genes in mouse embryonic [stem cells](#) (mESCs) prevented the immune system from recognizing them as foreign.

The modification effectively created an immune cloak around the cells following their injection under the skin of genetically unmatched hosts.

"Patient safety is paramount, and Dr. Andras Nagy is globally renowned for his sustained efforts to develop safeguards for future cell therapies," said Anne-Claude Gingras, director of the LTRI and vice-president of research at Sinai Health, who is also a professor of molecular genetics at Temerty Medicine.

"This study demonstrates the combined potential of FailSafe and immune cloaking for the creation of a universal source of cells that could be applied to a multitude of diseases," she said.

Uncloaked cells are typically rejected within ten days of transplantation. In contrast, the cloaked cells persisted for more than nine months at the endpoint of the experiment—a long time considering that mice live for about two years. "This is the first time that we've been able to achieve this length of time without rejection in a fully functional immune system," said Nagy, who is also a professor at Monash University in

Australia.

In another key finding, the researchers showed that unmodified cells can escape rejection when embedded into the tissue created by the cloaked donor cells below the skin surface. The protection extended to cells from another species, as shown by the ability of unmodified human cells to survive within the cloaked mouse graft.

This suggests that modified cells also act as an immune-privileged implantation site for unmodified cells, with implications for interspecies transplants. Researchers at other institutions are exploring the potential of pigs as donors because their organs are very similar in size and function to humans.

Building on this success, Ph.D. student Huijuan Yang selected human counterparts of the eight immunomodulatory genes and used them to create the first FailSafe and cloaked human cells. Co-culturing these cells alongside human immune cells from an unmatched host revealed their ability to escape destruction, unlike their unmodified counterparts.

This shows that cloaking has the potential to work for human patients as well, said Nagy, who holds an appointment in the department of obstetrics and gynecology at U of T.

While the research is still at an early stage, it holds great promise for regenerative medicine and cell-based therapies. Nagy envisions injecting uncloaked insulin-producing cells, or islets, into subcutaneous cloaked tissue to treat diabetes. Subcutaneous cell delivery may be less risky for patients than the current approach, where islets are delivered into the liver and may interfere with its normal function, Nagy said.

"This study gives invaluable insights into elegant alternatives to the toxic consequences of conventional immunosuppression," said Michael



Sefton, scientific director of Medicine by Design, a [regenerative medicine](#) initiative at U of T, and a university professor in the department of chemical engineering and applied chemistry as well as the Institute of Biomedical Engineering at U of T.

"These findings significantly advance [cell therapies](#) that can help people who live with chronic diseases such as type 1 diabetes or heart failure," said Sefton.

Beyond diabetes, Nagy is also developing applications for patients who have age-related macular degeneration, arthritis, chronic pain, and lung diseases. To bring these advances to patients faster, he co-founded a [startup company](#), panCELLa, which recently merged with the U.S. company Pluristyx to continue to develop safe and cost-effective clinical-grade, off-the-shelf cells for therapy.

**More information:** Jeffrey Harding et al, Immune-privileged tissues formed from immunologically cloaked mouse embryonic stem cells survive long term in allogeneic hosts, *Nature Biomedical Engineering* (2023). [DOI: 10.1038/s41551-023-01133-y](https://doi.org/10.1038/s41551-023-01133-y)

Provided by University of Toronto

Citation: Scientists create 'cloaked' donor cell and tissue grafts that escape rejection by the immune system (2023, November 29) retrieved 8 May 2024 from <https://medicalxpress.com/news/2023-11-scientists-cloaked-donor-cell-tissue.html>

<p>This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.</p>
--