Signed details of the excellence in research work for which the Sun Pharma Research Award is claimed, including references & illustrations:

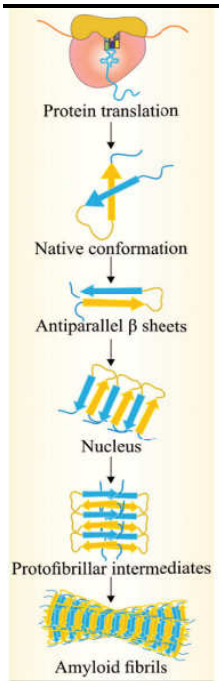
Contributions of the nominee: Entire Presented Work of Amit Mishra was Performed in India

Prof. Amit Mishra Research Contributions Medical Sciences under Basic Research:

Prof. 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 defense 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 in clarifying 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 that can induce autophagy pathways and serve 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 defense 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.

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.

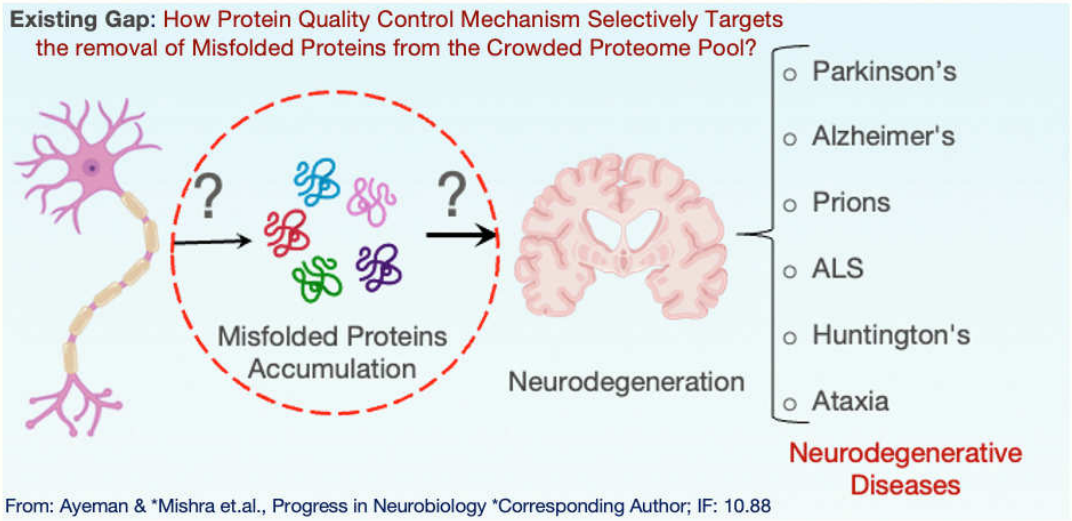
(Signature of Nominee) Prof. Amit Mishra, Indian Institute of Technology Jodhpur



From: Arun & *Mishra et.al
*Corresponding Author
Biological Reviews
IF: 14.35

Brief Research Profile: Amit Mishra

Problem: How the Depletion of Proteostasis Causes Multifactorial Complexity In Neurodegeneration and Imperfect Aging ?



