Frontotemporal Dementias: Clinical Correlates to Cellular Substrates
Thursday, May 11, 2:30 PM–5:00 PM
Location: Toronto
Chair: Anand Kumar
Co-Chair: Ralph Nixon

24. CLINICAL, NEUROPATHOLOGICAL AND NEUROIMAGING CORRELATES OF FRONTOTEMPORAL DEMENTIA (FTD)
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Frontotemporal dementias (FTD) comprise a heterogeneous group of neurobehavioral disorders characterized by behavioral aberrations and progressive cognitive decline. The behavioral features typically include disinhibition, verbal outbursts, and apathy. The cognitive abnormalities comprise of decline in memory, language and executive functions. Visual-spatial functions are noticeably spared. The pathological correlates of FTD include neuronal atrophy, gliosis and spongiosis in the frontal and temporal lobes with sparing of the more posterior regions. Neuritic plaques and neurofibrillary tangles are characteristically absent in FTD. Neuroimaging studies with single photon emission computed tomography and Xenon inhalation techniques demonstrate deficits in perfusion largely restricted to the frontal and anterior temporal regions. Both sporadic and familial forms of the disorder have been described and extrapyramidal features occur in certain, though not all, subgroups. FTD is a compelling model of behavioral disorders with clear-cut neurologic and neurobiological underpinnings. They comprise approximately 15 percent of early onset degenerative disorders and their clinical impact in getting increasing recognition. This presentation will focus on new developments within the clinical and neuropathological realm, and emphasize the neurobiological implications of the clinical and genetic heterogeneity frequently encountered in FTD. It will also serve as a broad based introduction to the other components of this panel—which will underscore the genetic, cellular and gene therapeutic aspects of FTD and closely related neurodegenerative disorders.

25. NEUROGENETICS OF FTD—RECENT DEVELOPMENTS
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There is a striking genetic predisposition to FTD, as from 40 to 50% of patients have a family history of an FTD spectrum disorder, and most are consistent with dominant transmission. Genetic analysis has determined that a series of disorders related clinically and pathologically to frontotemporal dementia (FTD), collectively labeled FTDP-17 disorders, are etiologically related. The relationship between these disorders although initially based on linkage analysis, has been confirmed by the discovery of causal mutations in the tau gene in some families with FTDP-17 disorders. Mutations affecting the expression or structure of the microtubule binding domain of the tau gene have been found about 25% of large families with chromosome 17q21-22-linked disease, but rarely in sporadic cases. Functional studies implicate alterations in the microtubule binding domain in various splice isoforms of tau, but other genes are likely to be involved. Remarkable heterogeneity in clinical and pathological presentations can be seen, even among those with the same mutation. The basis for this variability is unknown. The functional implications of known mutations will be emphasized and the phenotype/genotype correlations will be discussed.

26. THE PATHOBIOLOGY OF TAU PROTEIN IN NEURODEGENERATIVE DISEASES
R.A. Nixon, K. Duff, Y. Matsuoka
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Aggregates of the tau protein in the form of paired-helical filaments are one of the hallmark lesions of Alzheimer’s Disease. The significance of tau to mechanisms of neurodegeneration is now underscored by the identification of mutations of tau causing frontotemporal dementia (FTD). As one of a diverse group of microtubule-associated proteins (MAPs), tau binds and stabilizes microtubules (MT), which serve as structural elements and as tracks for the axonal transport of vesicular organelles, thereby supporting axon function and synaptic transmission. The six isoforms of tau generated by alternative splicing of a single gene vary in their affinity for MT and efficiency in inducing the polymerization of tubulin to form MT. FTD-causing mutations alter the proportions of tau isoforms and result in tau proteins with reduced ability to promote MT assembly although this effect alone is unlikely to account for the autosomal dominant nature of FTD. When the tau gene is deleted in mice, only subtle phenotypic changes are seen suggesting that other MAPs can substitute for tau function. These and other findings support a toxic gain of function, rather than loss of tau function, as the underlying effect of FTD-related mutations. In this regard, recent studies suggest that FTD-mutant tau may bind abnormally and disassemble MT, which might then lead to axonal transport failure. Another property of tau is its proclivity for aggregating into inclusions with distinctive morphologies (e.g. NFT in AD, ribbon-like filaments in FTD). As in other human neuronal inclusion diseases, the role of aggregation in the degenerative mechanism (e.g. protection vs toxicity) is unclear. Tau undergoes complex phosphorylation during development. In human tauopathies, tau is hyperphosphorylated, which decreases its association with MT and promotes its aggregation. Recently, tau has been found to interact with the non-receptor tyrosine kinase Lyn and other src family tyrosine kinases and is tyrosine phosphorylated suggesting a role for tau in signal transduction. A host of tau transgenic mouse models are being developed to investigate tau pathobiology and new findings on these models and their relationship to FTD in humans will be discussed.

27. REVERSAL OF SPONTANEOUS ATROPHY OF CHOLINERGIC BASAL FOREBRAIN NEURONS IN THE AGED PRIMATE BY EX VIVO GENE THERAPY
D.E. Smith (1), J. Roberts (2), F. Gage (3), M.H. Tuszynski (4)

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Recent pre-clinical developments in gene therapy in primates could have practical implications for degenerative disorders such as frontotemporal dementias (FTD) in humans. Ex vivo gene therapy is a