IRICoR

COMMERCIALIZATION OF RESEARCH
Institute for Research in Immunology and Cancer

NUR77/RXR: A NEW TARGET IN DRUG-INDUCED DYSKINESIA

THERAPEUTIC AREA - Neurodegenerative disease

INDICATION - Parkinson's disease (PD)

OBJECTIVES - To aim at screening for the first specific small molecule modulators (agonists and antagonists) of the activity of Nur77/RXR transcriptional complexes

CURRENT STAGE - Hit-to-Lead

PRINCIPAL INVESTIGATORS - ***Daniel Lévesque***, ***Sylvie Mader***

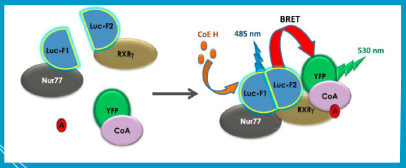
COMPETITIVE ADVANTAGES

+ The assay may enable discovery of compounds, which allow selective manipulation of the signalling pathways that underlie the adaptations of the striatum and nigro-striatal pathways in dyskinesia.

+ Access to the BRET assay and the animal models of dyskinesia

PUBLICATIONS

+ Lévesque and Rouillard, Trends Neurosci., 30: 22-30, 2006
+ Ethier et al., Biol. Psychiatry, 56: 522-526, 2004
Mahmoudi et al., Neurobiology of Disease, 36: 213-222, 2009
+ Mahmoudi et al., Eur. J. Neuroscience, 38: 2192-2198, 2013
+ Giner, Cotnoir-White, Mader and Lévesque, FASEB J., 29: 4256-4267, 2015



SCIENTIFIC BACKGROUND AND RATIONALE

In Parkinson Disease, dopamine levels in the striatum are depleted and the standard treatment is L-DOPA. However, pulsatile exposure to this dopamine precursor causes compensatory adaptations that push the striatum towards overactivity of the direct pathway neurons and characteristic abnormal involuntary movements that make up L-DOPA induced dyskinesia (LID). Dyskinesia affect around 50% of PD patients on L-DOPA within 3 years. The patient population suffering from LID is large and poorly served by current therapies. There are no alternatives to L-DOPA that sufficiently control the primary motor deficit in advanced disease and current research suggests that no disease-modifying or better symptomatic therapy is likely to be ready for patients in the short-medium term. Antipsychotics induce motor side effects described as tardive dyskinesia (TD). TD comprises semi-purposeful but involuntary movements including facial tics, postural abnormalities and tremors. TD is a major reason for patient non-compliance with medication regimens.

Dopamine receptor agonists (both L-DOPA and drugs of abuse) and antagonists (antipsychotics) have a profound effect on Nur77 expression and genetic ablation of Nur77 (gene knockout) significantly modulates dopamine-mediated effects. Nur77 is a transcription factors from one subgroup (NR4A) of the nuclear receptors family (NRs) and can heterodimerize with retinoid X receptor (RXR). Interestingly, RXR drugs also modulate dopaminergic drugs such as antipsychotics, but this effect is abolished in Nur77 knockout animals. Thus, we hypothesize that neuronal plasticity underlying LID and other dyskinesia occurs at the level of Nur77 and RXRγ-driven gene transcription in the striatum. Results from Dr. Rouillard (University of Laval) and Lévesque's (University of Montreal) laboratories strongly suggest that in animal models of PD, Nur77 is involved, together with RXR, in LID and also L-DOPA-induced behavioural sensitization. Evidence includes a positive correlation between mRNA expression of Nur77 and dyskinetic scores in PD-lesion monkeys treated with L-DOPA and RXR agonist (docosahexaenoic acid (DHA)). Furthermore, Nur77 knockout rats show less abnormal involuntary movements than wild type rats in a model of PD treated with daily L-DOPA injections. Over ten years of research in animal models of dyskinesia in the laboratory of Dr Lévesque suggests that facilitating Nur77:RXRγ activity will prevent antipsychotic-induced TD. This means that modulating Nur77:RXR activity may reduce dyskinesia.

COMPLETED WORK

Full screens for agonists and antagonists were completed using an innovative cell-based assay combining a Protein Complementation Assay (PCA) and BRET technology. Indeed, Drs. Levesque and Mader have developed a biosensor assay to allow the identification of molecules selectively acting at the Nur77/RXR hetero-dimer using cell-based bioluminescence resonance energy transfer (BRET). The ligand-dependent activity of nuclear receptors is monitored with recruitment of a co-regulator. The assay was performed in HEK cells transfected with 3 recombinant proteins. The nuclear receptor RXR and Nur77 were each fused to a portion of Renilla luciferase (RLuc). In the presence of an agonist, the co-activator, which was fused to the Yellow fluorescent protein (YFP, the energy acceptor) was recruited to the nuclear receptor complex (heterodimer), leading to energy transfer from the RLuc to the YFP, which will emit a bioluminescent signal at a specific wavelength. This RLuc complementation assay combined with BRET technology allows the detection of modulation of the Nur77-RXRγ complex by small molecules (agonists and antagonists mode).