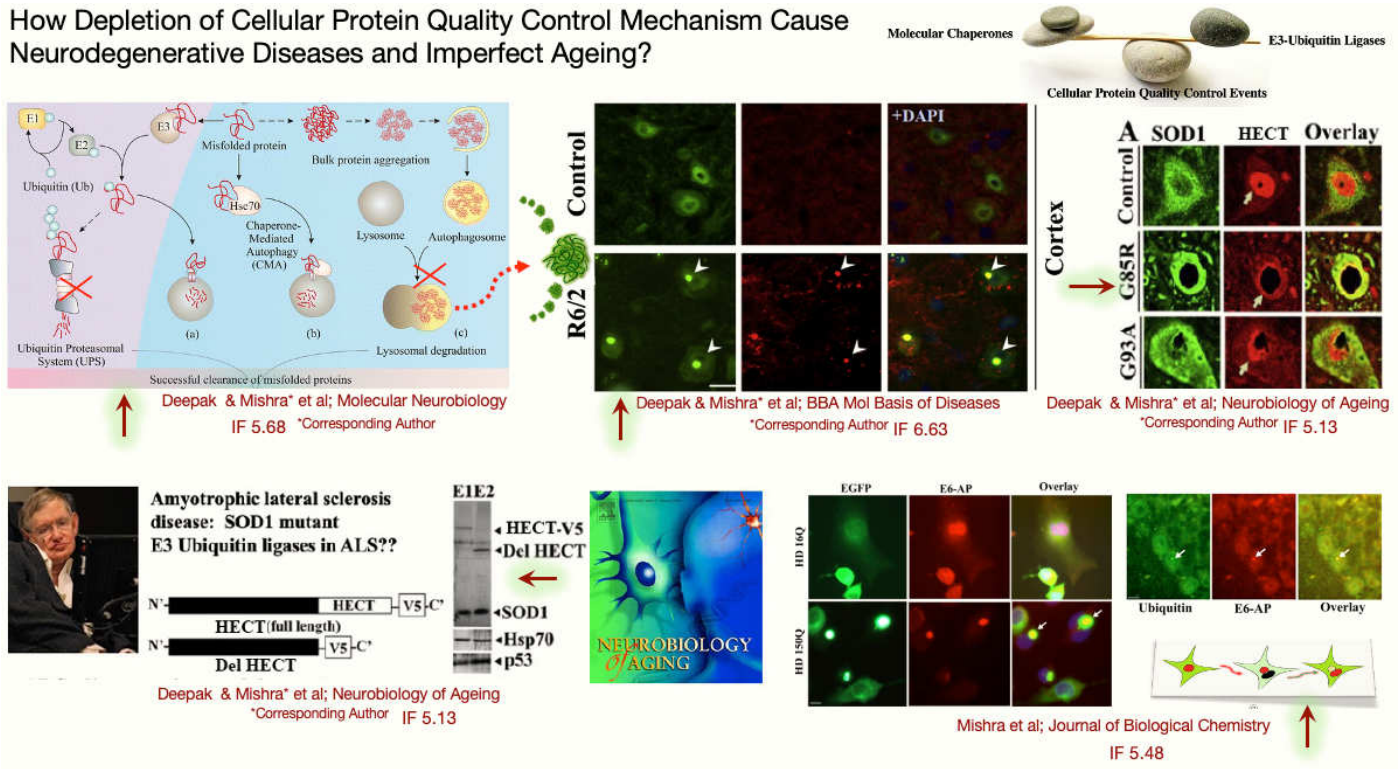
From: Ayeman & *Mishra et.al., Progress in Neurobiology *Corresponding Author; IF: 10.88

Major Contribution: Established a significant concept on selective **Quality Control E3 ubiquitin ligases** those can serve as **early first line of defense** ameliorative measures **against proteostasis failures** implicated in neurodegenerative diseases and imperfect aging.

Further detail information on research contributions in Medical Sciences (Basic Research):

