



टाटा स्मारक केंद्र
TATA MEMORIAL CENTRE

टाटा स्मारक अस्पताल
TATA MEMORIAL HOSPITAL



प. ऊ. वि. भारत सरकार का एक सहायता अनुदान प्राप्त संस्थान
A GRANT-IN-AID INSTITUTION OF THE DEPARTMENT OF ATOMIC ENERGY, GOVT OF INDIA

AA No. 1268228

STATEMENT BY TATA MEMORIAL CENTRE REGARDING THE USE OF A COMBINATION OF COPPER AND RESVERATROL IN CANCER PATIENTS

March 1, 2024

One of the mandates of Advanced Centre for Treatment, Research and Education in Cancer (ACTREC), Tata Memorial Centre, which is an aided institution under the Government of India, is to conduct research that is relevant to the Indian scenario, will advance knowledge of cancer biology, and produce results which are useful in management of cancer patients. Many research programs of Tata Memorial Centre have defined the management of various cancers nationally and worldwide. Reducing treatment-related toxicity is one of the focus research themes of TMC and has the potential to enhance the quality of lives and outcomes of cancer patients.

The research on cell-free chromatin (fragments of chromosomes) and resveratrol-copper by Dr. Indraneel Mittra and colleagues of ACTREC, Tata Memorial Centre, Mumbai, which was recently shared with the media, was conducted with the aim of finding out the mechanisms of toxicity related to cancer-directed treatment and the development of metastases. The studies by Dr. Mittra and colleagues in cell culture and experimental animals have shown that circulating cell-free chromatin could affect normal cells and tissues, causing inflammation, which, if definitively proven in humans, could potentially be one of the mechanisms of side effects of cancer treatment. This was a novel finding considered worthy of further evaluation.

Dr. Mittra and colleagues have shown that combinations of copper and resveratrol (a commercially available nutraceutical) in specific ratios degrade cell-free chromatin in preclinical *in vitro* and experimental animal studies. In experimental animal studies, and preliminary and Phase II human studies; there was some evidence that the use of copper plus resveratrol could reduce the toxicity of chemotherapy.

Dr. Mittra's research, both preclinical and in human patients, has been published in several papers in peer-reviewed scientific journals. The list of scientific publications (with weblinks to the articles) related to this topic from Dr. Mittra's laboratory is included below this statement.

Additional human studies with larger sample sizes are required and are underway to find out whether these findings apply to human patients or not. **It should be noted that resveratrol plus copper, including its tablet formulation, is not a substitute for established cancer treatments like surgery, radiotherapy, chemotherapy, hormone therapy and targeted therapy, which have been conclusively proven to provide benefits and result in cures in a substantial proportion of patients.**

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It is further clarified that the effectiveness of copper plus resveratrol, including its tablet formulation, in reducing treatment toxicity or increasing cures in cancer patients remains to be established and is currently under investigation.

We hope that this statement will be considered by all relevant stakeholders in a balanced manner and will clarify any questions that may have arisen as a result of recent media reports.


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PUBLICATIONS FROM DR MITTRA'S LABORATORY ON THIS TOPIC:

