Details of the research work duly signed by the applicant, for which the Sun Pharma Research Award is claimed, including references and

Prof. Ganesh, for the past two decades, has been focussing on dissecting the cellular pathways leading to neurodegeneration and associated pathologies, and to develop therapeutic interventions based on such discoveries. Specifically, he has been studying the link between glycogen metabolic pathway and its relevance to neuronal survival and death. The importance of the metabolic control neuronal health is attracting attention in the literature recently with studies on diabetes and cognitive abilities but Prof. Ganesh has been a forerunner in this field. The following narrative provides some of the recent highlights of this work in this field:

i: Targeting leptin signalling pathway to reduce glycogen rich Lafora bodies in the Lafora disease neurons and to supress neuroinflammation and seizure susceptibility:

Prof. S Ganesh is an internationally well-known expert in the field of Lafora disease pathology – a fatal genetic disorder with wide spectrum of neurological deficits including epilepsy. His group was instrumental in deciphering the mechanism behind the abnormal accumulation of glycogen in the neurons in Lafora disease, and the causal role for defects in the proteolytic processes in the neuronal death. His group has earlier demonstrated that increased glucose uptake underlie abnormally higher level of glycogen in the Lafora disease brain and blocks autophagy. Extending these findings, he proposed to check – as a proof of concept - if blocking the glucose uptake may prevent the formation of Lafora bodies and seizures susceptibility in Lafora disease. Using the knock-out mice models for the Lafora disease, his group has demonstrated that blocking the leptin signalling in the neurons suppress the abnormal accumulation of glycogen, reduces the seizures susceptibility and gliosis (**Hum Mol Genet. 2017, 26:4778**). Lafora disease is a teenage-onset fatal disorder and currently, there are no treatments available. This was only the second report on the target (other than glycogen synthase) for therapeutic intervention in Lafora disease. Thus, this discovery of Prof. Ganesh has gained attention and the Lafora disease consortium, in which Prof. Ganesh is a member, is attempting to use an FDA approved leptin antagonist to treat the disease.

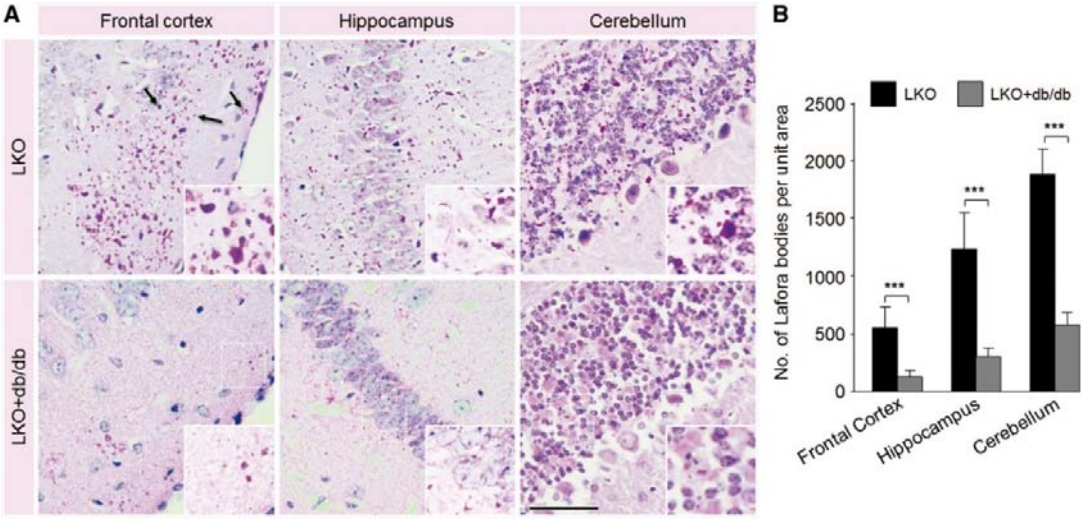


Fig. 1 Loss of leptin signaling in laforin-deficient mouse reduces Lafora bodies in the laforin-deficient mouse brain. Representative images showing the reduction in the number of PAS-positive Lafora bodies (pink granules) in the Lafora disease animals deficient for the leptin receptor (LKO+db/db) as compared to the control disease model (LKO). The bar diagram quantifies the number of Lafpra bodies in the indicated areas. (**Hum Mol Genet. 2017, 26:4778)**

