Targeting MGMT to Treat Therapy Resistance and Metastatic Melanoma Growth

Santhi D Konduri1,2, Dmitry Bosenko1,2, Deborah L Donohoe1,2, Maharaj Singh1,3, Richard A Rovin1,2 and George C Bobustuc1,2

1 Advocate Aurora Research Institute, Milwaukee, WI, 2 Aurora Neurosciences Innovation Institute, Milwaukee, WI, 3 Marquette University, Milwaukee, WI.

PROBLEM
Melanoma is one of the most aggressive form of skin cancer leads to 80% of skin cancer related deaths. The current standard of care includes combination of BRAF/MEK inhibitors which improves the prognosis for melanoma patients, but most patients do not show lasting response to this treatment.

RESULTS
The combination therapy significantly inhibited the growth of primary as well as metastatic melanoma growth compared to single agents, or combination of BRAF/MEK inhibitors. The combination therapy significantly inhibited MAPK signaling pathway to inhibit the melanoma growth. We show that triple lock – upstream and downstream, along the MAPK pathway - effectively restores durable BRAF and MEK inhibitor activity and significantly sensitizes melanoma cells to Temozolomide. The advantage of a multiple lock approach on the MAPK pathway is substantiated by the lack of signaling cross talk. MGMT is interacting with oncopage (cMYC) to promote the melanoma growth.

CONCLUSIONS
- In this study, we showed that combination of BRAF, MEK and MGMT inhibitors significantly inhibited primary as well as metastatic melanoma tumor growth.
- Combination therapy significantly inhibited MGMT, BRAF - MEK Pathway and induced PARP cleavage to inhibit melanoma growth.
- MGMT is interacting with c-Myc to promote melanoma growth

OBJECTIVE
O6 methylguanine DNA methyltransferase (MGMT) is a DNA repair protein over expressed in majority of cancers including melanoma. The purpose of this study is to show that MGMT inhibition not only decreases drug mediated resistance, but also inhibits the primary and metastatic melanoma growth.

METHODS
In this study, we used BRAF-mutated(V600E) primary and metastatic melanoma cells to investigate the combination therapeutic effect (Dabrafenib, Trametinib, Disulfiram/Cu, and Temozolomide) using cell viability assay. We also investigated the effects of these drug combinations on effector molecules of the BRAF/MAPK signaling pathway associated with melanoma by western blot analysis and furthermore, MGMT interacting partners that promotes melanoma growth was detected by protein-protein interaction.

REFERENCES