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The Roadmap to Novel Parkinson's Disease Therapies

By Professor Martin Lévesque and Anne-Marie Castonguay, M.Sc.

Parkinson's disease affects a growing number of people worldwide. Despite more than 200 years of research into this degenerative disease, there is still no treatment that can prevent or stop its progression. However, we have a much better understanding of what happens in the brains of Parkinson's patients.
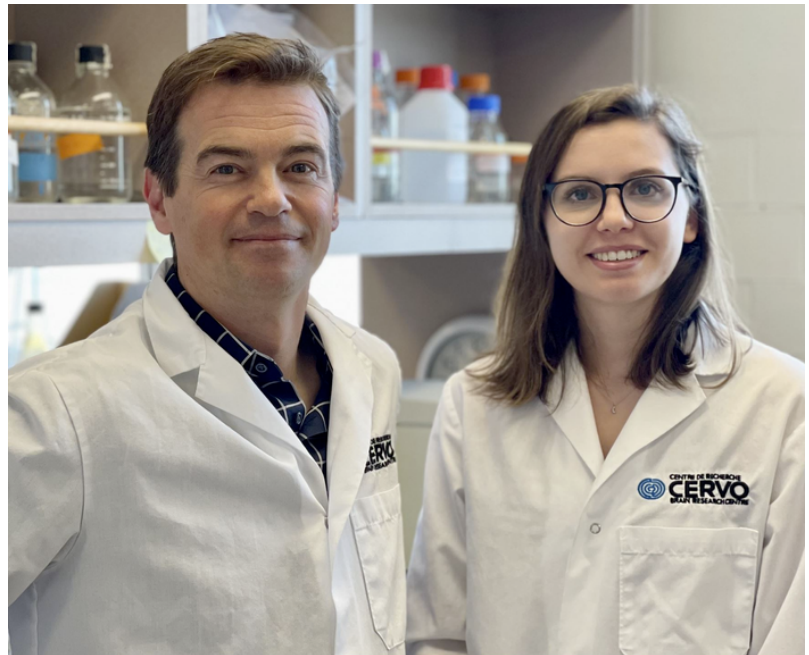
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The disease is very heterogeneous and its causes, symptoms and progression vary considerably from one person to another. Current treatments are aimed at alleviating the symptoms of the disease, but they tend to cause undesirable side effects and have only a limited effect on non-motor symptoms. Therefore, there is an urgent need to develop new therapies that can modify the progression of the disease.

Several laboratories are focusing on neuroprotective approaches, which aim to preserve neurons before they degenerate. This area of research is vast and varied and can take many forms. These include the development of small molecules, immunotherapy or even gene therapy.

In my laboratory, we have studied several target genes which, when repressed or overexpressed, have great neuroprotective potential. Indeed, our last published paper shows the importance of a protein encoded by the Rit2 gene in protecting mice from neurodegeneration when its expression is increased in the brain (Obergasteiger et al., 2023). In addition, one of our current major projects is to develop mini antibodies targeting the protein alpha-synuclein, which aggregates inside neurons and contributes to their death. Our mini antibody treatment almost completely prevents motor symptoms and signs of neuropathology in a preclinical model of Parkinson's disease (manuscript in preparation).

Immunotherapy is a fast-growing field of research, and many laboratories are developing full antibodies or mini antibodies as we are doing. Direct antibody delivery is called passive immunotherapy because it does not require activation of the immune system. In contrast, active immunotherapy is a vaccine that activates immune cells to either produce antibodies or to directly eliminate the target protein.

Both approaches are currently being evaluated in clinical trials for Parkinson's disease. One of the major challenges in immunotherapy is the translation of results obtained in preclinical models to human clinical trials. Because of the heterogeneity of the disease in humans, it is very difficult to reproduce the entire pathology in animal models. In addition, the immune mechanisms are very different between rodents and humans.

Nevertheless, immunotherapy approaches have shown considerable potential in several studies and could play an important role in the future treatment of patients with Parkinson's disease.

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Another area of research that is getting a lot of attention is cell replacement therapy. The idea is to replace lost neurons, especially those that produce dopamine. In the 1980s, autologous transplantation of cells from the adrenal gland was the first cell transplantation attempt tested in Parkinson's patients, but it had variable results and limited benefits. Cell transplantation from aborted fetal tissue was the second type of brain transplantation used in clinical trials in the 1990s. Despite encouraging results in some studies, side effects, ethical concerns, and limited tissue availability hampered further trials. Today, researchers are focusing on finding new sources of cells for transplantation, such as embryonic stem cells, neural stem cells, mesenchymal stem cells from various tissues, and induced pluripotent stem cells. Earlier this year, a multi-centric cell replacement clinical trial called STEM-PD treated its first patient with neurons derived from embryonic stem cells.

In addition to finding new sources of cells to produce dopamine, current research aims to facilitate graft delivery through improved guidance technologies during surgery. Further, to increase the survival of transplanted neurons and their functional integration, new graft sites and cell modification are both being explored.

In my laboratory, with the support of the Stem Cell Network, we are working to make transplanted neurons more resistant by expressing neuroprotective genes (such as Rit2) or by secreting mini antibodies against toxic aggregates of alpha-synuclein. The latter strategy would even help to protect the host neurons because the mini antibodies can diffuse into the brain.

Ideally, treatment for Parkinson's disease should be individualized based on the patient's genetics, stage of disease, and the specific characteristics of each patient's pathology. A combination of different therapies could also be used to manage most motor and non-motor aspects of the disease.

Finally, earlier diagnosis will be essential for neuroprotective strategies to be successful. For this reason, early biomarkers and imaging modalities are essential and are being actively studied.

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There is still much going on behind the walls of research centers and hospitals to find new treatments and improve the quality of life for patients with Parkinson's disease. We are confident that this extensive research will pay off in the years to come.

[Martin Lévesque Laboratory](#)