## FEATURED SPEAKER

**VIJAY RANGACHARI, PHD**

*Professor of Biophysical Chemistry, University of Southern Mississippi*

Dr. Rangachari obtained his Ph.D from the All India Institute of Medical Sciences (AIIMS), New Delhi, India in 2000. After a brief stint at Fredrich Schiller University in Jena, Germany as a visiting scientist, he did his post-doctoral work at the Institute of Molecular Biophysics at Florida State University until 2004. He followed it with a second post-doc at Mayo Clinic College of Medicine, where is started investigating amyloid proteins.

He joined the Department of Chemistry and Biochemistry at the University of Southern Mississippi in 2008. He is now a full professor of Biophysical chemistry. Dr. Rangachari's research interests include understanding the molecular mechanisms of intrinsically disordered proteins (IDPs) that are involved in liquid-liquid phase separation and amyloid aggregation in neurodegenerative diseases and the design and characterization of soft matter biomaterials.

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# SEMINAR FOR NEUROTRAUMA AND DISEASES

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PRESENTS

## α-SYNUCLEIN MODULATES TDP-43 PHASE TRANSITIONS TO INDUCE HETEROTYPIC AMYLOIDS – IMPLICATIONS IN NEURODEGENERATIVE DISEASES

**Date:** February 21, 2024 **Time:** 4:00 p.m. - 5:00 p.m. EST

**Location:** DLR 131 **Zoom Link:** http://bit.ly/42hhhJG

**Meeting ID:** 923 5486 2062 **Passcode:** CPR

## ABSTRACT

Emerging new phenotypes and clinical presentations in neurodegenerative diseases challenge the current paradigm of homotypic (single-protein) amyloids and implicate the possibility of heterotypic amyloid aggregates as the underlying cause. Our incomplete understanding is apparent when considering an increasing number of pathologies that exhibit distinct phenotypes and clinical presentations correlating better with colocalized cytoplasmic amyloid inclusions of different amyloid proteins. In particular, both α-synuclein (αS) and TDP-43 proteins are observed in pathologies such as limbic predominant age-related TDP43 encephalopathy neuropathological changes (LATE-NC), Lewy body dementia (LBD), and multiple system atrophy (MSA). Aberrant aggregates of the two proteins also form the hallmarks of frontotemporal lobar degeneration (FTLD) and Parkinson's disease. TDP-43 is present in two distinct phases in physiology and pathology. During stress, TDP-43 undergoes liquid-liquid phase separation (LLPS) with RNA and partitions into RNA-rich foci called stress granules in the cytoplasm, while in pathology, the protein forms toxic cytoplasmic insoluble amyloid aggregates. Our investigations reveal that αS and TDP-43 synergistically interact with each other to form distinct neurotoxic heterotypic aggregates that are dependent on TDP-43 phase behavior. In homogenous phase conditions, αS and prion-like c-terminal domain (PrLD) of TDP43 synergistically co-aggregate toward heterotypic fibrils containing both proteins, while in demixed solutions containing TDP43-RNA droplets, αS emulsifies the liquid droplets to promote heterotypic amyloid aggregates. Together these data suggest αS-TDP-43 heterotypic amyloids as potential molecular entities for distinct phenotype emergence in some neurodegenerative diseases.

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