**Claim for award:**

Over the past decade, **Prof. Benu Brata Das** and his research group at IACS have made groundbreaking advancements in DNA repair pathways, significantly enhancing the efficacy of chemotherapy for cancer. Their work focuses on overcoming resistance to camptothecin and its derivatives, utilizing mouse models to test innovative combination therapies in vivo for breast and ovarian cancers.

**Key Achievements:**

1. **Mechanistic Insights into Mitotic Catastrophe:** Prof. Das's research achieved a groundbreaking discovery in understanding mitotic catastrophe by identifying the CDK1-dependent phosphorylation of TDP1 at residue S61 during mitosis. His team demonstrated that a phosphorylation-defective TDP1 variant (TDP1-S61A) traps on mitotic chromosomes, causing DNA damage and mitotic defects. The study revealed that the repair of Top1cc during mitosis is mediated by a MUS81-dependent pathway. Under replication stress from camptothecin or aphidicolin, TDP1-S61A accumulates at fragile sites, leading to chromatid breaks, anaphase bridges, and micronuclei, which ultimately result in 53BP1 nuclear bodies in the G1 phase. Published in ***The EMBO Journal (2024),*** this work highlights the critical role of TDP1 phosphorylation in regulating mitotic stability and preventing genomic instability, marking a significant advancement in cancer biology.

2. **Breakthrough in mitochondria research:** Prof. Das's research represents a significant breakthrough in understanding the molecular basis of spinocerebellar ataxia with axonal neuropathy (SCAN1) caused by a mutation in tyrosyl-DNA phosphodiesterase 1 (TDP1). His work revealed that the TDP1-H493R mutant selectively traps on mitochondrial DNA, leading to mtDNA damage and initiating Drp1-mediated mitochondrial fission. This pathological process triggers mitophagy as a neuroprotective response, offering insights into the delayed onset of SCAN1 and highlighting novel therapeutic targets for neurodegenerative diseases. (***Science Advances, 2019***)

3. **Identification of PRMT5 as a Therapeutic Target:** Prof. Das's research identified PRMT5 as a key therapeutic target for repairing DNA breaks associated with Top1-DNA trapped complexes. His studies demonstrated that PRMT5 is a major resistance factor in cancer chemotherapy. Knockdown of PRMT5 enhances cancer cell sensitivity to camptothecin. Prof. Das's group elucidated the interaction between PRMT5-mediated arginine methylation and ubiquitination of TDP1. Their findings, published in ***Cell Reports* (2022),** reveal that TDP1 methylation at residues R361 and R586 is essential for its repair activity and stability. This research supports the combination of PRMT5 inhibitors with Top1-targeted drugs and has influenced ongoing clinical trials exploring novel therapeutic strategies.

Prof. Das's pioneering research has made significant contributions to cancer therapy, drug discovery, and the understanding of DNA repair mechanisms, solidifying his position as a leading figure in the field.

**Publications:**


1. Paul Chowdhuri S and ***Das, B. B***.* TDP1 phosphorylation by CDK1 in mitosis promotes MUS81-dependent repair of trapped Top1-DNA covalent complexes, ***The EMBO Journal*** ; 2024 Jul 16. doi: 10.1038/s44318-024-00169-3. **(IF: 9.4)**

2. Ghosh, A., Bhattacharjee, S., Paul Chowdhuri, S., Mallick, A, Rehman, I., Basu, S., and ***Das, B.B**. 2019**. SCAN1-TDP1 trapping on mitochondrial DNA promotes mitochondrial dysfunction and mitophagy. ***SCIENCE ADVANCES***, ***5, eaax9778***. **(IP: 14.1)**

3. Bhattacharjee S, Rehman I, Basu, S., Nandy S, Richardson J., ***Das, B.B****. **2022**. The interplay between symmetric arginine dimethylation and ubiquitylation regulates TDP1 proteostasis for the repair of topoisomerase I-DNA adducts. ***Cell Reports***, 39, 110940 **(IF: 9:43)**