Charbel Moussa, MB, Ph.D

Assistant Professor
Head of Laboratory for
Dementia and Parkinsonism
Department of Neuroscience
Georgetown University School of Medicine
3970 Reservoir Rd, NW
TRB, WP09B (office)
TRB, EG12 (Laboratory)
Ph: 202-687-7328 (office)
Fax: 202-687-0716
E-mail: cem46@georgetown.edu

The Laboratory for Dementia and Parkinsonism evaluates potential therapeutic drugs for neurodegenerative diseases in pre-clinical models and clinical trials.

We investigate cellular, biochemical and pathological mechanisms that underlie neurodegenerative diseases with dementia and Parkinsonism, including Alzheimer's disease (AD) and other dementias, and Parkinson's disease (PD) and related movement disorders. We also investigate the neuro-pathological and biochemical pathways involved in the spectrum of motor neuron disease (MND) with fronto-temporal dementia (FTD).

Background

Overwhelming evidence suggests that neurodegenerative pathologies share a common denominator: accumulation of misfolded and/or undigested proteins in the cell. For example, Tau is a major microtubule stabilizing protein that is abnormally hyper-phosphorylated in a group of diseases called the Tauopathies, including AD and other diseases that clinically manifest with Parkinsonism and dementia such as progressive supranuclear palsy (PSP), fronto-temporal dementia with Parkinsonism linked to chromosome 17 (FTDP-17) and cortical basal degeneration (CBD). Histologically, post-mortem AD brains have other inclusions called plaques, which are derived from the processing of beta-amyloid precursor protein (APP) and accumulate outside the cell. APP processing also leads to intracellular accumulation of beta-amyloid fragments that seem to impair clearance mechanisms via the ubiquitin-proteasome or the autophagy-lysosome systems, leading to plaque deposition. Alpha-synuclein accumulation into inclusions called Lewy bodies (LBs) also seems to impair protein clearance mechanisms, and these LBs are often found with Tau hyper-phosphorylation (p-Tau) in post-mortem PD brains with and without dementia. Therefore, patients who are first diagnosed with AD, the most common form of dementia in the elderly, develop Parkinsonian symptoms in later stages of disease. Patients who are initially diagnosed with PD, which is a complex group of different motor and non-motor symptoms, develop AD-like phenotypes. This clinical and symptomatic overlap between dementia and Parkinsonism may be due to protein inclusions that trigger pathologies in sub-population of brain cells or distinct nuclei. Another good example of clinical overlap between neurodegenerative diseases is the spectrum of MND-FTD that seems to be associated with modification of the ribonucleoprotein TDP-43 and, again, leads to cytosolic and/or nuclear protein accumulation.

Pre-clinical studies

Our laboratory is interested in the clearance of intracellular protein inclusions. The ubiquitin-proteasome or the autophagy-lysosome systems are quality control mechanisms, whereby excess or unwanted proteins are degraded. Autophagy is a physiologically normal multi-step process that depends on ubiquitination to clear cellular debris. Parkin is an E3 ubiquitin ligase, which tags protein with ubiquitin (ubiquitination) and targets them to the proteasome or lysosome (autophagy) for degradation. However, parkin activity is lost with and without genetic mutations in many neurodegenerative diseases due to loss of protein stability. We, therefore, employ strategies that increase parkin function to enhance protein clearance mechanisms. The current focus of our laboratory is:

1- To generate gene transfer animal models using stereotaxic lentiviral delivery to model or mimic neurodegenerative disease mechanisms
2- To study the effects of parkin activity on amyloid proteins, including Tau, alpha-synuclein, beta-amyloid and TDP-43
3- To investigate the genetic and pharmacological effects of tyrosine kinase inhibition (TKI) on parkin activity and protein metabolism and clearance
4- To validate the effects of de-ubiquitination on parkin activity and clearance via autophagy and the proteasome
5- To examine the differential roles of systemic and CNS immunity in the early stages of neurodegenerative diseases

Drug repositioning and clinical trials

We investigate the potential to reposition clinically relevant and therapeutically tolerated FDA-approved drugs to treat neurodegenerative diseases. We found that two anti-cancer drugs, including the TKI nilotinib (Tasigna) and bosutinib (Bosulif) cross the blood barrier, induce autophagic protein clearance and modulate brain and peripheral immunity in pre-clinical models of AD, PD, MND-FTD and other related diseases. These preclinical studies have led to pilot phaseI/II clinical trials to investigate the effects of an escalating oral dose of nilotinib on blood and CSF levels of alpha-synuclein and p-Tau in patients with early PD and PD with LB dementia. These trials will investigate the safety and tolerability of nilotinib and may lead to larger clinical trials that include other disease indications.