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Citation (summary) on the outstanding research work

Professor **Benu Brata Das** has been honored with **The Sun Pharma Science Foundation Research Award in Medical Science (Basic Research)** for his outstanding contributions to the understanding of the molecular mechanisms underlying DNA topoisomerase I (Top1)-induced DNA damage response and its repair by Tyrosyl-DNA-phosphodiesterase (TDP1). His pioneering research has provided the first evidence linking mitochondrial dysfunction to the etiology of the neurodegenerative disease SCAN1, caused by a point mutation in human TDP1 (*Science Advance* 2019). Among Professor Das's remarkable discoveries are the identification of novel therapeutic targets such as PRMT5 and PARP1, which play crucial roles in the repair of trapped Top1-DNA lesions and act as resistance determinants in cancer chemotherapy. His team has uncovered a novel role of PARP1 in regulating Top1 nuclear mobility through Top1 PARylation. Additionally, they have demonstrated that PRMT5 is a key modulator of TDP1's DNA repair function, specifically in the resection of trapped Top1-DNA complexes (*NAR* 2016; *NAR* 2018; *Cell reports* 2022).

Recent discovery work from Professor Das's group has shown that CDK1 kinase can regulate TDP1 activity during mitosis. Cells lacking TDP1 mitotic phosphorylation exhibit significant mitotic defects, including mitotic catastrophes indicative of genomic instability (*The EMBO Journal* 2024). These discoveries hold substantial relevance for ongoing clinical trials and promise advancements in precision medicine for cancer treatment.

A. Banerjee 14.08.2024

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Research Achievements:

Research Focus:

Prof. Benu Brata Das's group investigates the critical role of DNA topoisomerase 1 (Top1) in replication and transcription, with a focus on cellular responses to Top1-DNA covalent complexes (Top1cc) induced by anticancer drugs like Camptothecin and its derivatives. The lab identifies novel therapeutic targets and post-translational modifications of repair proteins, such as TDP1 and PARP1, crucial for genome maintenance. Their ultimate goal is to develop Top1-targeted anticancer drugs for precision medicine. This research significantly advances the understanding of genomic alterations in carcinogenesis and holds promise for novel cancer therapies.

Mechanistic Insights into Mitotic Catastrophe: In a fundamental study, Prof. Das's team discovered CDK1-dependent phosphorylation of TDP1 at residue S61 during mitosis. A phosphorylation-defective TDP1 variant (TDP1-S61A) accumulates on mitotic chromosomes, leading to DNA damage and mitotic defects. They revealed that Top1cc repair during mitosis is mediated by a MUS81-dependent pathway. Replication stress induced by camptothecin or aphidicolin causes TDP1-S61A to accumulate at fragile sites, resulting in chromatid breaks, anaphase bridges, and micronuclei, ultimately leading to 53BP1 nuclear bodies in G1 phase. This study, published in *The EMBO Journal* (2024), elucidates the critical role of TDP1 phosphorylation in regulating mitotic activity and preventing genomic instability and presented at the **EMBO Conference** (2024).

Molecular Mechanisms and Cancer Therapy: Prof. Benu Brata Das's research has significantly advanced our understanding of DNA repair mechanisms and their implications for cancer therapy. His lab identified PRMT5 as a key therapeutic target for repairing DNA breaks associated with Top1-DNA trapped complexes. **This discovery highlights PRMT5's role** in enhancing TDP1's repair activity and overcoming resistance to Top1 inhibitors like camptothecin, with findings published in *Nature Reviews Molecular Cell Biology* (2019) and presented at the Gordon Research Conference (2018).

Prof. Das's group also uncovered that PRMT5-mediated arginine methylation of TDP1 is essential for maintaining genome stability. Their study, published in *Cell Reports* (2022) and *Nucleic Acids Research* (2018), demonstrated that loss of TDP1 methylation leads to defective repair and increased sensitivity to Top1 poisons, suggesting that combining PRMT5 inhibitors with Top1-targeted drugs could improve cancer treatments.

Leishmania donovani DNA repair Research: Prof. Das's research on *Leishmania donovani* revealed a novel role for TDP1 in protecting the parasite from oxidative stress and drug resistance. TDP1 knockout *L. donovani* promastigotes showed hypersensitivity to Top1 poisons and antileishmanial drugs, with altered membrane morphology and increased oxidative stress. This study, published in *The FASEB Journal* (2022), suggests that LdTDP1 plays a critical role in safeguarding against DNA damage and enhancing drug resistance.

