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# PARKINSON'S DISEASE AND MOVEMENT DISORDERS

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## Novel insights and therapeutics for Parkinson's disease

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Besides the hallmark pathology of aggregated phosphorylated neuronal intermediate filament proteins it has been now well documented that cyclin-dependent kinase 5 (Cdk5), a critical neuronal kinase in nervous system development, function and survival, when deregulated and hyper activated induces AD, PD and ALS like phenotypes in mice. Under physiological conditions, Cdk5 activity is tightly regulated. The deregulation and hyper activation of Cdk5/p25 induces neuropathology. Thus, Cdk5/p25 becomes prime therapeutic target for AD and neurodegenerative diseases associated with the hyper activation of Cdk5. In order to prevent hyper activation of Cdk5/p25, we have designed several small peptides of p25 on the basis of Cdk5/p25 crystal structure and checked for competition with p25 and thus inhibiting selectively the hyperactivity of Cdk5, we discovered a small peptide (p5) comprising of 24 amino acids, inhibited Cdk5 hyper activation. The modification of p5 to TFP5 crosses blood brain barrier (BBB), which was tested in a transgenic AD, PD & ALS models. Post TFP5 injections in AD, PD and ALS model mice displayed significant reduction in Cdk5/p25 hyperactivity, neuroinflammation and hyperphosphorylation of cytoskeletal proteins, along with various behavioral rescues. TFP5 does not inhibit normal Cdk5/p35 activity, and therefore has no toxic side effects. In addition, treated mice rescued synaptic dysfunction and a reduction in phospho-neuronal intermediated neurofilaments and neuronal cell death. These results indicate that TFP5 and TP5 have a potential to be a therapeutic target for AD, PD and ALS neurological diseases.

### Biography

Harish C Pant received his M.A. and Ph.D. degrees in Physics from Agra University, Agra, India. His postdoctoral studies were conducted on the mechanisms of electron and ion transport in model membrane systems at the Department of Biophysics at Michigan State University. He joined the Laboratory of Neurobiology in the NIMH as a senior staff fellow in 1974 with Dr. Ichiji Tasaki where he studied the function of the axonal cytoskeleton in the squid giant axon. In 1979 he moved to the NIAAA extending his studies on the neuronal cytoskeleton and the effects of alcohol on its regulation. Dr. Pant moved to the NINDS, Laboratory of Neurochemistry in 1987 where he is presently chief of the section on Cytoskeleton Regulation.

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