1. Role of the Nominee in the development of scientific knowledge at national and international level:

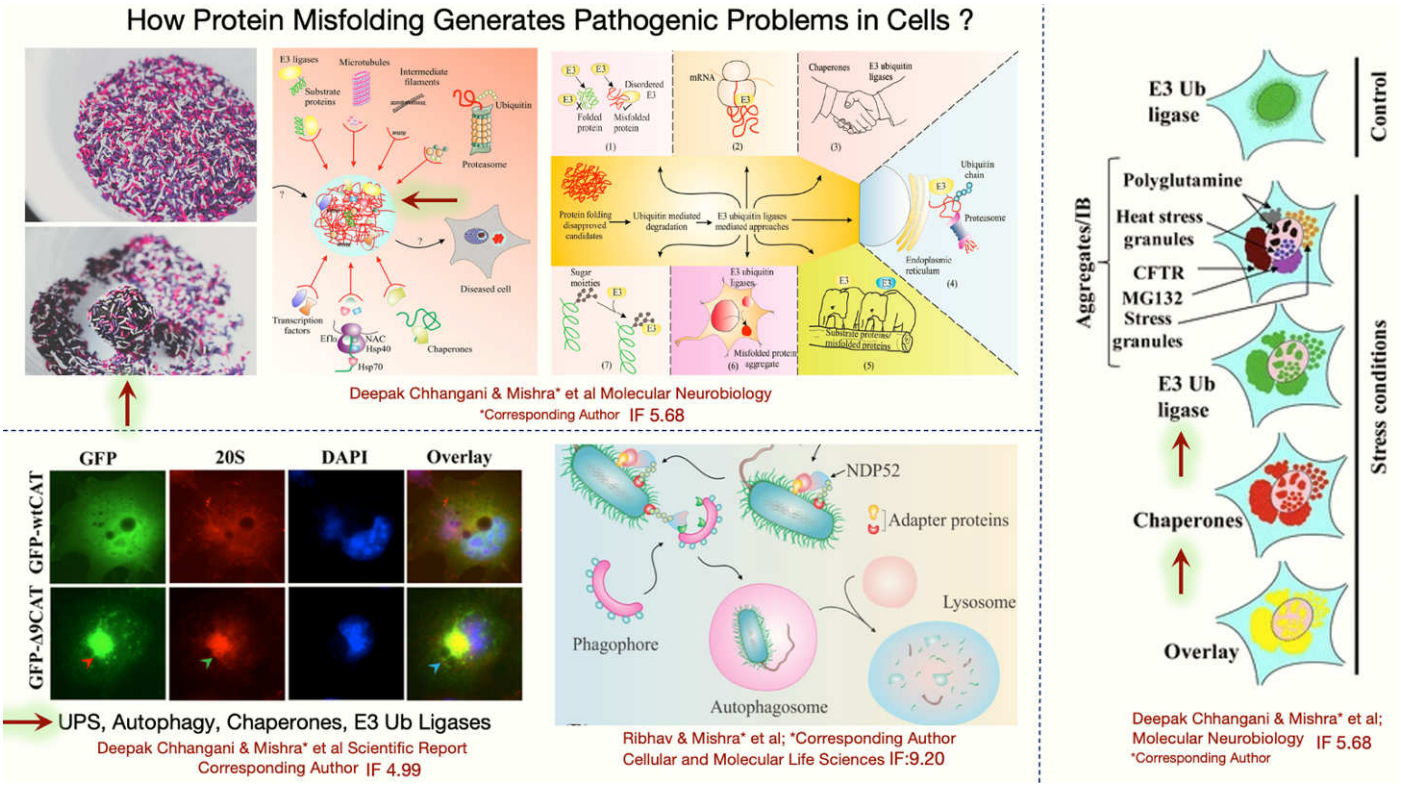
Prof. Mishra has established a new significant concept on selective E3 ubiquitin ligases those can serve as quality control first line of defense ameliorative measures against multifactorial proteostasis failures implicated in neurodegenerative diseases and imperfect aging". Research Impact on Society: 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. Our current research provides an innovative, clear and understandable framework of protein quality control system with new approaches against protein misfolding. In near future 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 ageing.



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. Our research work enlightens precise molecular mechanism of E3 ubiquitin ligases and molecular chaperones, their involvement in cellular quality control pathways and effect overall cellular homeostasis. 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.

2. <u>Usefulness of the Nominee's work for the benefit of mankind highlighting the technology transfer project</u>:

