List of 10 best papers of Prof. Subramaniam Ganesh with highlights

1. Sinha P, Verma B, and **Ganesh S*** (2021) Dexamethasone-induced activation of heat shock response ameliorates seizure susceptibility and neuroinflammation in mouse models of Lafora disease. ***Experimental Neurology*** 340:113656. **[Cover page article]**

   A significant discovery on the disease biology of Lafora disease. 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. 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.

2. Sinha P, Verma B, and **Ganesh S*** (2021) Trehalose ameliorates seizure susceptibility in Lafora disease mice models by suppressing neuroinflammation and endoplasmic reticulum stress. ***Molecular Neurobiology*** 58 (3): 1088-1101.

   A significant discovery on the disease biology of Lafora disease. While autophagy defects are reported in the Lafora disease, whether or not this defect contributes 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. This work 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.

3. Agarwal S and **Ganesh S*** (2020) Perinuclear mitochondrial clustering, increased ROS levels, and HIF1 are required for the activation of HSF1 by heat stress. ***Journal of Cell Science*** 133 (13): jcs245589. [**Highlighted in editorial**]

   This is a seminal work that demonstrated the functional link between the heat shock response pathway and the hypoxia response pathway. Using elegant cell biology tools, this paper demonstrated the requirement of hypoxia-inducing factor (HIF1) in the heat shock-induced activation of stress response pathway, and the critical role for mitochondrial positioning in the signalling cascade. Using pharmacological agents, the authors demonstrated how repositioning of the mitochondria with the cell can modulate both hypoxia and heat shock response pathways. These studies provide significant insight into the mammalian cells adapt to variations in temperature and oxygen and the pathways that could be targeted for pharmacological interventions. Given the impact of the study, this work was highlighted in the editorial of the issue.

4. Rai A, Singh PK, Singh V, Kumar V, Mishra R, Thakur AK, Mahadevan A, Shankar SK, Jana NR, and **Ganesh S*** (2018) Glycogen synthase protects neurons from cytotoxicity of mutant huntingtin by enhancing the autophagy flux. ***Cell Death & Disease*** 9 (2): 201. [**Highlighted in the Editorial of *FEBS J***]

An important discovery on a novel role of glycogen synthetic mechanism in the neurons. This study also establishes a functional link between the glycogen metabolic process and the autophagic process and explains why normal neurons do not store glycogen. Further, this work also demonstrates that activation of glycogen synthase could protect the neurons by inducing autophagy and clearing the aggregates of cytotoxic misfolded proteins. The work was selected for special editorial commentary in the FEBS Journal.

5. Rai A, Mishra R, and **Ganesh S*** (2017) Suppression of leptin signalling reduces polyglucosan inclusions and seizure susceptibility in a mouse model for Lafora disease. ***Human Molecular Genetics*** 26 (24): 4778–4785.

   An important publication in this field, demonstrating the potential therapeutic process for reducing the glycogen load in the neurons and seizure susceptibility in Lafora disease. Carried out entirely on the animal model for Lafora disease, this study demonstrates that blocking leptin signalling in the neurons could potentially correct the neuropathology. An international consortium of Lafora disease has taken up this lead for clinical trials.

6. Upadhyay M, Agarwal S, Bhadauriya P, and **Ganesh S*** (2017) Loss of laforin or malin results in increased Drp1 level and concomitant mitochondrial fragmentation in Lafora disease mice models. ***Neurobiology of Disease***, 100: 39-51.

   A significant discovery on the disease biology of Lafora disease and its similarities with Parkinson disease. Mitochondrial defects and fragmentation are known in a number of neurodegenerative disorders. However, they are the cause or consequence of the neuronal dysfunction was not well established. This study demonstrated that mitochondrial fragmentation is a primary defect in Lafora disease and that the fragmentation is due to the overactivation of mitochondrial fission GTPase Drp1. Using the genetic and pharmacological tools, the authors demonstrated that Drp1 could be an ideal target for preventing/delaying neurodegeneration in Lafora disease.

7. Goenka A, Sengupta S, Pandey R, Parihar R, Mohant G, Mukerji M and **Ganesh S*** (2016) Human satellite-III non-coding RNAs modulate heat shock-induced transcriptional repression. ***Journal of Cell Science***, 129: 3541-3552. **[Cover Page Article | Highlighted in the editorial]**

   An outstanding work to elucidate the role of a long non-coding RNA in heat shock response. The study demonstrated that the Satellite III non-coding RNA is required for the human cells to mount effective response against heat stress and provided a novel insight into how cells might bring about global transcriptional suppression during the heat shock. The work was highlighted on the cover page of the issue, and an editorial commentary on the work was also published on the same issue.

8. Kumar A, Singh PK, Parihar R, Dwivedi V, Lakhotia SC, **Ganesh S***.(2014) Decreased O-linked GlcNAcylation protects from cytotoxicity mediated by huntingtin exon1 protein fragment. ***Journal of Biological Chemistry,*** 289(19):13543-53.

   This is one of the first two reports in the literature that linked O-GlcNAcylation process in regulating autophagic process. This work, using cell and animal models for Huntington

disease, demonstrates that suppression of O-GlcNAcylation induces autophagy and protect neurons by clearing the cytotoxic mutant huntingtin aggregates

9. Singh PK, Singh S, and **Ganesh S*** (2013) Activation of serum/glucocorticoid-induced kinase 1 (SGK1) underlie increased glycogen levels, mTOR activation, and autophagy defects in Lafora disease. ***Molecular Biology of the Cell*** 24 (24):3776-86.

    This is one of significant work on the cross talk between glycogen metabolic pathway and the autophagy pathway. Through delicate cell biological assays, it is demonstrated here that the Lafora disease proteins laforin and malin are in fast forward loop with the mTOR-meduated pathway and that the SGK1 is is the functional link. The loss of laforin results in the activation of SGK1, and as a result the increased glucose uptake and autophagy blockade. Reducing the glycogen level in the cells lacking laforin restores the autophagy. Given the potential, this report was discussed in ***NewsRx,*** a technology company for drug discovery

10. Singh, PK, Singh S, and **Ganesh S*** (2012) Laforin-malin complex negatively regulates glycogen synthesis by modulating the cellular glucose uptake via glucose transporters. ***Molecular and Cellular Biology*** 32(3):652-63

    A study that elucidated the mechanism behind the increased glycogen in Lafora disease neurons. Demonstrated that laforin-malin are glucose sensors, and that abnormal activation of the glucose transporters underlie increased glucose uptake and concomitant increase in the cellular glycogen is the mechanism behind glycogen build-up in Lafora disease.