Drug Discovery and Development: Prof. Das's lab has developed new Top1 inhibitors to address camptothecin's limitations. They discovered hydantoin and thiohydantoin derivatives as potent

Top1 poisons and identified a class of neutral porphyrin derivatives, such as compound 8, which inhibits Top1 at nanomolar concentrations and overcomes CPT resistance, as detailed in the *Journal of Medicinal Chemistry* (2023; 2018). Additionally, compound 28, a quinoline-based Top1 inhibitor, demonstrated high potency and stability, showing promise for overcoming CPT-related limitations, with results published in *Nucleic Acids Research* (2016) and *Journal of Medicinal Chemistry* (2019).

Molecular Mechanisms of Drug Action: Prof. Das explored the role of Poly(ADP-ribose) polymerase (PARP1) in regulating Top1 nuclear mobility through Top1-PARYlation. His work revealed that inhibiting Top1-PARYlation leads to increased Top1 trapping and compromised DNA repair, highlighting the relevance of combining PARP and Top1 inhibitors in cancer therapy. This work was published in *Nucleic Acids Research* (2014)

Mitochondrial Dysfunction and Disease Pathogenesis: Prof. Das's research has made key discoveries in mitochondrial dysfunction related to neurodegenerative diseases. He initially discovered nuclear encoded TDP1 is imported to mitochondria (*Proc Natl Acad Sci U S A.*, 2010). He revealed that the SCAN1-mutant TDP1 protein traps on mitochondrial DNA, causing damage and increased fission rates, impairing mitochondrial function, and triggering mitophagy in neurons. This study, published in *Science Advances* (2019), provides new insights into mitochondrial DNA damage in neurological disorders and has been highly cited in the field. The work was highlighted in *Nature Reviews Neurology*, 2022, and *Mitochondrion* 2022.

Top 10 best papers of the applicant: * Corresponding authors

1. Paul Chowdhuri S and **Das, B. B.*** TDP1 phosphorylation by CDK1 in mitosis promotes MUS81-dependent repair of trapped Top1-DNA covalent complexes, *EMBO Journal* ; 2024 Jul 16. doi: 10.1038/s44318-024-00169-3. (IF: 9.4)
2. 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)
3. Rehman, I.; Basu, S.; Das, S.K.; Bhattacharjee, S.; Ghosh, A.; Pommier, Y.; and **Das, B.B.***. 2018. PRMT5-mediated arginine methylation of TDP1 for the repair of topoisomerase I covalent complexes. *Nucleic. Acids Research.*, 46: 5601-5617. (IP: 16.97)
4. 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)
5. Roy Chowdhury S., Das SK., Banerjee B., Paul Chowdhuri S., Majumder H.K., and **Das, B.B.***. 2022. TDP1 knockout *Leishmania donovani* accumulate Topoisomerase I-linked DNA damage and are hypersensitive to clinically used antileishmanial drugs. *The FASEB Journal*, 36(4): e22265.(IP: 5.1)
6. **Das, B.B.**, Dexheimer TS, Maddali K and Pommier Y. Role of Tyrosyl DNA Phosphodiesterase

(TDP1) in mitochondria. *Proc Natl Acad Sci U S A.* 16;107(46):19790-19795. 2010. (IF: 10.23)

7. . Chowdhuri SP, Dhiman S, Das SK, Meena N, Das S, Kumar A, Das, B.B.*. Novel Pyrido[2',1':2,3]imidazo[4,5- c]quinoline Derivative Selectively Poisons *Leishmania donovani* Bisubunit Topoisomerase 1 to Inhibit the Antimony-Resistant Leishmania Infection *in vivo*. J. Med. Chem., 2023, 66(5):3411-3430. (IF: 8.01)

8. Das, BB. Antony S, Gupta, S, Dexheimer TS, Redon CE, Garfield S, Shiloh Y and Pommier Y. Optimal function of the DNA repair enzyme TDP1 requires its phosphorylation by ATM and/or DNA-PK. *EMBO Journal.* 28, 3667-3680. 2009. (IF: 10.12)

9. Das, S.K., Rehman, I., Ghosh, A., Sengupta, S., Majumder, P., Jana, B and Das BB*. Poly(ADP-ribose) polymers regulate DNA topoisomerase I (Top1) nuclear dynamics and camptothecin sensitivity in living cells. 2016. Nucleic. Acids Res. 44, 8363-75. (IP: 16.60)

10. Das, B.B*, Huang S.N., Murai J., *Rehman I*[@]., Amé J.-C., *Sengupta S*[@]., *Das S.K.*[@]., *Majumdar, P*[@]., Zhang H., Biard D., Majumder H.K., Schreiber V., Pommier Y.*, 2014. PARP1-TDP1 coupling for the repair of topoisomerase I-induced DNA damage, Nucleic. Acids Res., 42:4435-49. (IP: 16.60)



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