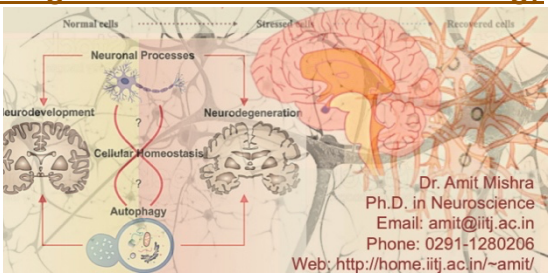
Research Achievements of Prof. Amit Mishra:

Web: http://home.iitj.ac.in/~amit/

*Described work of Amit Mishra was performed in India

Neurons Intelligence: Defensive Proteostasis Strategy



Personal definition of science: Science is an art with measurements that provides new thinking, unlimited imagination and a solid platform to discover hidden truths on our planet.

Most Inspiring Finding in the field: Dr. Mishra has established a new significant concept on selective E3 ubiquitin ligases that can serve as quality control first line of defence ameliorative measures against multifactorial proteostasis failures implicated in neurodegenerative diseases and imperfect aging.

Brief Introduction of Scientific Findings: Dr. Amit Mishra has done significant work in neuronal protein quality control mechanisms involved in neurodegenerative diseases. This has been achieved by understanding the quality control functions of selective multifaceted E3 ubiquitin ligases, which barricade extreme defence against misfolded proteins aggregation. His findings provide a clear and better understanding of this innovative concept that can develop new therapeutic targets for neurodegeneration and aging. His studies have helped clarify the molecular pathways of misfolded recognition strategies based on E3 Ubiquitin Ligases. Amit's findings enlighten the precise molecular mechanism of E3 ubiquitin ligases and molecular chaperones, their involvement in neuronal quality control pathways, and affect overall neuronal homeostasis. Amit designs a different mechanism to modulate the proteasomal functions, inducing autophagy pathways and serving as the anti-aggregation program of affected cellular proteostasis. Research from his lab proposes that E3 Ubiquitin Ligases can act as the first line of defence against proteostasis failure under different protein conformation conditions. Amit developed an innovative harnessing method of molecular protein quality control system that can inhibit aberrant protein aggregation and deregulated proliferation. His group's significant contributions have substantially added knowledge on the progressing neurobiological approaches against multifactorial challenges in neurodegeneration. Shortly results of our studies may offer the more suitable substitute proteolytic machinery therapeutic strategies to balance the proteostasis for the defective events specifically linked with late-onset neurodegenerative diseases and aging.

Research Impact on Society: In the present-day scenario, the major challenge, which the scientific community is facing, is to achieve success in developing some therapeutics for the diseases, like cancer and neurodegeneration. We, the cellular and molecular neurobiology unit at IIT Jodhpur, are currently focusing on precisely understanding the underlying molecular mechanisms and affected pathways, behind these diseases. Many of these incurable diseases develop because of some genetic abnormalities. Therefore, to investigate the possible alterations and modifications at the genetic level is needed to effectively address these kinds of disorders. The improved understanding of the pathology of neurodegeneration and cancer can translate into improved diagnosis, prognosis, and, ultimately, treatment of such disease. Investigating Protein Quality Control (PQC) components can illuminate other protein misfolding disorders too, including cystic fibrosis. The dysregulation in levels of PQC components, such as chaperones and E3 enzymes, can serve as a platform for potential biomarkers when tracked with disease progression studies. The reporting of FDA-approved drugs aspirin, ibuprofen, diclofenac, and indomethacin as PQC modulators can overall decrease their clinical development translational time period for complex diseases. Similarly, natural compounds lanosterol, myricetin, and resveratrol are also proven as PQC modulators. As representatives of their respective chemical classes/families, they can also lay the foundation for similar pharmacological compounds with improved characteristics. For a long time, cancer has presented a great challenge before scientists, and unfortunately, we are still hunting for a successful cure. The same is also applicable for neurodegeneration and dementia. My group is currently indulged into basic research, around these two disorders. We have investigated some probable proteins, which undergo functional loss because of any loss of function mutation or may sometimes lose their native structure. To avoid all such kinds of protein modifications and alterations, which are very common in a crowded cellular milieu, cells have evolved a line of strategies to counter such challenges. These systems, consisting multiple arms like molecular chaperones, autophagy, and ubiquitin proteasome system, may collectively be referred as cellular protein quality control system. Vision of existing research is to improve our existing knowledge about crucial mechanisms, which can provide new opportunities to modulate protein in cellular quality control mechanism in neurodegenerative diseases, ageing and cancer that are caused by abnormal protein accumulation in cells.