Pilot screens for both agonists and antagonists were done.

Full screen for agonists and antagonists detection both at IRIC and CDRD sites were completed. A total of ≈ 300,000 compounds were tested. Seven hundred active molecules in the primary assay were tested in a gene reporter secondary assay monitoring downstream effect on gene transcription. Several Hits were identified and confirmed including potency determination.

LEAD SCIENTIST

Daniel Lévesque Ph.D. (Pharmacy)

+ Full Professor, Molecular Neuropharmacology Laboratory, Faculty of Pharmacy, Université de Montréal

+ Member of the Central Nervous System Research Group (CNSRG)

+ Member of the Drug Research Quebec Network (RQRM)

After a post-doctoral training in the laboratory of Professor Jean-Charles Schwartz and Doctor Pierre Sokoloff at the Paul Broca Center, INSERM U109, Paris, France (neurobiology/pharmacology, dopamine D3 receptor), Dr Daniel Lévesque joined the Faculty of Medicine of the Laval University as an adjunct professor in 1995. In 2006, he transferred his research and academic activities at the Faculty of Pharmacy of the University of Montreal, where he obtained a full professor position in 2009. As an independent investigator, Dr Lévesque obtained numerous salary awards and research grants from the Fonds de la Recherche en Santé du Québec, the Canadian Institutes of Health Research (CIHR), Canadian Foundation for Innovation (CFI), Natural Science and Engineering Council (NSERC) Canada, the National Alliance for Research on Schizophrenia and Depression (USA), the Stanley Medical Research Institute (USA), the Parkinson Society of Canada, the Michael J. Fox Foundation and the Parkinson's Disease Foundation (USA) during his career. He has published over 80 peer-reviewed articles in the field of neuroscience.

Dr Lévesque's research team is the first to establish a role of transcription factors of the nuclear receptor family in abnormal involuntary movements associated with dopamine drug therapies (antipsychotics, anti-Parkinsonians and drogues of abuse). In collaboration with Dr Sylvie Mader (IRIC), his team has developed innovative cell-based assay combining Protein Complementation and bioluminescence resonance energy transfer (BRET) technology. These biosensors have been optimized to high throughput screening to identify new molecules selectively acting at the Nur/RXR hetero-dimers.

CO-LEAD SCIENTIST

Sylvie Mader Ph.D.

+ Principal Investigator, Molecular Targeting in Breast Cancer research unit, IRIC

+ Professor, Department of Biochemistry, Faculty of Medicine, Université de Montréal

+ Adjunct Professor, Department of Medicine, Experimental Medicine Program, McGill University

After training in France at Ecole Normale Supérieure de Paris, Université Paris VI and Institut Pasteur, Sylvie Mader joined the team of Professor Pierre Chambon in Strasbourg for a Ph.D. in Biochemistry at the Laboratoire de Génétique Moléculaire des Eucaryotes, during which she characterized the mechanisms of target gene regulation by nuclear receptors. She then trained as a postdoctoral fellow with Professor Nahum Sonenberg at the Biochemistry department at McGill University, where she uncovered a mechanism of translational control involving formation of competitive complexes with the translation initiation factor eIF4E. Sylvie Mader put together her research team at Université de Montréal in 1995, with a focus on the therapeutic modulation of molecular signaling pathways involved in breast cancer. Since 2002, she holds the CIBC Breast Cancer Research Chair at Université de Montréal. Since joining IRIC in 2005, Sylvie Mader and her team aim to identify novel therapeutic targets and design new drugs for breast cancer treatment. They use cutting-edge technologies such as functional genomics, proteomics, bioinformatics and biophysics to identify novel therapeutic targets and design new drugs for breast cancer treatment. In particular, her team is studying nuclear receptor signaling pathways, which are attractive targets for drug development. She is also analyzing the mechanisms of mammary cell differentiation and tumorigenesis in cultured cells and animal models. Her group has developed collaborations with clinician scientists, including Dr. André Robidoux at the Centre hospitalier de l'Université de Montréal, to exploit basic research results in order to improve the efficacy of existing treatments and design new therapeutic approaches.

For additional information, please contact:

Steven Klein, PhD, MBA
Vice-President, Business Development
steven.klein@iricor.ca | 514 343 6647