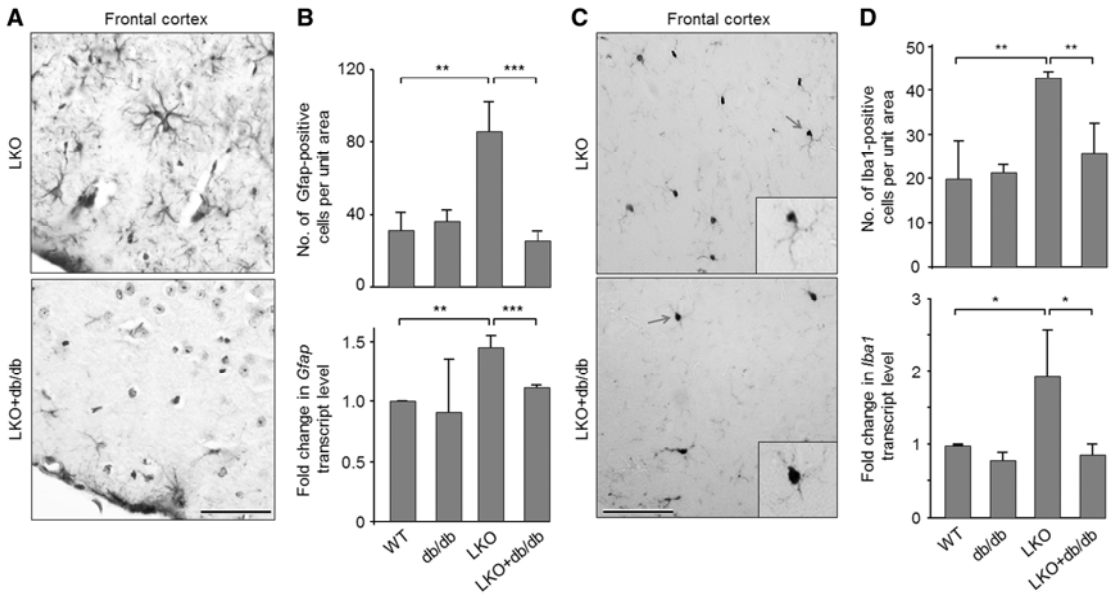


Fig. 2: Reduced gliosis in Lafora animals deficient for the leptin receptor. Representative images of the brain from the Lafora disease animals (LKO) and the disease naimals in which the leptin signalling blocked (LKO + db/db) showing the distribution of Gfap-positive cells in the frontal cortex region. Note the reduced immunoreactivity for Gfap in the LKO + db/db animal as compared with the LKO animal. The bar diagram shows the quantification of the activated glial cells. (**Hum Mol Genet. 2017, 26:4778)**

