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Dopaminergic neurons entering the brain under the immunological cover of darkness

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The ability to transplant immunologically foreign cells into an animal without immune suppression would be transformative. Pavan et al. show that human pluripotent stem cell-derived dopaminergic neuron progenitors engineered to express eight immune-evasive proteins can engraft in humanized mice and a rat model of Parkinson's disease without recourse to immune suppression.¹

Ever vigilant, the immune system perennially protects us from marauding viruses, bacteria, parasites, and cancer cells. However, the immune system is a potent barrier to many potentially life-saving regenerative therapies, as it vigorously rejects foreign organs and cells. Two strategies are presently being pursued. First, a patient's own "autologous" cells can be transplanted back into them, thereby negating the immune barrier. However, it is challenging, expensive, and time consuming to generate a personalized autologous therapy for each individual patient, especially if thousands or millions of patients will eventually require such a therapy. Second, immunologically foreign "allogeneic" cells can be transplanted into a patient. An allogeneic "off-the-shelf" cell therapy could be generated

en masse and transplanted into many patients without manufacturing a custom cell product for each patient. However, immune suppression is necessary for immunologically foreign cells to survive in patients, which consequently renders patients more susceptible to infection and cancer.²

What if one could immunologically "cloak" cells so that they were essentially invisible to the immune system?² This would enable foreign cells to engraft without immune suppression, thus ushering forth the widespread clinical deployment of "off-the-shelf" cell therapies.² Immune cloaking also enthralls basic scientists. The immune system is tenacious and employs myriad means to detect and destroy foreign cells. What is the identity and minimum number of im-

mune pathways that must be ruptured for the immune system to permit a foreign cell to exist in its midst?

Pavan et al. drew inspiration from a previous study³ wherein eight immune-evasive proteins (PD-L1, CD200, CD47, HLA-G, FASL, SERPINE1, CCL21, and MFGE8) were overexpressed in human pluripotent stem cells (hPSCs). Each of these proteins disrupts distinct arms of the immune system, including dendritic cells (CCL21) and T cells, natural killer (NK) cells, monocytes, and macrophages (PD-L1, FASL, HLA-G, SERPINE1, CD47, CD200, and MFGE8).^{1–3} Overexpression of these eight immune-evasive proteins tempered some aspects of immune rejection *in vitro*.³ However, can this immune "cloaking" strategy likewise mitigate immune rejection *in vivo*?



In this issue of *Cell Stem Cell*, Pavan et al. address this important question in the context of Parkinson's disease, a fatal neurodegenerative disease that affects 2%–3% of individuals over 65 years of age.⁴ Midbrain dopaminergic neurons die in Parkinson's disease, leading to movement difficulties, including tremors.⁴ Pioneering efforts have differentiated hPSCs into dopaminergic neuron progenitors.⁵ Transplantation of such progenitors into the brains of Parkinson's patients has led to potentially encouraging motor symptom improvements, as evidenced in clinical trials.⁵

First, Pavan et al. transplanted control hPSC-derived dopaminergic neuron progenitors into humanized mice bearing some aspects of the human immune system.¹ As expected, immunologically mismatched neuronal progenitors elicited an immune reaction in recipient mice, with sharp increases in human T cell numbers and the inflammatory cytokines IFN γ and TNF α , and peripheral immune organs such as the lymph nodes and spleen swelled in size.¹ Remarkably, transplantation of hPSC-derived dopaminergic neuron progenitors expressing the eight immune-evasive proteins led to starkly different effects. T cell numbers did not increase, inflammatory cytokines were minimally elevated, and there was less inflammatory activation of astrocytes surrounding the transplanted neurons.¹ Importantly, the number of engrafted dopaminergic neurons was 3-fold higher than in control neuron transplants,¹ suggesting that deterring immune assault led to improved neuronal survival.

Taken collectively, the authors provide compelling evidence that dopaminergic neuron progenitors derived from their immune-cloaked hPSCs exhibit better immune system evasion compared to neuron progenitors generated from wild-type hPSCs. Additionally, these immunologically cloaked neuron progenitors improved motor function in an immune-deficient rat model of Parkinson's disease.¹

Pavan et al.'s encouraging findings open many further questions. The first and foremost question concerns safety. The immune system constantly surveils the body for infection and cancer. If immunologically cloaked cells become infected or cancerous, they could potentially prove deadly, as they may remain

invisible to the immune system. Cognizant of this concern, Pavan et al. introduced a "kill switch" to eliminate proliferating cells upon the addition of a drug.⁶ Future all-inclusive hPSC therapies will likely follow this precedent and combine immune cloaking with a kill switch. However, the kill switch⁶ was partly, but not completely, effective in neural progenitors transplanted *in vivo*.¹ An enhanced kill switch that completely eradicates transplanted cells *in vivo*⁷ may prove more effective in the event of a clinical emergency.

Second, will the immune system exclusively ignore the cloaked cells, or will the cloaked cells broadly dampen immune responses across the entire body? Can animals transplanted with cloaked cells mount an immune response against a pathogen or another immune stimulus elsewhere in the body?

Third, what is the extent and duration of immunological cloaking? Pavan et al.'s impressive study focused on immunologically cloaked neurons within 2 months of transplantation into humanized mice. While serving as useful models, current-generation humanized mice harbor imperfect facsimiles of the human immune system.⁸ There are marked limitations in the immune responses that they can mount, and human immune cell numbers often decline over time.⁸ Will cloaking perform equally well in a patient and, if so, for how long?

Fourth, Pavan et al. transplanted immunologically cloaked cells into the brain, but it is generally believed that the brain is immunologically surveilled less than other organs in the body are.¹ Will Pavan et al.'s immune cloaking strategy likewise prove effective for other cell types, such as hPSC-derived cardiomyocytes and pancreatic β -cells? These cell types would be transplanted into locations outside of the brain and thus would be subject to a greater degree of immune surveillance, thereby "stress testing" the immune cloak. Testing the generality of immune cloaking represents a critical next step in constructing a truly universal pipeline for stem cell-based therapies. Along these lines, Hu et al. discovered that immunologically cloaked pancreatic islets isolated from a rhesus monkey survived for 6 months upon intramuscular transplantation into a fully immunologically competent cynomolgus monkey and reversed diabetes.⁹ Hu et al.⁹ and

Pavan et al.¹ employed distinct immunological cloaking approaches. A future step would be to overexpress Pavan et al.'s eight immune-evasive proteins in non-human primate pluripotent stem cells and to test whether they can engraft in immunologically mismatched primates with functional immune systems.

Finally, Parkinson's likely starts in other brain regions—including the hindbrain—before spreading to the midbrain.¹⁰ Degeneration of the hindbrain and other brain regions likely underlies Parkinson's non-motor symptoms, which can precede the classical movement symptoms by years.¹⁰ Given that Pavan et al. have transplanted midbrain dopaminergic neuron progenitors under the immunological cover of darkness, will it be similarly possible to cloak, transplant, and replace additional neuron types that degenerate in Parkinson's? This could culminate in more holistic regenerative treatments for this deadly neurodegenerative disease.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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