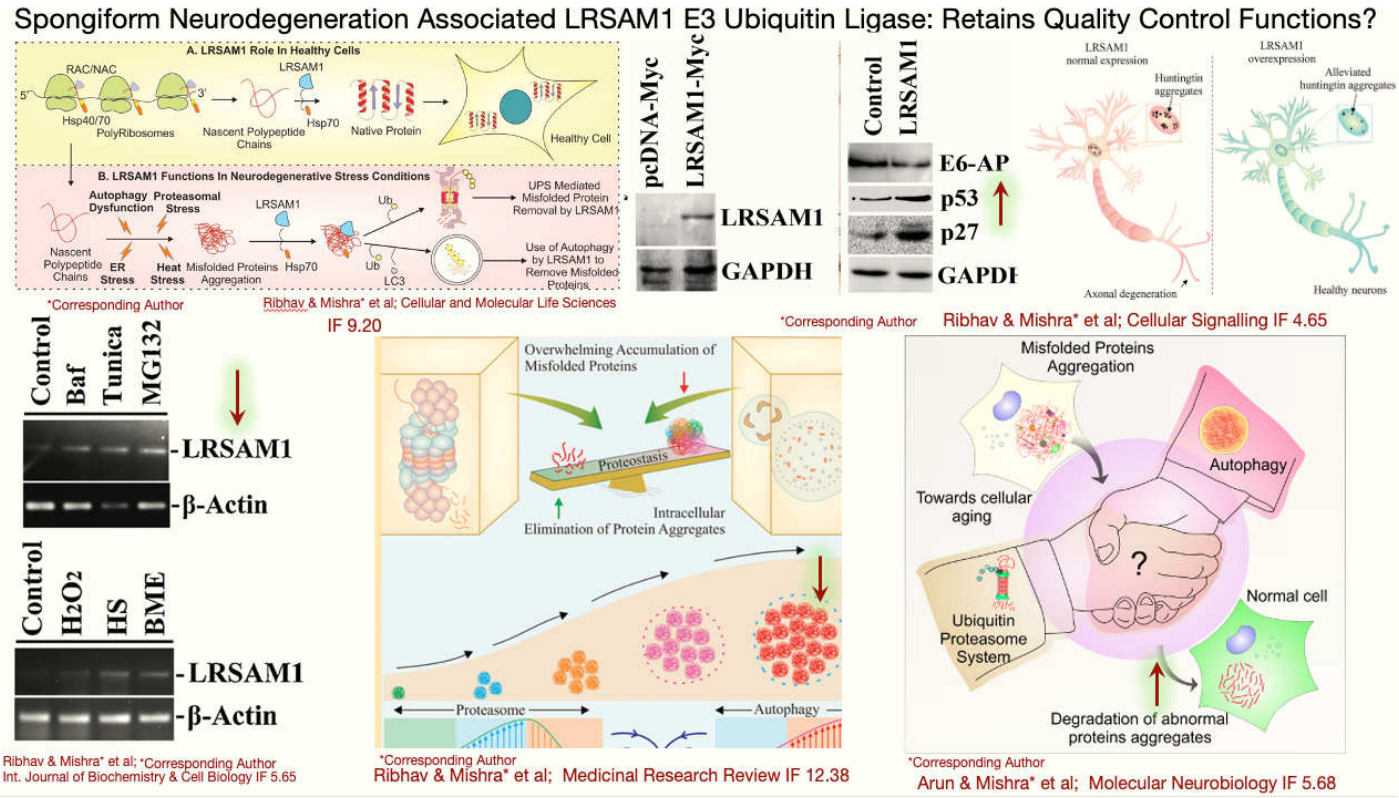
In our confidence current research of my group are paying serious attention on quality E3 ubiquitin ligases mediated regulation of cellular protein quality control mechanism linked with misfolded protein aggregation and their clearance via ubiquitin proteasome system and/or autophagy pathway. Is there any specific recognition mechanism possible which figures out difference among normal proteins or damaged proteins? On the basis of existing information, we can say that cells retain a protein quality system (QC) whose potential function is to fight against protein aggregation problem. What molecular mechanisms regulate its exquisite functionality and determine overall specificity? In our current research, we are trying to find out QC based "E3 Ubiquitin Ligases First Line of Defense" that can develop emerging cytoprotective strategies against multifactorial toxic proteins implicated in protein conformation disorders. Development of drugs, which can modulate and improve the functions of chaperones and quality control E3 ubiquitin ligases is needed. However, it is very important to first consider efficacy of "First Line of Defense" as well as their cumulative behavior against proteotoxic aggregation. One of the major causes of debilitating disorders of the brain and neurodegeneration is impairment of cellular protein quality control (PQC) machinery, leading to an increased load of misfolded/non-functional proteins in cells. The two major PQC machineries for degradation of such 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 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 (Parkinson's disease), in a proteasome-dependent manner, whereas triterpenoid lanosterol increases misfolded protein clearance via upregulating E3 CHIP and autophagy. 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.