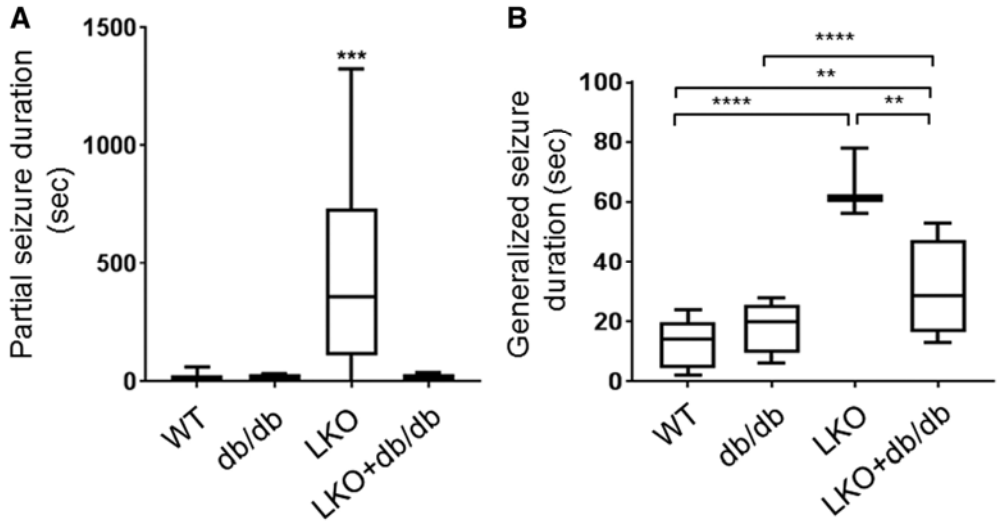
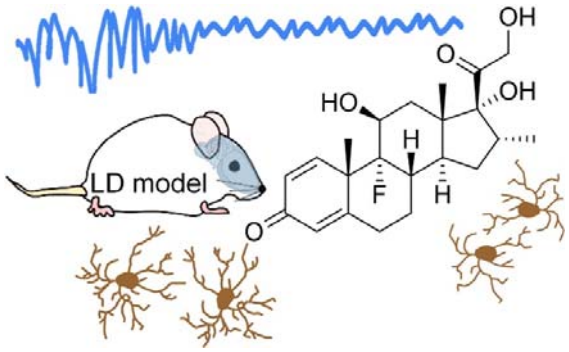


Fig. 3: Reduced susceptibility for induced seizures in Lafora animals deficient for the leptin receptor. Box plot showing the duration of induced partial seizures (A) and generalized seizures (B) observed in animals with indicated genotype. (**Hum Mol Genet. 2017, 26:4778)**

ii: Therapeutic approaches to ameliorate neuroinflammation and epileptic seizures in Lafora disease:

Lafora disease is a fatal form of genetic disorders with the formation of glycogen rich inclusions in the brain as one of the primary pathologies. Besides the inclusions, Lafora disease is also characterized by the autophagy defects and neuroinflammation. However which one of these defects is the primary contributor to the epileptic seizures was not established. This is a pertinent question since the majority of the anti-epileptic drugs currently used offer symptomatic relief and does not fix the route cause. Using genetic models for the Lafora disease, Prof. Ganesh has demonstrated the cause-consequence relationship Lafora bodies, proteolytic processes and the epileptic seizures. He has used two distinct pharmacological approaches. In his first attempt, he demonstrated that trehalose (an inducer of autophagy) ameliorates gliosis, neuroinflammation, and endoplasmic reticulum stress and reduces susceptibility to induced seizures in LD animals. This work has also demonstrated that trehalose did not affect the formation of Lafora bodies, suggesting the epileptic phenotype could be secondary to Lafora bodies (**Mol Neurobiol, 2021, 58: 1088-1101**). In his second attempt, he group demonstrated that the compromised heat shock response could underlie the neuroinflammation and neuropathology. The study also demonstrated that pharmacological activation of heat shock factor1 (HSF1), here in this case with dexamethasone, can ameliorate the neuroinflammation and susceptibility to induced seizures in the Lafora disease mouse models (**Exp Neurol, 2021, 340: 113656**). This is a first report that connects HSF1 with epileptic seizure. A variety of small molecular activators of HSF1 are being screened in the lab now. Given the impact of this work, this publication was highlighted on the cover of the issue.



