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Activation of p53 pathway in combination with photon irradiation for treatment of cancer

Medulloblastoma (MB) and glioblastoma (GB) are highly aggressive brain tumours that exhibit substantial resistance to radiotherapy, largely due to impaired DNA damage repair mechanisms. The cellular response to radiation-induced DNA double-strand breaks (DSBs) is a critical determinant of radiosensitivity. This study investigated the effects of the MDM2 inhibitor AMG232 in combination with photon irradiation on DNA damage signalling in MB and GB cell lines using γH2AX foci analysis. Photon irradiation induced a clear dose-dependent increase in γH2AX foci across all cell lines, confirming effective DSB formation. Treatment with AMG232 resulted in prolonged persistence of γH2AX foci, particularly in MB cell lines, indicating delayed or compromised DNA repair. Residual foci detected at later time points suggest increased reliance on error-prone repair pathways, notably non-homologous end joining (NHEJ), especially in G0/G1-arrested cells. In contrast, GB cell lines exhibited sustained γH2AX foci levels irrespective of AMG232 treatment, consistent with intrinsic radioresistance. These findings demonstrate that AMG232 enhances radiosensitivity primarily by extending DNA damage signalling rather than increasing initial DNA damage, highlighting impaired repair kinetics as a key mechanism influencing treatment response in aggressive brain tumours.

Primary author: MALULEKA, Musa

Co-authors: Dr NEMANGWELE, Fhulufhelo (University of Venda); Dr ENGELBRECHT, Monique (iThemba LABS and UWC); Dr FISHER, Randall (Division of Radiation Biophysics, NRF iThemba LABS)

Presenter: MALULEKA, Musa

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