Design, Synthesis and Structure-Activity Relationships of Small Molecule ER-β Agonists for Glioblastoma (GBM) Therapies

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Although the incidence of glioblastoma (GBM) in the United States is only 4.7 per 100,000 the devastating nature of this disease cannot be overstated with 5-year prognosis approaching 5%. There are no agents with proven survival benefit in the recurrent setting with anti-angiogenic or further alkylating therapy often chosen in the absence of better drugs. At issue remains the selective permeability of the blood brain barrier (BBB) to pharmaceutical intervention, the heterogeneous and immunosuppressive nature of the glioma microenvironment, and the associated morbidity of tumors with central nervous system (CNS) involvement. Our teams preliminary studies suggested that GBM selectively express estrogen receptor β (ERβ) and demonstrated that ERβ agonists exert tumor suppressive functions in GBM. Our results also demonstrated that ERβ knockout increases GBM GSC representation whereas overexpression results in loss of GSCs. Thus, the goal of this highly collaborative and multi-disciplinary program is to develop novel, potent, and CNS penetrant ERβ agonist with therapeutic potential and thus create a new paradigm of using ERβ specific agonist as novel therapy for curbing GBM progression. This seminar will focus on the development of structurally-novel ERβ specific agonists to help support translational studies and advance the program toward a viable clinical candidate. The seminar will focus on the design, synthesis and iterative structure-activity relationship (SAR) studies to improve the ER-β potency and physicochemical properties of lead compounds. In vivo efficacy in GBM models and pharmacokinetic profiles of two lead compounds, CIDD-0149897 and CIDD-0150184, will also be presented.