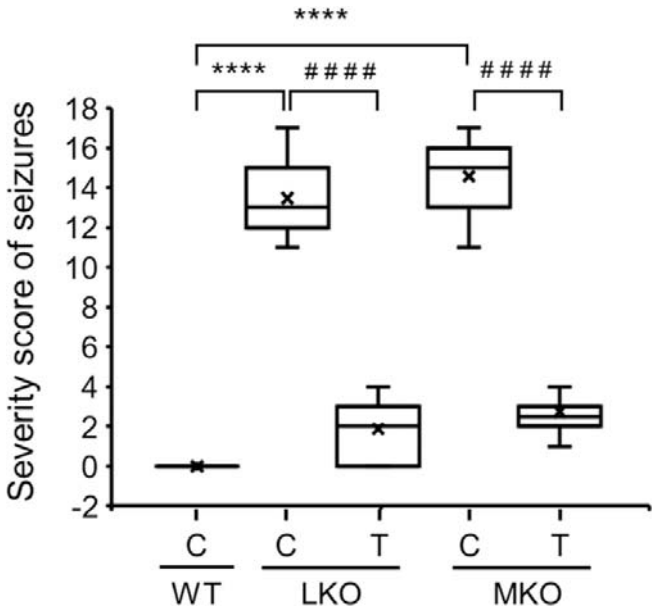


Fig 4: Trehalose is protective against pentylenetetrazol-induced seizures in Lafora disease mice. Box plot showing the protective effect of trehalose in reducing the seizure severity in LD mouse models. Here, "C" refers to controls, and "T" refers to the trehalose treatment group. (**Mol Neurobiol, 2021, 58: 1088-1101**)

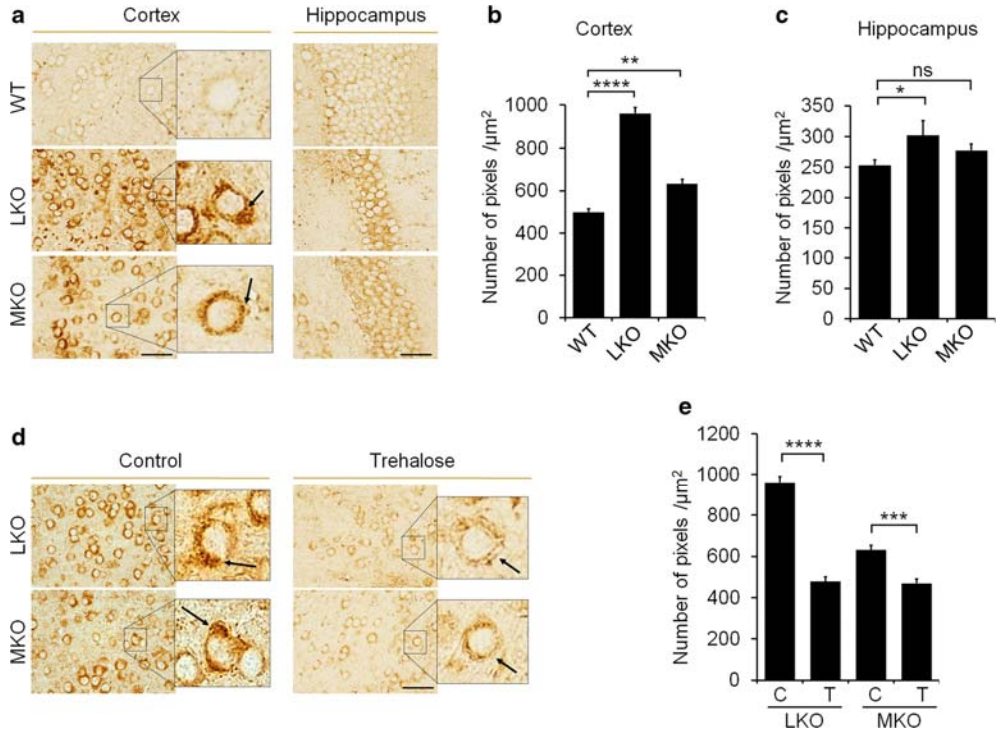


Fig. 5: Trehalose treatment reduces the accumulation of neuronatin in the cerebral cortical areas of the Lafora disease mouse brain. Box plot showing the duration of induced partial seizures (A) and generalized seizures (B) observed in animals with indicated genotype. (**Mol Neurobiol, 2021, 58: 1088-1101)**