How existing research driven forward understanding in the field? The two major protein quality control (PQC) machineries for degradation of abnormal proteins in cells include autophagy and ubiquitin-proteasome system (UPS), which include marking them with ubiquitin via E3 enzymes, directing them to proteolytic proteasome complex. Amyotrophic lateral sclerosis (ALS), a major neuromuscular disorder, exhibits protein aggregates of misfolded SOD1 in motor neurons, which we found to be degraded by cell in an autophagy-dependent manner by E3 ubiquitin ligase MGRN1. We also reported MGRN1 to be involved in the clearance of other misfolded proteins expanded polyglutamine ataxin 3 (spinocerebellar ataxia) and huntingtin (Huntington's disease) with the possible aid of chaperone Hsp70. We also found the clearance of these polyglutamine misfolded proteins by autophagy and UPS to be promoted by quality control E3 enzyme ITCH. Another E3 enzyme E6AP, also promotes SOD1 degradation. We had attempted to understand the cellular turnover of E6AP by another E3 ligase LRSAM1, which also provides cytoprotection via its quality control function. This new information on the network of E3 enzymes and chaperone proteins can aid in understanding neuron degenerative and development disorders, such as Angelman syndrome, polyglutamine diseases, and others, from a different vantage point. The natural compound flavonoid myricetin stabilises E3 E6AP and induces Hsp70 to clear misfolded proteins, such as a-synuclein (Parkinsons disease), in a proteasome-dependent manner. We also presented evidence of the anti-proliferative potential of NSAIDs diclofenac, ibuprofen, and indomethacin in their capacity as proteasome inhibitors. These investigations have provided newer molecules and targets with therapeutic potential. The research into the components of UPS and autophagy, as well as their modulators, contribute to their molecular mechanism as well as disease pathology.

Outcomes Observed in the Research: The inherent complexity of cancer and neurodegeneration is due to the presence of multiple signalling and regulatory pathways of the cell, as well as the pleiotropic nature of many biomolecules. We have attempted to investigate and understand this complexity by focusing on the aspect of PQC. The network of E3 enzymes and chaperones interfere cellular proteome and act appropriately to recognise misfolded/unfolded proteins, directing their clearance from the cell to maintain homeostasis. The results from our collective studies indicate the involvement of multiple E3 enzymes – ITCH, MGRN1, and LRSAM1 and chaperone Hsp70 in clearing possible pathogenic misfolded proteins in neuronal degenerative conditions. The dysregulation of these PQC components in neurodegeneration can exacerbate the effect of loss-of-function or gain-of-function of misfolded proteins and aggregates. Myricetin and lanosterol, natural compounds reported by us as PQC component modulators, can be further investigated for their therapeutic effects on neurodegeneration with the possible benefits of better pharmacokinetics. Similarly, NSAID-mediated modulation of PQC elements can offer the additional benefit of drug repurposing. Interestingly, we also introduced the theme of turnover of E3 enzymes being regulated by other E3 enzymes, which can be explored as a potential common biological theme. The widespread and diverse library of chemical compounds in nature also requires further investigation for their potential as PQC modulators.

Amit's Scientific Journey: The significant contribution of Amit's research has been elucidating the role of E3 Ubiquitin Ligases in the degradation of aberrant proteins associated with neurodegenerative diseases. Since Ph.D. Amit consistently represents an excellent scholarly ability, his Ph.D. Thesis received Best Ph.D. Thesis Award from the Indian Society of Chemists and Biologists (ISCB), India; he was also awarded the first Prize by the Indian Academy of Neuroscience (IAN). Amit's group is delivering serious attention on quality E3 Ubiquitin Ligases mediated regulation of protein quality control mechanism against misfolded proteins aggregation. He has been awarded Ramalinganswami Fellowship and Innovative Young Biotechnologist Award by the DBT, Government of India. Amit is a recipient of the Early Career Researcher Award from The Royal Society, London, and the National Academy of Sciences, India-Young Scientist Platinum Jubilee Award. Amit's research emphasizes an urgent need that now we need to recognize the fundamentals of proteostasis to design a new molecular framework and fruitful strategies to uncover how the proteome defects are associated with aging and neurodegenerative diseases. At the international forum, his research contribution was recognized and awarded by Prof. Venkatraman Ramakrishnan (Nobel Laureate) and Bharat Ratna Prof. C.N.R Rao in the presence of the Prime Minister of Singapore under the Royal Society of London Program. His study conclusively demonstrated that few quality control E3 Ubiquitin Ligases are involved in eliminating misfolded proteins via the selective autophagy pathway. His entire work was executed in India, and at a young age, he could understand the complex problem of Neurodegeneration. Prof. Huda Y Zoghbi from Howard Huges Medical Institute, Baylor College of Medical awarded him the young scientist award at the Japan Neuroscience Society meeting. Further, Mishra's team observed a novel interaction between E3 Ubiquitin Ligases and Molecular Chaperones.

