ET-58. THE GENETICALLY ENGINEERED CLOSTRIDIUM NOVYI-NT IS EFFICACIOUS IN THE TREATMENT OF INTRACRANIAL GLIOBLASTOMAS
Verena Staedtke1,2, Renyuan Bai1, Kenneth Kinzler2, Shibin Zhou2, Bert Vogelstein2, and Gregory Riggins1; 1Department of Neurology & Neurosurgery, Johns Hopkins University School of Medicine, Baltimore, MD, USA; 2Department of Oncology, Sidney Kimmel Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Glioblastomas (GBM) exhibit a remarkable histopathologic heterogeneity with extensive necrotic regions intermixed with cell proliferation that generate local hypoxia and thus, limit the effectiveness greatly of traditional cancer therapies. The spore-forming bacterium Clostridium spp., however, has the ability to precisely target and lyse tumor cells in hypoxic environments. Here we show that Clostridium novyi-NT (C. novyi-NT), an engineered strain devoid of the lethal alpha-toxin, induces a microscopically tumor-localized response in orthotopically implanted syngeneic F98 and human xenograft 060919 rat GBM models. Both, intravenous and intratumoral, injections of C. novyi-NT spores resulted in germination within 24 hours and a rapid fall in luciferase activity, an indicator of tumor burden, in both animal models. C. novyi-NT germination was evidenced by the appearance of vegetative forms of C. novyi-NT bacteria. Strikingly, C. novyi-NT precisely localized to the tumor and micro-invasive tumor islands buried in the normal brain parenchyma, sparing adjacent normal cells only a few microns away. This bacterial “biosurgery” led to a significant survival advantage in these extremely aggressive rat models. Brain edema and increased intracranial pressure as a result of C. novyi-NT infection was common and medically managed while brain abscess formation was not clearly observed with appropriate use of antibiotics. Abscessation, however, is a potential side effect and can develop in human patients possibly requiring neurosurgical abscess drainage, a routine clinical procedure. In summary, C. novyi-NT can act as a tool to precisely eradicate GBM and significantly extend survival. Despite concerns on treatment-related toxicity, bacterial C. novyi-NT treatment may have a place in selected GBM patients in the future given the lack of alternative therapy options and dismal prognosis.