3. <u>Contribution of the Nominee in establishing institutions of scientific excellence</u>:

What Our Lab-Based Research Innovatively Contributes in "Cellular-Proteostasis And Health" Including National Mission Health Care of Country: We *present* here that how a better understanding of a conserved machinery for cellular health and diseases i.e. cellular protein quality control mechanism can be helpful to comprehend a new molecular framework based on intrinsic and extrinsic cellular mechanisms that drive the assembly of protein clearance to induce cellular survival against proteostasis imbalance and diseases conditions. Remarkably, several cellular functions and cellular morphologically changes are preserved by proper functions of cellular protein quality control pathway, which is capable to integrate various cellular circuits and able to elicit complex molecular mechanism after clearance of misfolded proteins, indicating that blockade of cellular protein quality control signaling results in long-term functional loss of protein homeostasis. Here we provided the *systematic outcome* of lab-based research, which determine the functional depth of the cellular protein quality control mechanism because a clear understanding of cellular protein quality control mechanism and the structural features of this system can reveals important mechanistic insights of aberrant proteins degradation. These observation in near future may indicate significant differences between the early activation phase of the functional cellular protein quality control system and a more elaborative understanding of why and how cellular protein quality control machinery have been chosen to be there in healthy cellular proteome.



4. <u>Current Research Impact on Therapeutic Interventions Linked Positive Changes</u>:

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. Lab colleagues including myself in the cellular and molecular neurobiology unit at IIT Jodhpur are currently focusing on precisely understanding the *molecular mechanisms* and affected pathways, behind these diseases. Therefore, to investigate the possible alterations and modifications at the genetic level are needed to effectively address these kinds of disorders. Present outcome of research objectives addresses few most important questions in modern cellular protein quality control research, i.e. how aberrant or lack of functions of quality control (QC) E3 ubiquitin ligases and chaperones can contribute in the molecular pathogenesis of neuronal degeneration and why QC E3 ubiquitin ligases are partially colocalizes with components of the endosome to lysosome trafficking pathway? A critical challenge, which was recognized by our lab is to understand how the systematic QC E3 ubiquitin ligases facilitated machinery influences the protein quality control events during stress conditions and suppress the aggregation of damaged proteins. Despite few scientific groups are studying other E3 ubiquitin ligases involved into other human disease context. Present key research describes development efforts involved potential of translating science knowledge into a commercially available product. In future our aim is develop biomarkers that can target specifically neurodegenerative disorders resulted due to protein aggregation is primarily caused because of *impairment* in *cellular protein quality control machinery* of the cell. Research retains a *deep impact* that can provide highly qualitative cutting edge direct and indirect benefits of the innovation and its value in terms of its public good to treat neurodegenerative diseases and ageing. The commercial outcome of existing research is also very important to establish a new business or in partnership, for example with an existing research organization where the relevant research or early stages of developing the innovation were conducted. The above described innovation and the underlying research and trial pathway leading to it will be considered of equal importance. The current research is also contributing and explores the *qualitative research prospects* for those who are specifically linked with *chaperone-assisted protein folding* and *organelle-specific* protein quality control systems in India and worldwide.

Awards/Honors/Fellowships: Candidature Selected for **48** International/National/Bilateral Awards

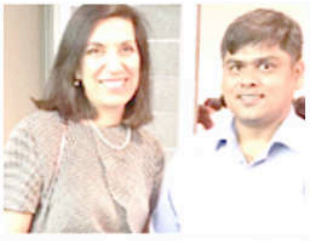
Few Selected International/Bilateral Awards:

Young Scientist Awarded by Nobel Laureate–(Prof. Harald)
Riken Brain Science Institute Fellowship, Japan
Max Planck Society Fellowship, Germany
DST-JSPS International Bilateral fellowship
Fellow of Royal Society of Biology, London
INSA-JSPS International Bilateral Fellowship
New York Academy of Sciences: Potential Scientific Feature
Fellow of Royal Society of Medicine, London
Neuroscience Young Investigator Award: APSN
Member of Royal Society of Chemistry (RSC), London
Fellow of Royal Society of Medicine, London
Young Investigator Award from Japan Neuroscience Society
Early Career Researcher Award: Royal Society of London
Best Presentation Award: Neuroscience (Parmar Foundation, USA)