Amit has demonstrated that treatment of lanosterol and myricetin can diminish aberrant proteotoxic aggregation and mitigates neurotoxicity. Interestingly he has received Best Faculty Research Excellence Award in the presence of the Principal Secretary (Pramod Kumar Mishra) to the Prime Minister of India. Padma Vibhuhassan Prof. P.N Tandon and Shanti Swarup Bhatnagar Prize, Padma Shri Prof. Vijaylakshmi Rabindranath also awarded him S. S. Parmar Foundation Prize, USA under Indian Academy of Neuroscience. The major histochemical hallmark in the remaining motor neurons of ALS is the intracellular accumulation of ubiquitinated inclusions consisting of insoluble aberrant protein aggregates. However, the molecular pathomechanisms underlying the process have been elusive. For the first time, Amit's lab reported that E6-AP E3 ubiquitin ligase depleted in Amyotrophic Lateral Sclerosis mouse models before Neurodegeneration. His remarkable findings suggest that enhancing the activity of E6-AP ubiquitin ligase might be a viable therapeutic strategy to eliminate mutant SOD1-mediated toxicity in Amyotrophic Lateral Sclerosis. He received a prestigious Max Planck Society Fellowship by Prof. Ulrich Hartl (Director of Max Planck); he has also received a highly competitive Riken Brain Science Institute Fellowship by Presidents of Riken BSI Prof. Masao Ito and Prof. Shunichi Amari. DBT India awarded him Ramalinganswami Fellowship at 28 Years of age and the IYBA Award. He has published high-quality more than 100 Publications, some of which were selected as Cover Page of International Journals. SERB India, DBT India, BRNS/BARC, DST-JSPS, INSA-JSPS, and DST awarded him crucial research projects. Well-recognized national and International scientific organizations filtered Amit's candidature at multiple levels under different Honors/Awards/fellowships. His research contributions were awarded by different Academic & Research e.g., CSIR, IITs, MHRD, ICMR, DBT, DST, SERB, BRNS/BARC, INSA, NASI, ISCA, INYAS, IABS, BRSI, NAMS, JSPS, Max Planck, RIKEN, RSC, RSB, NYAS, IGC, and IAN. Amit's research contribution improves our basic and applied understanding of progress linked with proteome and neurobiological challenges that may provide new basic concepts in the near future, based on pharmacological agents linked with impaired proteostasis and neurodegenerative diseases.

Additional Benefits Expected in the Future: For the first time, Amit's research demonstrates that MGRN1 E3 ubiquitin-protein ligase is depleted in cells expressing expanded-polyglutamine proteins. MGRN1 interacts with expanded-polyglutamine huntingtin and ataxin-3 proteins. His observations suggest that stimulating the activity of MGRN1 ubiquitin ligase might be a potential therapeutic target to eliminate the neurotoxic threat in polyglutamine diseases. His findings were designated among TOPNOTCH 10 Young Innovative Entries from ASIA under BioAsia Drug Discovery and Innovation Programme. A better understanding of the basic molecular mechanism of disease and its associated risk factors can not only improve its therapy but also suggest potential preventive measures via changes in people's day-to-day lives. The potential PQC biomarkers can also be studied for their potential for early detection of complex disorders, improving patient survival, and reducing stress on healthcare systems. The possibility of lesser invasive biomarkers is also advantageous over conventional diagnostic techniques, including biopsies and radiological methods. Impaired PQC is a significant contributing factor to imperfect ageing and its associated disorders, including increased incidence of cancer and neurodegeneration. We also intend, with our current and potential future interdisciplinary collaborators, to facilitate the translation of our research findings at the molecular and cellular level to animal studies and clinical development. Such research studies can benefit society by aiding in decreasing the national and global burden of these diseases.