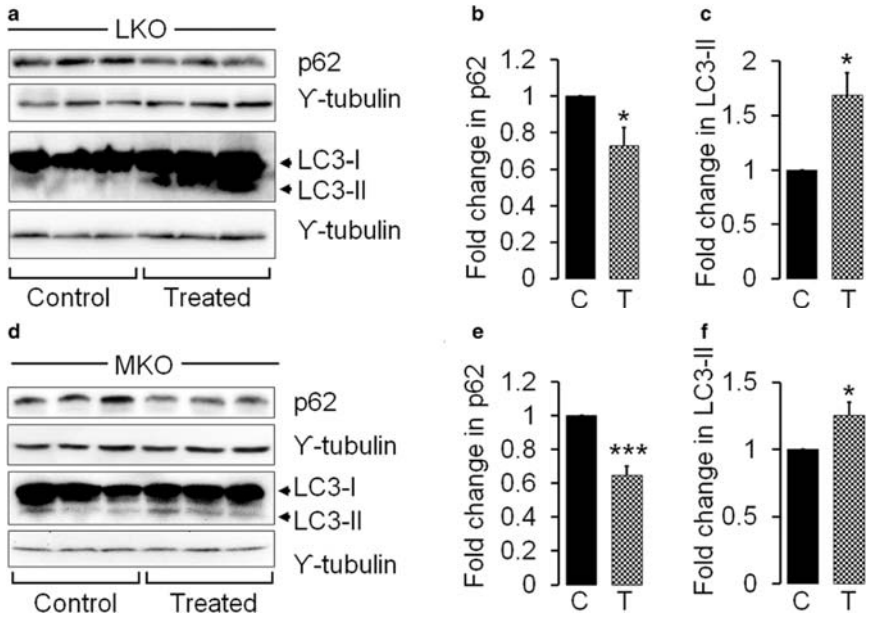


Fig. 6: Trehalose treatment induces autophagy in Lafora disease mouse brain. epresentative images of immunoblots showing relative levels of autophagy markers LC3 and p62 and the loading control (γ -tubulin) in the brain lysate of control and trehalose-treated animals that are deficient for laforin (LKO) (a) or malin (MKO) (d), as indicated. Bar diagram represent the quantitation of the signa. (**Mol Neurobiol, 2021, 58: 1088-1101).**

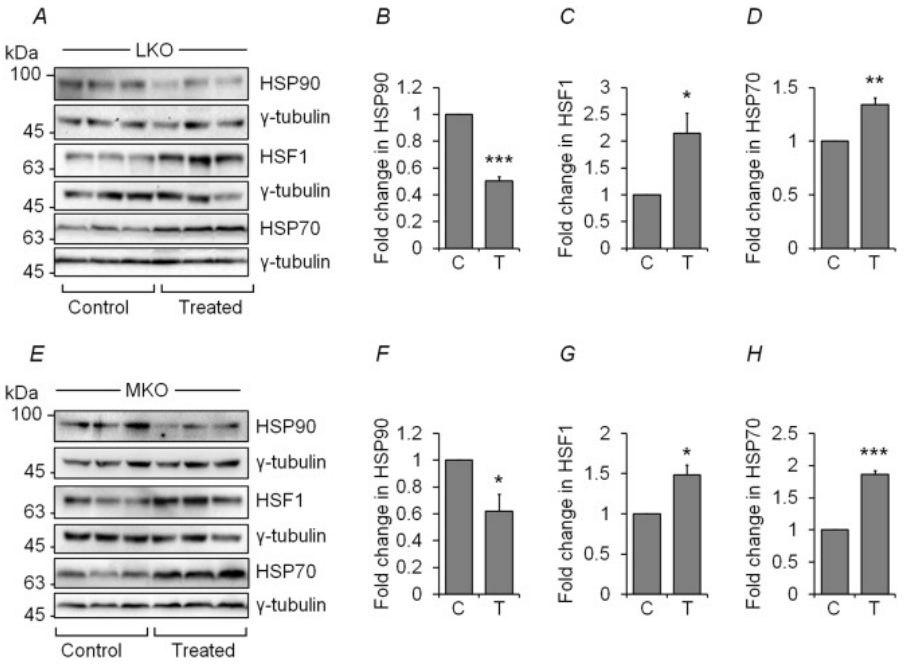


Fig. 7: Dexamethasone induces HSF1 by inhibiting HSP90 in Lafora disease mice brains. Representative images of immunoblots showing relative levels of HSF1, HSP70, HSP90 and the loading control (γ -tubulin) in the brain lysate of control and dexamethasone-treated Lafora disease animals that are deficient for laforin (LKO) (a) or malin (MKO) (d), as indicated. Bar diagram represent the quantitation of the signa. (**Exp Neurol, 2021, 340: 113656).**

