Statement of achievements of Prof. S Ganesh

Dissecting molecular pathways to neurodegeneration and therapeutic interventions

A majority of neurodegenerative disorders are associated with the formation proteinaceous inclusions in the neurons implying defects in proteolytic systems as the primary cause for the anomalies (*see 2010, Neuorsci Res*) Intriguingly, the neurodegeneration in the fatal form of progressive epilepsy, known as Lafora disease (LD), is associated with accumulation of abnormal glycogen as Lafora bodies in the neurons (*2009*, *Hum Mutat; 2018, J Genet*). Thus, LD was traditionally thought to be a metabolic disorder associated with defective glycogen synthesis, although the molecular mechanism underlying the glycogen accumulation was not very well understood (*loc cit*). However, recent reports, primarily the work of Dr Ganesh's group, suggest that defects in proteolytic process could underlie the neuropathology and some of the symptoms in LD (*2010, Autophagy*; 2012, *Autophagy*). Dr Ganesh has elucidated the molecular basis of basis of Lafora bodies (*2012, Mol Cell Biol; 2013, Mol Biol Cell*), and has further shown how these inclusions contribute to the impaired proteolytic process in LD (*2012, Hum Mol Genet; 2017, Cell Stress Chap*). His group has also shown that defects in the mRNA processing might as well underlie some of the disease symptoms in LD (*2012, RNA Biol*). His most recent findings demonstrate mitochondrial dysfunction could also underlie neuropathology in LD (*2017, Neurobiol Dis*), and a cell bases assay to screen for compounds that inhibit mitochondrial fragmentation has been filed for a patent (2018, 121/DEL/2015).

Through series of publications (*2007, Hum Mol Genet*; *2007, Hum Mutat*; *2008*, *Hum Mol Genet*; *2009, Hum Mol Genet*, *2009, J Biol Chem*; *2011, J Cell Sci*), Dr Ganesh has shown that the protein products of the LD genes EPM2A (encoding laforin phosphatase) and NHLRC1 (encoding malin E3 ubiquitin ligase) work together as a functional complex in the in the cellular stress response pathways. Firstly, he has shown that laforin and malin are recruited to the perinuclear proteolytic centres, called aggresomes, possibly as a protective response to the increased load of abnormal proteins and that the recruitment is dependent on the microtubular network (*2007, Hum Mol Genet*). Secondly, he demonstrated that laforin and malin, together with chaperone Hsp70 as a functional complex, suppress the cellular toxicity of diverse set misfolded proteins by promoting their degradation, and that the laforin-malin complex functions as a co-chaperone (*2009*, *Hum Mol Genet*). He further demonstrates that the laforin-malin complex translocates to the nucleus upon heat shock and all these proteins are required for full protection against heat shock-induced cell death. Laforin and malin interact with heat shock factor-1 (HSF1), a transcription factor that activates transcription of heat shock genes, and contribute to its activation during stress (*2011, J Cell Sci*). Thus, loss of laforin and malin is likely impairs the cells' ability to sense the levels of misfolded proteins and to elicit the protective response by activating the heat shock response via the induction of heat shock proteins. He has also shown that the laforin-malin complex regulates cellular glucose uptake by modulating the subcellular localization of glucose transporters; thus loss of malin or laforin results in an increased abundance of glucose transporters in the plasma membrane, the excessive glucose uptake, and the abnormal glycogen as Lafora bodies (*2012, Mol Cell Biol; 2013, Mol Biol Cell*). Using animal models, Dr Ganesh has shown that these glycogen inclusions recruit several critical players of the endosomal-lysosomal and autophagy pathways, and might contribute to the defective proteolytic process (*2012, Hum Mol Genet*). Thus, suppressing the glycogen accumulation of neurons, by blocking the excessive glucose uptake, could be one of the ways the LD phenotype can be corrected. Beyond LD, Dr Ganesh has made seminal contributions by linking the glycosylation process with the autophagy (*2014, J Biol Chem*), and a long non-coding RNA in cellular stress response pathway (*2016, J Cell Sci*).