Few Selected National Awards:

NASI: Young Scientist Platinum Jubilee Award
DBT: Ramalinganswami Fellowship
INSA: Young Scientist Medal Award
DBT: Innovative Young Biotechnologist Award (IYBA)
ISCA: Best Young Scientist Award (New Biology)
BRSI: Young Scientist Award
NAMS: Best Biomedical Scientist Award
IIT Jodhpur: Faculty Research Excellence Award
ISCB: Young Scientist Award
BRSI: Malviya Memorial Award" of BRSI
ICMR: Shankunta Amir Chand Prize
ISCA: Prof. Umakant Sinha Memorial Award
BRNS: Young Scientist Research Award
ISCB: Prof. Rita Mulhekar Award






Publications

- **Total Publications: 111**
- **Present: h-index: 31**
- **i10-index: 69**
- **Citations More than 15360**
- **Total Impact Factor of Publications: 667.42**
- **Average Impact Factor of each paper: 6.05**

Selective HIGH STANDARD CLASSICAL Publications

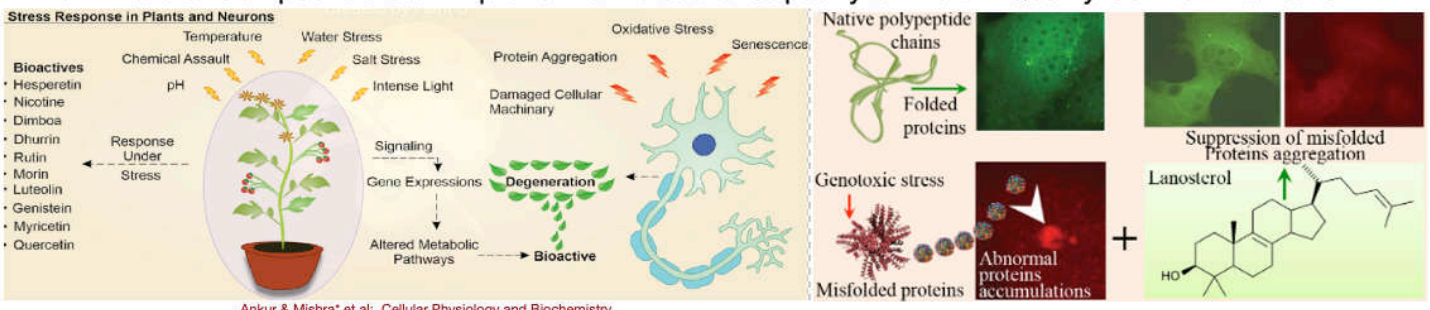
Journal of Biological Chemistry (JBC)
Molecular Neurobiology
Neurobiology of Disease
Progress in Neurobiology
Biological Reviews
Scientific Reports (Nature Publishing Group)
Neurobiology of Aging
Journal of Neurochemistry
Cellular and Molecular Life Sciences
BBA Molecular Basis of Diseases
Ageing Research Reviews
Neurotoxicity Research
Biochemical and Biophysical Research
Medicinal Research Review
Autophagy
Genes & Diseases

ACS Chemical Neuroscience
Cancers
Journal of Cellular Physiology
The Neuroscientist
Journal of Cellular Biochemistry
Cellular Signalling
Drug Metabolism Review
Mechanism of Ageing & Development
Acta Neuropathologica Communication
Neurochemistry International
Journal of Biological Macromolecules
ACS Chemical Biology
Advance Medicinal Chemistry
Biochemical Journal
Neurochemical Research
BBA General Subjects

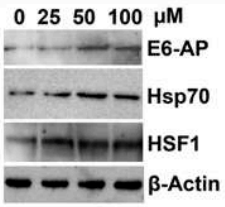
Research Grants/Project Awarded:
Secured Nine Projects after IIT Jodhpur Joining: 200.40 Lakhs
Completed Projects: Eight

1. DBT India, Ramalinganswami Fellowship
2. DST-Japan Society for the Promotion of Science (JSPS)
3. INSA-Japan Society for the Promotion of Science (JSPS)
4. Innovative Young Biotechnologist Award (IYBA)- DBT India
5. Board of Research in Nuclear Sciences (BRNS) India
6. SERB Extra Mural Research Funding (Individual Centric)
7. Board of Research in Nuclear Sciences (BRNS): Extra Mural

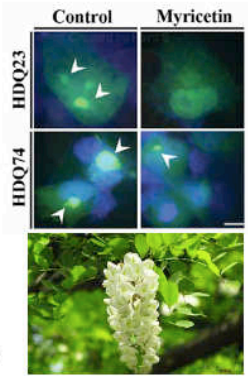
How Natural Compounds Can Improve the Molecular Capacity of Protein Quality Control Mechanism ?



