Government of India
Bhabha Atomic Research Centre
Radiation Biology and Health Sciences Division

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Sub: Brief summary of research worksubmitted by Ms. Archita Rai for the Sun Pharma Science Foundation Science Scholar Awards 2023

Ms. Archita Rai is pursuing doctoral work entitled "Modification of Nrf-2 activity in radio-resistance and inflammatory responses". Under this project, she has addressed the problem of radio-resistance in lung cancer which is a clinical challenge faced by oncologists and researchers. Role of Nrf-2 in managing oxidative stress and cellular redox balance is well-established. Nrf-2 expression is found to be altered in ~25% lung cancers (Sanchez-Vega, Francisco et al., Cell, 2018) and high expression of Nrf-2 is associated with relatively poor prognosis in lung adenocarcinoma patients (Wang, Qingsong et al., PLoS One, 2020). Nrf-2 inducers like dimethyl fumarate, bardoxolone methyl, oltipraz, and sulforaphane have been studied substantially and have been approved or are in various stages of clinical trials for disorder like multiple sclerosis, cancers, renal and inflammatory diseases (Yagishita, Yoko et al., Antioxidants, 2020). Nrf-2 hyperactivation in lung cancers leads to radiotherapy resistance. To address this, she used Nrf-2 inhibitor Clobetasol propionate (CP) as a candidate radio-sensitizer. A series of in vitro studies were conducted to show that CP induced significant radio-sensitization in Keap-1 mutant human lung cancer cells and in spheroid model. CP inhibited Nrf-2 expression, nuclear translocation and activity. The radio-sensitizing activity of CP was also observed in vivo. CP being an FDA-approved drug expedites clinical reach as radio-sensitizers. Transcriptomic analysis revealed ferroptosis as one of the modes of cell death regulated by Nrf-2 in CP mediated radiosensitization. This was confirmed by morphological changes, increased lipid peroxidation, decreased expression of GPX-4, higher release of free iron and also using ferroptosis inhibitors. The project also highlighted the role of mitochondrial ROS in ferroptosis.

Overall, the project has helped in identification of a novel radio-sensitizer and also enhanced the understanding of ferroptosis in radiation mediated cancer cell killing.

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