1. Mitra I, Pal K, Pancholi N, Shaikh A, Rane B, Tidke P, Kirolikar S, Khare NK, Agrawal K, Nagare H, Nair NK. Prevention of chemotherapy toxicity by agents that neutralize or degrade cell-free chromatin. *Ann Oncol.* 2017 Sep 1;28(9):2119-2127. doi: 10.1093/annonc/mdx318. PMID: 28911066. <https://pubmed.ncbi.nlm.nih.gov/28911066/>
2. Raghuram GV, Pal K, Sriram G, Khan A, Joshi R, Jadhav V, Shinde S, Shaikh A, Rane B, Kangne H, Mitra I. Therapeutic interventions on human breast cancer xenografts promote systemic dissemination of oncogenes. *PLoS One.* 2024 Feb 12;19(2):e0298042. doi: 10.1371/journal.pone.0298042. PMID: 38346047; PMCID: PMC10861051. <https://pubmed.ncbi.nlm.nih.gov/38346047/>
3. Shabrish S, Pal K, Khare NK, Satsangi D, Pilankar A, Jadhav V, Shinde S, Raphael N, Sriram G, Lopes R, Raghuram GV, Tandel H, Mitra I. Cell-free chromatin particles released from dying cancer cells activate immune checkpoints in human lymphocytes: implications for cancer therapy. *Front Immunol.* 2024 Jan 11;14:1331491. doi: 10.3389/fimmu.2023.1331491. PMID: 38274821; PMCID: PMC10808321. <https://pubmed.ncbi.nlm.nih.gov/38274821/>
4. Raghuram GV, Tripathy BK, Avadhani K, Shabrish S, Khare NK, Lopes R, Pal K, Mitra I. Cell-free chromatin particles released from dying cells inflict mitochondrial damage and ROS production in living cells. *Cell Death Discov.* 2024 Jan 15;10(1):30. doi: 10.1038/s41420-023-01728-z. PMID: 38225229; PMCID: PMC10789803. <https://pubmed.ncbi.nlm.nih.gov/38225229/>
5. Ostwal V, Ramaswamy A, Bhargava P, Srinivas S, Mandavkar S, Chaugule D, Peelay Z, Baheti A, Tandel H, Jadhav VK, Shinde S, Jadhav S, Gota V, Mitra I. A pro-oxidant combination of resveratrol and copper reduces chemotherapy-related non-haematological toxicities in advanced gastric cancer: results of a prospective open label phase II single-arm study (RESCU III study). *Med Oncol.* 2022 Nov 13;40(1):17. doi: 10.1007/s12032-022-01862-1. PMID: 36372825. <https://pubmed.ncbi.nlm.nih.gov/36372825/>
6. Pal K, Raghuram GV, Dsouza J, Shinde S, Jadhav V, Shaikh A, Rane B, Tandel H, Kondhalkar D, Chaudhary S, Mitra I. A pro-oxidant combination of resveratrol and copper down-regulates multiple biological hallmarks of ageing and neurodegeneration in mice. *Sci Rep.* 2022 Oct 14;12(1):17209. doi: 10.1038/s41598-022-21388-w. PMID: 36241685; PMCID: PMC9568542. <https://pubmed.ncbi.nlm.nih.gov/36241685/>
7. Pilankar A, Singhavi H, Raghuram GV, Siddiqui S, Khare NK, Jadhav V, Tandel H, Pal K, Bhattacharjee A, Chaturvedi P, Mitra I. A pro-oxidant combination of resveratrol and copper down-regulates hallmarks of cancer and immune checkpoints in patients with advanced oral cancer: Results of an exploratory study (RESCU 004). *Front Oncol.* 2022 Sep 16;12:1000957. doi: 10.3389/fonc.2022.1000957. PMID: 36185249; PMCID: PMC9525028. <https://pubmed.ncbi.nlm.nih.gov/36185249/>

8. Agarwal A, Khandelwal A, Pal K, Khare NK, Jadhav V, Gurjar M, Punatar S, Gokarn A, Bonda A, Nayak L, Kannan S, Gota V, Khattry N, Mittra I. A novel pro-oxidant combination of resveratrol and copper reduces transplant related toxicities in patients receiving high dose melphalan for multiple myeloma (RESCU 001). *PLoS One*. 2022 Feb 4;17(2):e0262212. doi: 10.1371/journal.pone.0262212. PMID: 35120140; PMCID: PMC8815866. <https://pubmed.ncbi.nlm.nih.gov/35120140/>
9. Shabrish S, Mittra I. Cytokine Storm as a Cellular Response to dsDNA Breaks: A New Proposal. *Front Immunol*. 2021 Feb 1;12:622738. doi: 10.3389/fimmu.2021.622738. PMID: 33597956; PMCID: PMC7882731. <https://pubmed.ncbi.nlm.nih.gov/33597956/>
10. Tripathy BK, Pal K, Shabrish S, Mittra I. A New Perspective on the Origin of DNA Double-Strand Breaks and Its Implications for Ageing. *Genes (Basel)*. 2021 Jan 26;12(2):163. doi: 10.3390/genes12020163. PMID: 33530310; PMCID: PMC7912064. <https://pubmed.ncbi.nlm.nih.gov/33530310/>
11. Mehrotra S, Mittra I. Origin of Genome Instability and Determinants of Mutational Landscape in Cancer Cells. *Genes (Basel)*. 2020 Sep 21;11(9):1101. doi: 10.3390/genes11091101. PMID: 32967144; PMCID: PMC7563369. <https://pubmed.ncbi.nlm.nih.gov/32967144/>
12. Mittra I, Pal K, Pancholi N, Tidke P, Siddiqui S, Rane B, D'souza J, Shaikh A, Parab S, Shinde S, Jadhav V, Shende S, Raghuram GV. Cell-free chromatin particles released from dying host cells are global instigators of endotoxin sepsis in mice. *PLoS One*. 2020 Mar 4;15(3):e0229017. doi: 10.1371/journal.pone.0229017. PMID: 32130239; PMCID: PMC7055819. <https://pubmed.ncbi.nlm.nih.gov/32130239/>
13. Chaudhary S, Mittra I. Cell-free chromatin: A newly described mediator of systemic inflammation. *J Biosci*. 2019 Jun;44(2):32. PMID: 31180045. <https://pubmed.ncbi.nlm.nih.gov/31180045/>
14. Raghuram GV, Chaudhary S, Johari S, Mittra I. Illegitimate and Repeated Genomic Integration of Cell-Free Chromatin in the Aetiology of Somatic Mosaicism, Ageing, Chronic Diseases and Cancer. *Genes (Basel)*. 2019 May 28;10(6):407. doi: 10.3390/genes10060407. PMID: 31142004; PMCID: PMC6628102. <https://pubmed.ncbi.nlm.nih.gov/31142004/>
15. Kirolikar S, Prasanna P, Raghuram GV, Pancholi N, Saha T, Tidke P, Chaudhari P, Shaikh A, Rane B, Pandey R, Wani H, Khare NK, Siddiqui S, D'souza J, Prasad R, Shinde S, Parab S, Nair NK, Pal K, Mittra I. Prevention of radiation-induced bystander effects by agents that inactivate cell-free chromatin released from irradiated dying cells. *Cell Death Dis*. 2018 Nov 15;9(12):1142. doi: 10.1038/s41419-018-1181-x. PMID: 30442925; PMCID: PMC6238009. <https://pubmed.ncbi.nlm.nih.gov/30442925/>
16. Chaudhary S, Raghuram GV, Mittra I. Is inflammation a direct response to dsDNA breaks? *Mutat Res*. 2018 Mar;808:48-52. doi: 10.1016/j.mrfmmm.2018.02.002. Epub 2018 Feb 22. PMID: 29518635. <https://pubmed.ncbi.nlm.nih.gov/29518635/>