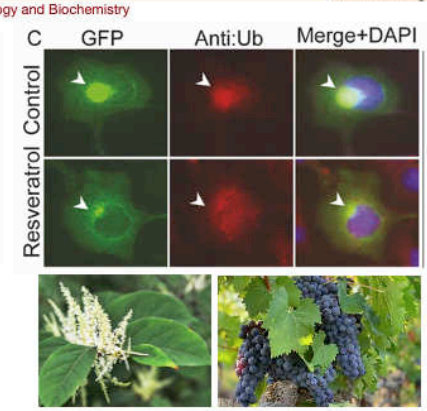
Ankur & Mishra* et al; Cellular Physiology and Biochemistry



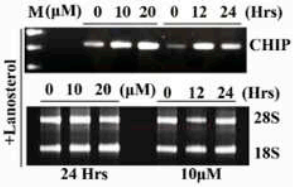
Vibhuti & Mishra* et al;
Journal of Cellular Physiology

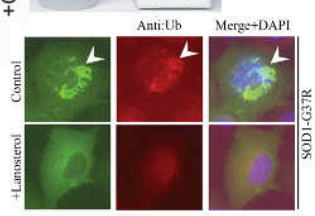


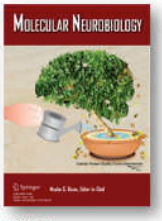
Eshan, Mishra and Amit K* et al;
ACS Chemical Biology



Ankur & Mishra* et al;
Cellular Physiology and Biochemistry







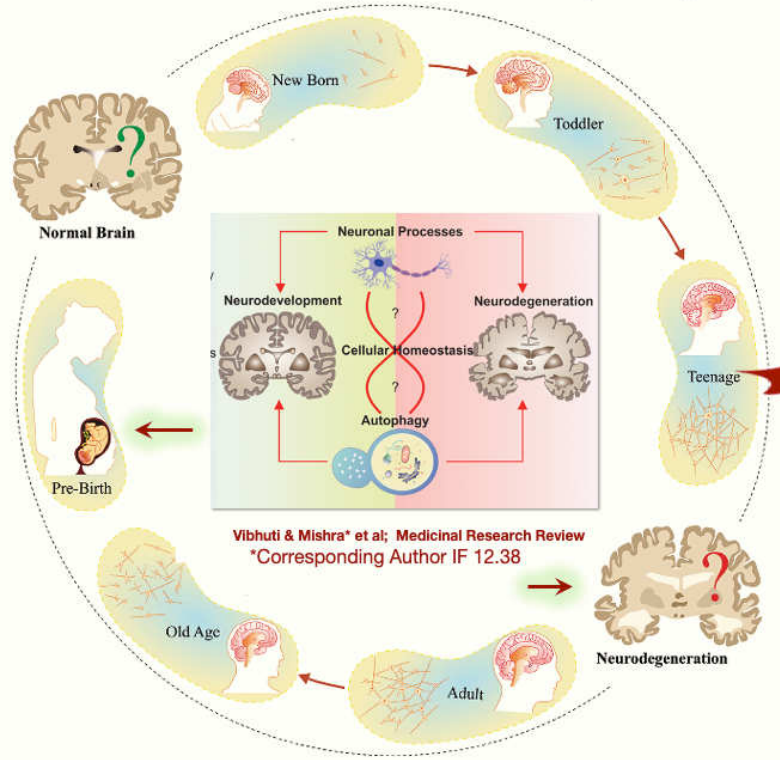
Arun & Mishra* et al; Molecular Neurobiology

Research Associated Roles & Responsibilities:

