Lay Abstract

Malignant glioblastoma is one of the most aggressive of human tumors and is difficult to control by conventional surgery, radiotherapy, or chemotherapy. More recently introduced cytotoxic photodynamic therapy (PDT) has advantages over other glioblastoma treatments, but still has limitations, a key one being treatment-induced resistance and greater growth/migration/invasion rates of residual and/or bystander cells largely due to nitric oxide (NO) from inducible NO synthase (iNOS). These negative effects were first described in neuroblastoma tumor by PI and collaborators. PDT is more effective when combined with low level chemotherapy, e.g. cisplatin, but again, iNOS/NO acts antagonistically. Preliminary experiments with glioblastoma and other cancer cells demonstrated that inhibitors of iNOS enzymatic activity only partially suppress the described negative effects. In this project, we will explore a new approach for curbing iNOS/NO which we postulate will be much more effective than inhibition of iNOS activity. This approach involves pharmacologic inhibition of BET bromodomain epigenetic “reader(s)” of an acetylated lysine (KAc) on subunit p65 of transcription factor NF-κB, which we have shown regulates iNOS transcription in PDT-stressed glioblastoma cells. Ability of BET inhibitors (JQ1, I-BET762) to restrain acquired resistance/aggressiveness after PDT and combined cisplatin/PDT will be investigated, using human glioblastoma cells (U87, U251) in 2D monolayer (Aims 1 and 2) and in more tumor-like 3D spheroid format (Aim 3). This is the first study to test BET inhibitor ability to overcome iNOS/NO antagonism in any type of cancer therapy. In addition to being highly significant and innovative, this project has great translational potential, since several BET inhibitors are now in cancer clinical trials