INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI
SHORT ABSTRACT OF THESIS

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Programme of Study	:	Ph.D.

Thesis Title: **Understanding the role of alpha-synuclein in Japanese encephalitis virus replication and evaluation of pyrazole derivatives as therapeutics against its infection**

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SHORT ABSTRACT

In the prognosis of Japanese encephalitis virus (JEV) infection, many host factors have been identified as being involved in the various steps of the viral life cycle. Since it is a neurotropic virus, understanding the role of neuronal-specific proteins and local cellular homeostasis in developing therapeutics against JEV is an active area of research. Alpha-synuclein (α-syn) is one of the neuronal-specific proteins regulating synaptic plasticity and has been reported to have antiviral potential in related neurotropic viruses. JEV-infected patients displaying Parkinson's disease (PD)-like symptoms have been reported to have α-syn overexpression in the brain regions. As per reports, phosphorylation at S129 position plays a major role in aggregation and α-synucleinopathy. Therefore, exploring the function of α-syn in JEV induced death of dopaminergic neurons and α-synucleinopathy is essential. To this day, the present study reports the functional role of α-syn in JEV pathogenesis as well as explores the anti-JEV therapeutic candidates. There is a significant increase in endogenous α-syn expression during JEV replication, demonstrating a substantial reduction in JEV replication, suggesting an anti-JEV effect. α-syn was found to modulate the anti-oxidative pathway by increasing the expression of superoxide dismutase 1 (SOD1). The pathological implications of α-syn phosphorylation were carried out by studying casein kinase 2 (CK2) and Polo-like kinase (PLK2) involved in α-syn phosphorylation. Detailed analyses of CK2 and PLK2 reveal a notable reduction in these kinases, particularly during the late phase of JEV replication, thereby reducing the phosphorylated α-syn (pα-synS129) protein level. The intracellular α-syn oligomerization was increased in JEV-infected cells. Pyrazole derivatives with anti-oxidative properties were found to have anti-JEV activity. Comprehensive in vitro and in vivo studies showed compounds suppressed JEV-induced reactive oxygen species (ROS) generation through NRF2-SQSTM1 signaling mechanisms. This study contributes valuable insights into the interplay between α-syn and JEV, shedding light on avenues to study further the potential role of α-syn aggregation in JEV pathogenesis and exploit it to develop broad-spectrum antiviral therapeutics.