Parkinson’s disease (PD) is a chronic, progressive neurological condition, which is thought to affect between seven to ten million people worldwide. PD is caused by a loss of nerve cells in a region of the midbrain, the substantia nigra. This leads to a reduction in dopamine – the neurotransmitter that plays a vital role in regulating movement – which is responsible for many of the symptoms of PD including tremors, slowness of movement, changes in speech and rigid muscles.

Although there is currently no cure for PD, treatments are available to provide some relief from many of the symptoms. It is one of these treatments that ignited the interest of Dr. Tim Collier, Professor of Translational Science and Molecular Medicine at Michigan State University (MSU). Excitingly, Professor Collier’s research suggests that this treatment may have a new purpose: slowing progression of PD.

UNRAVELLING THE NEUROPROTECTIVE EFFECTS OF NOR

Nortriptyline (NOR) is an antidepressant which has been used very effectively for over 50 years to treat depression and nerve pain, symptoms commonly associated with PD. Together with collaborator Katrina Paumier, Assistant Professor of Molecular Medicine at MSU, Professor Collier noticed that NOR and other tricyclics (similar antidepressants belonging to the same class) affect neuron cell survival. The team were intrigued by the idea that these antidepressants might modify the way in which PD progresses.

Exploring their hypothesis further, Collier and Paumier undertook retrospective analysis of clinical trial data from an early cohort of PD patients. Intriguingly, those patients who had taken tricyclic antidepressants required standard PD therapy significantly later than those who hadn’t received antidepressant medication, suggesting that the drug may well have influenced their disease progression.

The team validated their idea in animal studies. They administered the antidepressant to rats which had a toxin-induced disease that models PD. The drug had a neuroprotective effect compared to sham-administered animals: antidepressant-treated rats had significantly less neuron loss, a smaller reduction in dopamine levels and reduced motor deficit symptoms. Interestingly, their studies revealed that the protective effect was associated with increased levels of the neurotrophic factor.
What first sparked your interest in Parkinson’s disease?

During my postdoctoral training I became fascinated with the emerging field of cell transplantation as an experimental therapy. Much of this work was focused on transplanted dopamine neurons to replace those lost in Parkinson’s disease (PD). Comprehensive understanding of PD was limited and completely focused on replacing dopamine. This seemed to me at the time an ‘easy fix’ for a terrible syndrome, that I could accomplish during my career. Needless to say, with the passage of time we learned the true complexity of the problem. I never lost my passion for developing therapeutics for PD, but 30 years later, the problem remains unresolved.

To what extent do you believe that Parkinson’s is related to ageing?

An association between ageing and PD has been recognised for several decades. Ageing is the number one risk factor for developing PD. Our work demonstrates that the dopamine neurons vulnerable to degeneration in PD, changes that occur in these neurons during ageing share important biological characteristics with the changes seen in PD. The pattern of change we’ve examined differ not in kind, but severity, suggesting that ageing and PD exist along the same biological continuum. So, is ageing pre-PD? Yes, there is no PD without ageing, although an individual does not need to be elderly to be diagnosed with PD. Yet, even the aggressive inherited forms of PD take decades for symptoms to be expressed. And, no, ageing is not PD. The majority of individuals live out their lives without becoming parkinsonian. The biological evidence suggests that ageing actively creates a vulnerable pre-PD state that tips into PD through contributions of other genetic and environmental factors.

There is evidence suggesting that PD acts like a prion disease, like CJD. What are the similarities between the two conditions?

The question is whether pathological α-synuclein can be passed between interconnected nerve cells, over long distances and many connections, to produce the entirety of pathology in PD. Over 10 years ago, investigators in Germany and the Netherlands, proposed just such a hypothesis, based on multiple sequential connections between brain regions exhibiting pathology in PD. Ultimately, the hypothetical prion-like spread of α-synuclein was suggested to be instigated in the gut and disseminated to the brain. In my view, the experimental evidence to test this kind of spread in animal models is not convincing. But, I’m likely to be in the minority.

Your research shows that tricyclics could provide significant benefit for early PD patients but not clear existing pathology. Are there treatments in the pipeline that could help treat advanced disease?

Most experimental therapies for PD, to be effective, rely on intervention at a time when a sufficient number of neurons have not succumbed to degeneration. Once the cells are gone, they’re not coming back. This is a significant problem in late stage PD, when degeneration is at its maximum. Conceptually, the only way to address this is by pharmacologically replacing the lost cells with cell transplantation or stimulation of neurogenesis. If pathology is advanced, but a significant population of cells remain, administration of antisense oligonucleotides directed at α-synuclein shows promise. These small molecules might engage an ‘easy fix’ for a terrible syndrome, that has already been approved and shown to be safe and efficacious. A convincing answer. But, I’m likely to be in the minority.

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What are your future plans for your research?

My immediate efforts are focused upon generating the momentum required to test NOR in a clinical trial of early PD individuals. Also, I am engaged in my collaboration with Dr Lapidus to use the combination of her test tube assay and my animal models to explore a large panel of FDA-approved drugs for agents that have anti-aggregation properties for α-synuclein. Last, but not finally, I continue to study the connection between ageing and PD, to determine whether promoting “successful” ageing will reduce the incidence of PD through interventions including lifestyle.

RESEARCH OBJECTIVES

Professor Collier’s research explores the mechanisms of central nervous system ageing, neurodegenerative diseases and the relationship between the two. His work is focused on the etiology of Parkinson’s disease.

FUNDING

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COLLABORATORS

Dr Lisa Lapidus, Dept. Physics & Astronomy, Michigan State University.

Dr Katrina Paumier, previously MSU, now private sector; Dr Craig Justman, Lysosomal Therapeutics Inc, Cambridge, MA; Dr Peter Lansbury, Center for Neurologic Diseases, Harvard Medical School, Boston, MA.

BIO

Prof Collier trained at the University of Minnesota, Northwestern University and the University of Rochester, and has been a faculty member at the University of Rochester, Rush University Medical School in Chicago and the University of Cincinnati. In 2010 he was recruited to the Michigan State University College of Human Medicine where he is E.A. Brophy Endowed Chair in Central Nervous System Disorders.

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The sequence of molecular events through which normal monomeric functional α-synuclein fibrils and accumulates into toxic oligomers, and then forms highly ordered fibrils that contribute to intracellular aggregates of protein termed “Lewy bodies”, that are a hallmark of Parkinson’s disease. It remains a topic of debate whether these inclusions protect the nerve cell by sequestering abnormal proteins, or contribute to the degeneration of these neurons. Adapted from image originally published in Nature Reviews Neuroscience 2003.

BDNF (brain derived neurotrophic factor), which is essential for dopamine neuron survival and function. Their study sparked interest to have a role in dopamine release. In its functional or contribute to the degeneration of these neurons. Adapted from image originally published in Nature Reviews Neuroscience 2003.

The chemical structure of the tricyclic antidepressant, which is essential for dopamine neuron survival and function. Their study sparked interest in Parkinson’s disease. Their study sparked interest to have a role in dopamine release. In its functional or contribute to the degeneration of these neurons. Adapted from image originally published in Nature Reviews Neuroscience 2003.

IDNP (brain derived neurotrophic factor), which is essential for dopamine neuron survival and function. Their study sparked interest to have a role in dopamine release. In its functional or contribute to the degeneration of these neurons. Adapted from image originally published in Nature Reviews Neuroscience 2003.

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