Having discovered the defective pathways leading neurodegeneration and neuropathology, his group in recent years has specifically focussed on the therapeutic interventions – using both pharmacological and genetic approaches. Through a series of publications, Dr Ganesh has shown that suppression of leptin signalling reduces the glycogen build up, neuroinflammation and seizure susceptibility in Lafora disease models (*2017, Human Mol Genet*). He has also the epileptic phenotype could be secondary to Lafora bodies, and the neuroinflammation could be the primary trigger for epilepsy in Lafora disease (*2021, Mol Neurobiol, Exp Neurol*). Supressing the neuroinflammation – either activation of the autophagy pathway (*2021, Mol Neurobiol*) or the heat shock response pathway (*2021, Exp Neurol*) – ameliorates the neuroinflammation and susceptibility to induced seizures in the Lafora disease mouse models. His group has also demonstrated the neuroprotective function of glycogen synthase clearing aggregated cytotoxic proteins associated with disorders such as Huntington disease, Parkinson's disease and several forms of ataxias (*2018, Cell Death & Disease*).

IN recognition of his outstanding contributions in the area of disease biology and therapeutics, Prof. Ganesh has been honoured with the following awards and fellowships:

- Scopus Young Scientist Award in Biological Sciences (Elsevier South Asia, 2008)
- National Bioscience Award for Career Development (Dept. of Biotechnology, 2008)
- B.M. Birla Science Prize in Biology (Birla Science Academy, 2008)
- DAE-SRC Outstanding Research Investigator Award (Dept. of Atomic Energy, 2010)
- Gill-Joy Chair Professor (IIT Kanpur, 2011)
- Rajib Goyal Prize in Biology (Goyal Foundation, Kurukshetra University 2011)
- CDRI Award for Excellence in Drug Research (CDRI-CSIR, Lucknow 2012)
- Ramanna Fellowship (Dept. of Science & Technology, Govt. of India, 2012)
- Fellow, National Academy of Sciences, India (Allahabad, 2012)
- KT Shetty Memorial Oration Award (Indian Academy of Neurosciences, 2015)
- Fellow, Indian Academy of Sciences (Bangalore 2015)
- OPPI Scientist Award (Organisation of Pharmaceutical Producers of India 2016)
- Basanti Devi Amir Chand Prize (Indian Council of Medical Research, 2016)
- P.K. Kelkar Chair Professor (IIT Kanpur, 2017)
- Tata Innovation Fellowship (Dept. of Biotechnology, Govt. of India, 2017)
- Prof. J. Das Memorial Award Lecture of the Indian Society of Cell Biology (2019)

Due to its immense contributions in the field, Prof. S Ganesh has also invited expert member of the following task forces of the government funding bodies:

- Nominated expert member, Search-cum-selection committee for POWER Fellowship Science and Engineering Research Board (SERB), Department of Science & Technology (2020 onwards)
- Nominated expert member, SERB – POWER PAC for Biomedical and Health Science, Science and Engineering Research Board (SERB), Department of Science & Technology (2020 onwards).
- Nominated Expert Member of the Research Advisory Committee of HRDG, Council of Scientific and Industrial Research (2019 onwards)

- Nominated Expert Member of the Program Advisory Committee of Science and Engineering Research Board (SERB), Department of Science & Technology (2019 onwards).
- Nominated Expert Member of the Human Genetics/Genomics Task Force of the Department of Biotechnology (2017 onwards).
- Nominated Expert Member of the Committees that evaluates the proposal submitted for the FAST Track Young Scientists scheme of SERB, Dept. of Science & Technology, Govt. of India (2017-2018).
- Nominated Expert Member of the PAC (Biochemistry, Biophysics, Molecular Biology and Microbiology), SERB, Dept. of Science & Technology, Govt. of India (2016-18)