Statement of Research Achievements, if any, on which any Award has already been received by the Applicant.

Prof. Benu Brata Das is working on the molecular basis of Topisomerase 1-induced DNA damage and repair pathways in the nuclear and mitochondrial genome for the last 20 years. Dr. Das has published above 50 papers in peer-reviewed journals including *Science Advances, EMBO Journal, PNAS, Cell Reports, EMBO Reports, Nucleic Acids Res, FASEB journal, Cancer Res, NAR Cancer, JBC, J Med Chem (ACS), European Journal of Medicinal Chemistry* and three book chapters.

Prof. Das is elected a fellow of the National Academy of Science, India (*FNASc*, 2020), West Bengal Academy of Science & Technology (*FAScT, 2019*), and GUHA research Conference-2019. Prof Das is also the recipient of several awards and honors including the ICMR-Prem Nath Wahi award 2019, DBT-National Bioscience award 2019, Senior Visiting Professor Fellow award-2016 (University of Bologna, Italy), DBT/Wellcome Trust/India alliance Fellowship 2013-2018, DST-Ramanujan Fellowship 2013; DBT-Ramalingaswami Re-entry Fellowship 2013; NIH-Fellows Award for Research Excellence 2012 and 2010.

Homozygous mutation of human TDP1 (H493R) is responsible for the severe neurodegenerative hereditary syndrome, spinocerebellar ataxia with axonal neuropathy (SCAN1) that leads to cerebellar atrophy, and defects in motor coordination and brain function disorder. TDP1 is critical for mitochondrial DNA (mtDNA) repair, however, the role of mitochondria remains largely unknown for the etiology of SCAN1. However, the molecular mechanism of the SCAN1 disease was unknown, because independent mouse models generated for TDP1 knockout failed to show the signs of neurodegeneration.

Das group provides the first evidence that mitochondria in cells harboring SCAN1-mutant TDP1 are selectively trapped on the mitochondrial DNA (mtDNA), generate mtDNA damage, and show increased fission rates. $TDP1^{H493R}$-trapping prevents mitochondrial transcription, energy production, and mitobiogenesis. Further, to match the metabolic demand, the neuronal cell expressing SCAN1- TDP1-triggers mitophagy that allows identification and removal of dysfunctional mitochondria in neurons through PINK1-dependent mitophagy. Therefore, the mitophagy operation in SCAN1 neurons is a mechanism of survival. (***Ghosh et al., Science Advances, 2019***). This fundamental work opens a new avenue for understanding the role of mtDNA damage in neurological disorders and is highly cited in the field. The work was highlighted in Nature Reviews Neurology, 2022, and Mitochondrion 2022. *This work was awarded the prestigious DBT-National Bioscience Award 2019.*

Progress has been remarkable in recent years regarding the elucidation of the repair pathways involved in the removal of Top1 cleavage complexes. The nominee has made seminal contributions in the field by discovering that TDP1 is epistatic to PARP1 for the repair of Top1cc.

PARP1 appears to act as a molecular determinant between TDP1 and the endonuclease pathway for the repair of Top1cc. They also show that TDP1 is PARylated by PARP1. PARylation stabilizes TDP1 and enhances its recruitment to DNA damage sites without interfering with TDP1 catalytic activity. TDP1-PARP1 complexes, in turn, recruit XRCC1 in camptothecin-treated cells. These studies uncover mechanisms of PARP activation and molecular networks of PARP1 for the repair of Top1-induced DNA breaks. PARP inhibitors are FDA-approved anticancer drugs (***Das et al., Nucleic Acids Research 2014***). They have generated considerable interest as single agents for tumors defective in homologous recombination (HR) such as BRCA1 or BRCA2 mutation. These clinical responses seem to be transient, as cases of revertants and PARP inhibitor resistance are on high. The nominee's mechanistic work has opened a new rationale for the combination of PARP inhibitors with Top1 inhibitors in cancer, especially in tumors that are defective in DNA repair pathways like in ovarian and breast cancer (mutation in BRCA genes) or Lung cancer (frequent mutations in XPF-ERCC1 pathways) and was awarded ICMR-*Prem Nath Wahi award 2019.*