Combined inhibition of nicotinamide phosphoribosyltransferase (NAMPT) and poly (ADP-ribose) polymerase (PARP) impairs glioblastoma cell growth

Lee Hwang MD1,2, Yu-Ting Su PhD3, Michael Vogelbaum MD PhD2, Mark Gilbert MD1, Jing Wu MD PhD1
1 Neuro-Oncology Branch, Center for Cancer Research, National Cancer Institute, Bethesda, Maryland, 20892, USA
2 Brain Tumor and Neuro-Oncology Center, Department of Neurological Surgery, Cleveland Clinic, Cleveland, Ohio, 44195, USA

**Introduction**

- Glioblastoma is aggressive with poor prognosis
- Due to heterogeneous and highly aggressive nature of glioblastoma, improvement in clinical outcome is more likely when multiple treatment modalities are combined
- In glioblastoma, NAD is constantly required for rapid proliferation and high energy requirements
- Main source of cellular NAD is from salvage pathways
- Nicotinamide is main niacin-derived NAD precursor and converted to nicotinamide mononucleotide by rate-limiting nicotinamide phosphoribosyltransferase (NAMPT)
- NAMPT also regulates poly (ADP-ribose) polymerase (PARP), which is crucial for DNA repair
- *NAMPT* gene is highly overexpressed in glioblastoma
- Inhibition of NAMPT and PARP can act synergistically to prevent repair of DNA damage and promote cell death, representing a treatment strategy in glioblastoma

**Methods**

- NAMPT expression was determined in multiple human glioblastoma cell lines and normal human astrocytes (NHA) by Western blotting
- Human glioblastoma cell lines were treated with FK866 (NAMPT inhibitor), Olaparib (PARP inhibitor), or combination for 72 hours prior to cell viability assays to analyze dose-dependent cytotoxicities
- Combination index plots were used to evaluate synergism
- Potential mechanisms underlying cytotoxicity were evaluated by Western blotting

**Results**

- **NAMPT is strongly expressed in multiple glioblastoma cell lines**
  - U251, LN229, LN18, GSC827, HS683, GSC923, NHA

- **NAMPT inhibitor causes decrease in cellularity**
  - U251 cells, not treated (20X)
  - U251 cells, treated with 30 nM FK866 (20X)

- **Combination treatment enhances cytotoxicity in human glioblastoma cells**

**Mechanisms of cytotoxicity**

- NAMPT activity is decreased after combined treatment

- **Inhibition of NAMPT and PARP has a synergistic effect**

**Conclusions**

- FK866 and Olaparib synergistically cause cytotoxicity in glioblastoma cells by inducing autophagy and DNA damage
- Combined treatment is more effective than single-agent therapy, representing a promising therapeutic strategy

**Future Directions**

- Toxic effects on NHA are concerning and warrant further investigations to determine a precise therapeutic window in preclinical models
- Animal model for optimal drug delivery to bypass the blood-brain barrier and minimize systemic toxicity is currently under development

**Acknowledgement**

Financial support was provided by the Intramural Research Program of the National Institutes of Health, National Cancer Institute