TIMOTHY A. JOHNSON MEDICAL SCHOLAR LECTURE SERIES

Presented by the Fralin Biomedical Research Institute at VTC and the Virginia Tech Carilion School of Medicine

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Mechanism of Treatment Resistance in Human Glioblastoma

The standard therapy for Glioblastoma (GBM), the most lethal primary brain tumor, has been surgical resection followed by chemoradiation and adjuvant temozolomide (TMZ).
However, the survival of patients with GBM remains unacceptably low at 16-18 months with little improvement over the last 20 years. This is due to a high level of resistance to therapy attributing to tumor heterogeneity, and intrinsic tumor cell resistance and tumor environment suppression. The cytotoxicity of TMZ is mediated by its addition of methyl groups at N^7 and O^6 sites on guanines and the O^3 site on adenines in genomic DNA. In approximately 60% of patients, O6-methylguanine (O6-MetG) is rapidly removed by O6-methylguanine-DNA methyltransferase (MGMT), conferring resistance to TMZ chemotherapy. Thus, inhibition of TMZ-induced DNA damage repair represents an attractive strategy for potentiating the activity of TMZ. Yung's lab has discovered a unique function of Poly-ADP-ribose polymerase (PARP) inhibitor in reversing tumor resistance to TMZ chemotherapy in patients with MGMT unmethylated GBM: blocking BER/SSBR pathway to repair TMZ induced N^7-Met and O^3-MetA, and more importantly, suppressing MGMT activity to repair O6-MetG, resulting in augmented TMZ cytotoxicity. The lab also demonstrated EGFR amplification could serve as a biomarker for PARP inhibitor activity. Based on these data, the lab is planning clinical trials to test the combination of TMZ and a brain penetrant PARP inhibitor in MGMT unmethylated GBM.

FRIDAY, APRIL 16, 2021 at 1:00 p.m.

This seminar will be webcast live at https://fbri.vtc.vt.edu/events/live-webcast.html and via Zoom at https://virginiatech.zoom.us/j/88901202830.