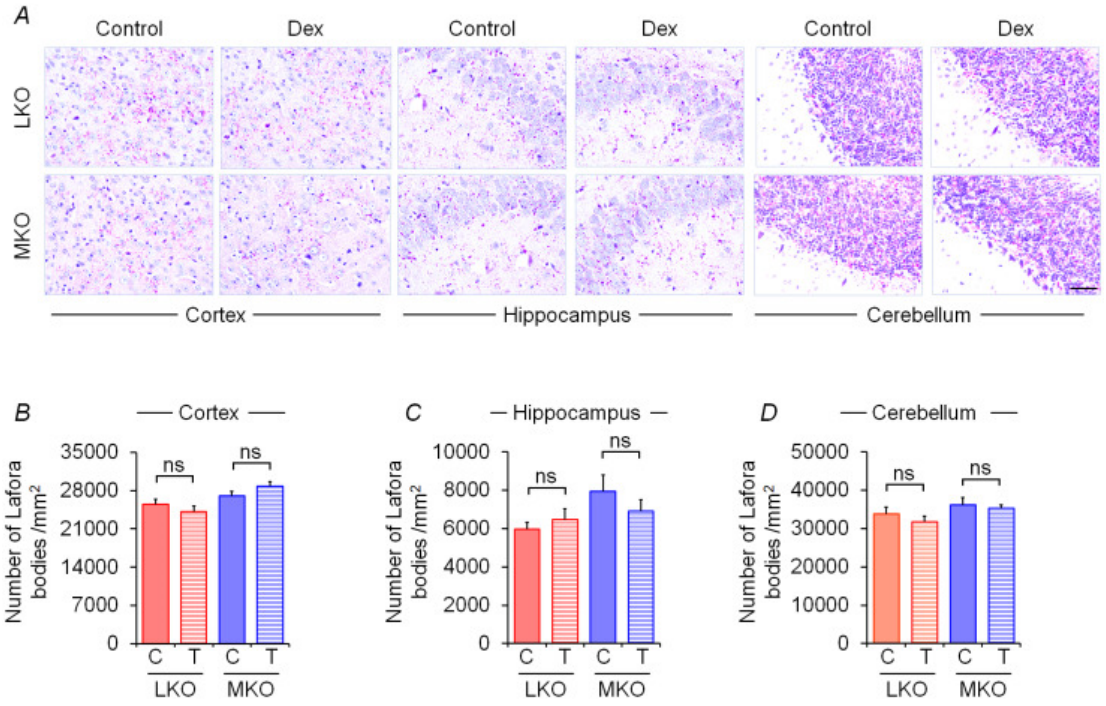


Fig. 8: Dexamethasone treatment does not affect Lafora body formation. Representative images showing the distribution of PAS+ Lafora bodies in the cortex, hippocampus, and cerebellum of the brain sections from the control or dexamethasone treated Lafora disease animals. Bar diagram showing the quantification of the Lafora bodies. (**Exp Neurol, 2021, 340: 113656).**

iii: Deciphering the role of glycogen metabolic pathways in the neuronal physiology

Healthy neurons do not store glycogen yet they do have the functional machinery to synthesize glycogen. Neurons in the degenerating brain show glycogen accumulation and forced synthesis of the glycogen in neurons induce cell death Thus, the role of the glycogen synthase - the primary enzyme involved in glycogen synthesis, in the neuronal physiology remained an enigma. Using cell, animal models and human brain samples, Prof. Ganesh has demonstrated that the glycogen synthase is essential for the neurons to survive under physiological stress (**Cell Death & Disease 2018, 9: 201**). Intriguingly, neurons require glycogen synthase for the induction of autophagy. Thus, neuronal stressors such as oxidative stress or proteasomal stress lead to the activation of glycogen synthase and as a result in the autophagy induction as a pro-survival mechanism. His group also demonstrated that excessive autophagy flux is the molecular basis of cell death caused by the activation of glycogen synthase in unstressed neurons. This perhaps could be one of the reasons why healthy neurons do not store glycogen. This work has gained much attention in the scientific community and in fact, an editorial in the FEBS Journal discussed these findings and their implications (**https://doi.org/10.1111/febs.14412**). Currently his group is testing three lead compounds that activate glycogen synthase as a therapeutic approach for Huntington disease using transgenic mouse models. Indeed his group has also shown that the glycogen inclusions are common among neurodegenerative disorders (Fig 11) and hence the glycogen synthase pathway is a critical therapeutic target.