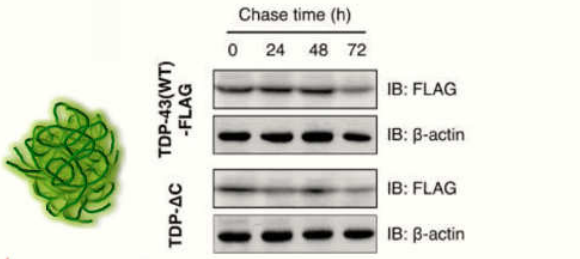
Membership in Professional Organizations & Scientific Academies
1. The Biotech Research Society India (BRSI-Life Member)
2. Indian Society of Chemists and Biologists (ISCB-Life Member)
3. Indian Association for Cancer Research (IACR-Life Member)
4. Society of Applied Biotechnology India (SAB-Life Member)
5. Indian Science Congress Association (ISCA-Life Member)
6. Indian Academy of Neuroscience (IAN-Life Member)
7. National Academy of Biological Sciences (NABS-Life Member)
8. Indian Society of Cell Biology (ISCB-Life Member)
9. Society of Pharmaceutical Education and Research (SPER-Life Member)
10. The American Society For Biochemistry and Molecular Biology (Member)
11. The New York Academy of Sciences (Member)
12. International Brain Research Organization (IBRO-Member)
13. Japan Neuroscience Society (JNS-Associate Member)
14. National Academy of Sciences India (NASI-Member)
15. Royal Society of Chemistry (RSC London-Member)
16. Royal Society of Medicine (RSM London-Fellow)
17. International Society for Neurochemistry (ISN-Member)
18. The New York Academy of Sciences (Bicentennial Ambassador)
19. Royal Society of Biology (RSC London-Member)
20. National Academy of Medical Sciences India (Life Member)
21. Royal Society of Biology, London (RSB London-Fellow)
22. Indian Biophysical Society (Life Member)
23. Transnational Biomedical Research Society (TBRS) India (Life Member)
24. Indian Immunology Society (Life Member) 25. Society of Biological Chemists (SBC)-IISC Bangalore India (Life Member) 26. Society for free Radical Research India (Life Member)

Following Classical Journals Selected Candidature as a Member/Reviewer in Their Respective Editorial Manager Board:
1. Biotechnology Advances
2. Molecular Phylogenetics and Evolution
3. Neuroscience
4. Bioorganic and Medicinal Chemistry
5. Biochemie
6. Scientific Reports (Nature Publishing Group)
7. Frontiers in Molecular Neuroscience
8. Molecular and Cellular Neuroscience
9. Bioorganic & Medicinal Chemistry
10. Neuroimmunology and Neuroinflammation
11. European Journal of Biophysics
12. Journal of Clinical Medicine
13. Journal of Virological Methods
14. Frontiers in Bioscience
15. Ageing Research Reviews
16. European Journal of Medicinal Chemistry
17. Progress in Neurobiology
18. BBA-Gene Regulatory Mechanisms
19. Pharmacological Research
20. Biomedicine & Pharmacotherapy
21. Medicinal Research Review 22. Biotechnology & Bioinformatics
23. Frontiers in Molecular Biosciences

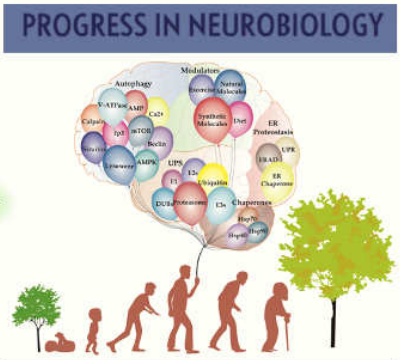
How Quality Control E3 Ubiquitin Ligase Targets Cellular Proteome Complexity?



Vibhuti & Mishra* et al; Medicinal Research Review
*Corresponding Author IF 12.38



Kohei, Mishra & Yamanaka* et al; Acta Nero Commu IF 7.57



Progressing Neurobiological Strategies Against Proteostasis Failure: Challenges in Neurodegeneration

Ayeman & Mishra* et al; Progress in Neurobiology
*Corresponding Author IF 10.88