Dr. Jean-Pierre Julien holds a Senior Canada Research Chair in Neurodegeneration at Laval University since 2003. He obtained his Ph.D. in Biochemistry from McGill University and carried out his postdoctoral work at the National Institute for Medical Research in London (UK). From 1989 to 2003, he was Professor at the Centre for Research in Neuroscience of McGill University. In 2000, he was awarded with the prestigious Sheila Essey Award for research on ALS from the American Academy of Neurology. He is a Fellow of the Canadian Academy of Health Sciences and he is also a member of the Robert Packard Center for ALS Research at Johns Hopkins University. He served as the Chair of several successful international conferences including a Gordon Research Conference on IFs (1998) and Annual Symposia of Fondation André-Delambre on ALS (2005-present). He is currently a member of the Board of Institute of Genetics of CIHR and member of the selection committee for the Gairdner Awards. Dr. Julien is recognized as one of the most influential scientists in the field of neurofilament biology and the neurobiology of amyotrophic lateral sclerosis (ALS). His studies with transgenic mice led to the first demonstration that disorganization of neurofilaments may cause neuronal dysfunction and degeneration. Dr. Julien has also studied the role of microglia, the innate immune cells of the CNS, in mice models of ALS. He recently discovered the therapeutics effects of immunization in mice models of ALS. This seminal contribution is a proof-of-principle for potential therapy of familial ALS.

Update on Transgenic TDP43 Mice: New Insights

Amyotrophic lateral sclerosis (ALS) is an adult-onset neurological disorder that is characterized by the selective loss of motor neurons leading to progressive weakness, muscle atrophy with eventual paralysis and death within 5 years of clinical onset. Approximately 10% of ALS cases are familial, the remainder ALS cases being diagnosed as sporadic (90%). The discovery 18 years ago of missense mutations in the gene coding for the Cu/Zn superoxide dismutase 1 (SOD1) in subsets of familial cases directed most ALS research to elucidating the mechanism of SOD1-mediated disease. Studies with these transgenic mice expressing mutant
SOD1 yielded complex results with multiple targets of damage in disease including mitochondria, proteasomes, axonal transport and secretory pathways. Recently, much attention has been devoted to two genes coding for DNA/RNA binding proteins which have been implicated in the pathogenesis of ALS. Transactive response DNA-binding protein 43 (TDP-43) ubiquitinated inclusions are a hallmark of amyotrophic lateral sclerosis (ALS) and of frontotemporal lobar degeneration with ubiquitin-positive inclusions (FTLD-U). Dominant mutations in the TARDBP gene, which codes for TDP-43, were reported by several groups as a primary cause of ALS for ~3% familial cases and ~1.5% sporadic cases. Mutations in the FUS/TLS gene were also detected in ~4% of familial ALS cases. Recent transgenic mouse studies revealed high degree of toxicity of TDP-43 proteins when overexpressed under the control of strong neuronal gene promoters resulting in early paralysis and death, but without the presence of ALS-like ubiquitinated TDP-43 inclusions. To better mimic the human ALS situation, we generated transgenic mice that exhibit moderate and ubiquitous expression of TDP-43 species using genomic fragments encoding human TDP-43 wild-type or FALS-linked mutants TDP-43G348C and TDP-43A315T. These novel TDP-43 transgenic mice develop many age-related pathological and biochemical changes reminiscent of human ALS including ubiquitinated TDP-43 inclusions, TDP-43 cleavage fragments, intermediate filament abnormalities, axonopathy and neuroinflammation. All three transgenic mouse models (TDP-43Wt, TDP-43G348C and TDP-43A315T mice) exhibited during aging impaired learning and memory capabilities as well as motor dysfunction. Real-time imaging with the use of biophotonic TDP-43 transgenic mice carrying GFAP-luc reporter revealed that the behavioural defects were preceded by induction of astrogliosis, a finding consistent with a role for neuroinflammation in ALS pathogenesis. Evidence will be presented that an upregulation of TDP-43 mRNA can cause exaggerated innate immune responses suggesting new therapeutic targets for ALS disease.