17. Raghuram GV, Gupta D, Subramaniam S, Gaikwad A, Khare NK, Nobre M, Nair NK, Mitra I. Physical shearing imparts biological activity to DNA and ability to transmit itself horizontally across species and kingdom boundaries. *BMC Mol Biol.* 2017 Aug 9;18(1):21. doi: 10.1186/s12867-017-0098-8. PMID: 28793862; PMCID: PMC5550992. <https://pubmed.ncbi.nlm.nih.gov/28793862/>
18. Mitra I, Samant U, Sharma S, Raghuram GV, Saha T, Tidke P, Pancholi N, Gupta D, Prasannan P, Gaikwad A, Gardi N, Chaubal R, Upadhyay P, Pal K, Rane B, Shaikh A, Salunkhe S, Dutt S, Mishra PK, Khare NK, Nair NK, Dutt A. Cell-free chromatin from dying cancer cells integrate into genomes of bystander healthy cells to induce DNA damage and inflammation. *Cell Death Discov.* 2017 May 29;3:17015. doi: 10.1038/cddiscovery.2017.15. PMID: 28580170; PMCID: PMC5447133. <https://pubmed.ncbi.nlm.nih.gov/28580170/>
19. Basak R, Nair NK, Mitra I. Evidence for cell-free nucleic acids as continuously arising endogenous DNA mutagens. *Mutat Res.* 2016 Nov- Dec;793-794:15-21. doi: 10.1016/j.mrfmmm.2016.10.002. Epub 2016 Oct 12. PMID: 27768916. <https://pubmed.ncbi.nlm.nih.gov/27768916/>
20. Subramaniam S, Vohra I, Iyer A, Nair NK, Mitra I. A paradoxical relationship between Resveratrol and copper (II) with respect to degradation of DNA and RNA. *F1000Res.* 2015 Oct 27;4:1145. doi: 10.12688/f1000research.7202.2. PMID: 27134724; PMCID: PMC4833056. <https://pubmed.ncbi.nlm.nih.gov/27134724/>
21. Mitra I. Circulating nucleic acids: a new class of physiological mobile genetic elements. *F1000Res.* 2015 Sep 30;4:924. doi: 10.12688/f1000research.7095.1. PMID: 26664710; PMCID: PMC4654457. <https://pubmed.ncbi.nlm.nih.gov/26664710/>
22. Mitra I, Khare NK, Raghuram GV, Chaubal R, Khambatti F, Gupta D, Gaikwad A, Prasannan P, Singh A, Iyer A, Singh A, Upadhyay P, Nair NK, Mishra PK, Dutt A. Circulating nucleic acids damage DNA of healthy cells by integrating into their genomes. *J Biosci.* 2015 Mar;40(1):91-111. doi: 10.1007/s12038-015-9508-6. PMID: 25740145; PMCID: PMC5779614. <https://pubmed.ncbi.nlm.nih.gov/25740145/>
23. Rekha MR, Pal K, Bala P, Shetty M, Mitra I, Bhuvaneshwar GS, Sharma CP. Pullulan-histone antibody nanoconjugates for the removal of chromatin fragments from systemic circulation. *Biomaterials.* 2013 Sep;34(27):6328-38. doi: 10.1016/j.biomaterials.2013.05.019. Epub 2013 Jun 5. PMID: 23746856. <https://pubmed.ncbi.nlm.nih.gov/23746856/>
24. Mitra I, Nair NK, Mishra PK. Nucleic acids in circulation: are they harmful to the host? *J Biosci.* 2012 Jun;37(2):301-12. doi: 10.1007/s12038-012-9192-8. PMID: 22581336. <https://pubmed.ncbi.nlm.nih.gov/22581336/>