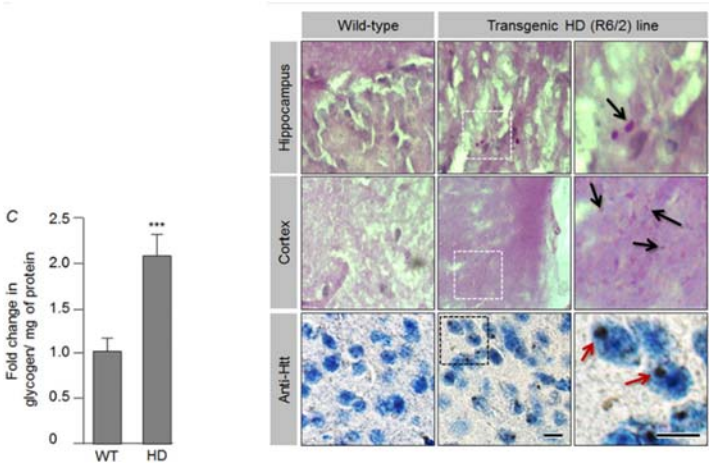


Fig. 9: Increased glycogen levels in the brain of Huntington's disease mouse. Representative images showing the distribution of PAS+ glycogen accumulation in the Huntington's disease mouse brain. Bar diagram showing the quantification of the glycogen bodies. (**Cell Death & Disease 2018, 9: 201).**

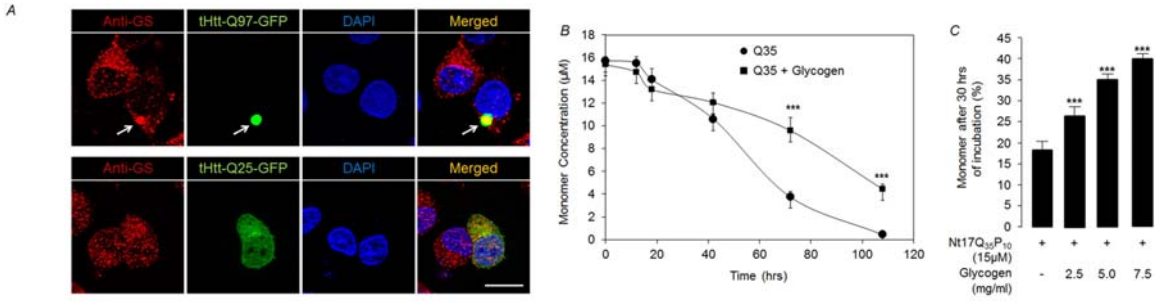


Fig. 10: Pure glycogen delays aggregation kinetics of polyglutamine peptide in vitro. Representative fluorescence images of Neuro2A cells transiently expressing tHtt-Q25-GFP or tHtt-Q97-GFP immunostained with an antibody to detect the endogenous glycogen synthase (red). Nuclei were stained with DAPI (blue). Note the GS localization with GFP-positive aggregates of mutant huntingtin (arrow). Scale bar, 10 µm. b A line diagram showing the levels of the monomeric form of the synthetic polyglutamine peptide (Q35) (in µM), as determined by RP-HPLC, when incubated alone or with pure glycogen (5 mg/ml) at indicated time points. (**Cell Death & Disease 2018, 9: 201).**

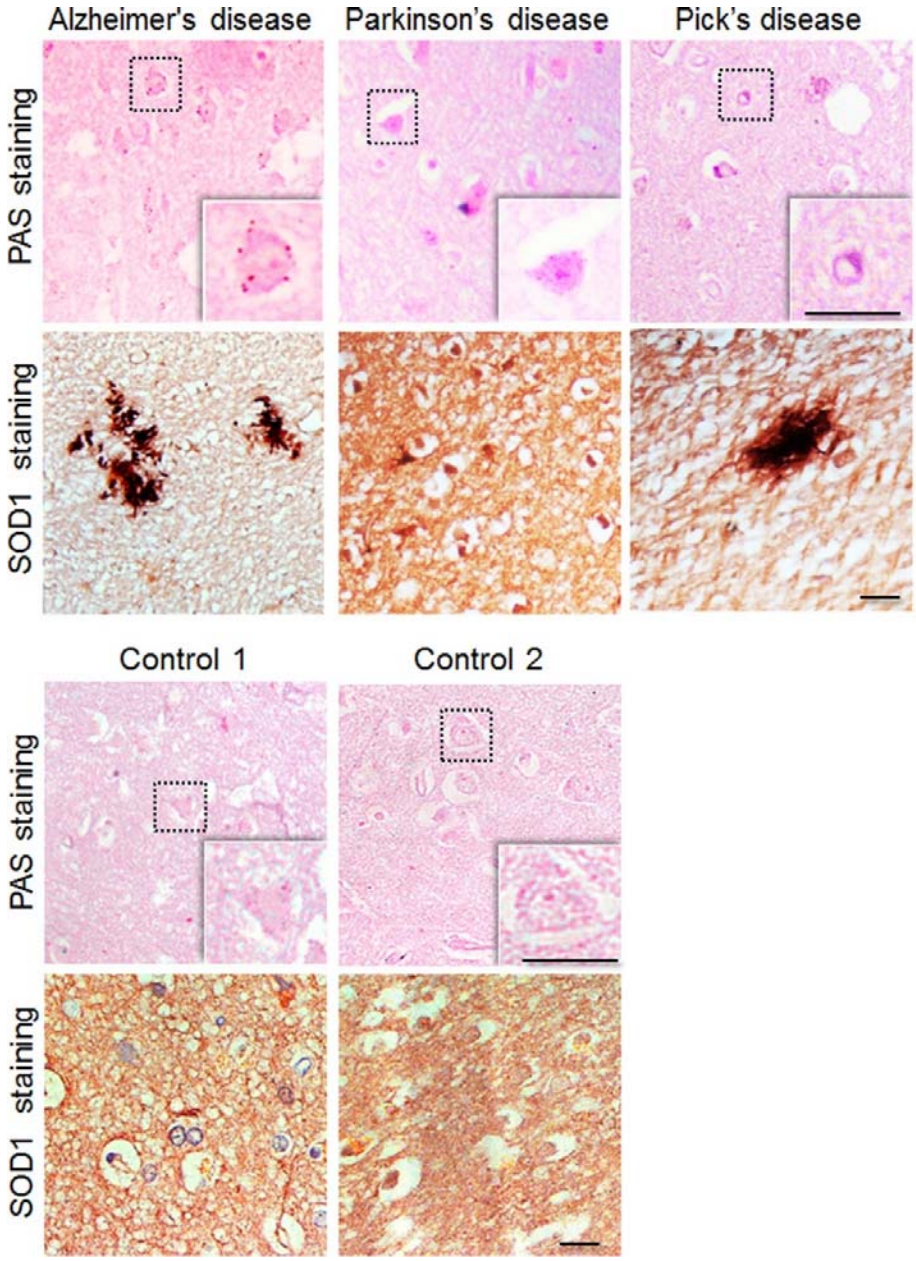


Fig. 10: : Glycogen inclusions in the frontal cortex region of subjects with neurodegenerative disorders. Representative bright field images showing PAS-positive glycogen granules in the frontal cortex region of autopsied brain tissues of subjects clinically diagnosed to have Alzheimer's disease, Pick's disease, or Parkinson's disease as identified. (**Cell Death & Disease 2018, 9: 201).**

[S.Ganesh]