**DOTTORATO DI RICERCA IN BIOLOGIA CELLULARE E DELLO SVILUPPO (38° Ciclo)**

**Proposta di progetto per una borsa Dottorato Sapienza Linea di ricerca principale “Gruppo Neurobiologia dello sviluppo”**

**Titolo della ricerca:** Interaction between M2 muscarinic receptor and β1-arrestin in human glioblastoma: implication in cell proliferation and migration

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**Summary (max 300 parole)**

Glioblastoma multiforme is the most frequent malignant astrocytic tumor. A key feature of malignant gliomas is their cellular heterogeneity. In particular, the presence of an undifferentiated cell population defined Glioblastoma Stem cells (GSCs) has been reported. GSCs are considered the main cell population responsible for the beginning of neoplastic process and recurrence formation. Several studies report how muscarinic receptors (mAChRs) are involved in the regulation of cell cycle, chemotaxis and angiogenesis of brain tumors. For years, our research group has been studying the antiproliferative effects of M2 mAChR activation in different tumors, such as glioblastoma, neuroblastoma and breast cancer [1]–[5]. Our previous data have showed that the activation of M2 mAChR by orthosteric agonist Arecaidine Propargyl Ester (APE) caused a significant decrease of cell proliferation and survival in GSCs [2]. In our lab we have also characterized the N-8-Iper (N8), a dualsteric agonist able to activate M2 mAChR with higher affinity than APE. N8 is able to induce a pro-apoptotic and cytotoxic effect already at low doses [3]. These results suggest that N8 may be a promising therapeutic drug for the treatment of glioblastoma, reducing possible side effects of the high doses. M2 mAChR belongs to the class of G-protein-coupled receptors (GPCRs). After activation, GPCR signaling is mediated by G-proteins and is followed by their rapid desensitization. This process is mainly orchestrated by GPCR kinases and β-arrestins [6]. Recently, new roles for the β-arrestins were proposed. These proteins, upon activation of a GPCR, are in turn able to activate several signaling pathways relevant for the tumor progression, such as cell proliferation, cytoskeleton remodeling, migration and angiogenesis [7,8]. Based on this evidence, the aim of this project will be to study the signaling pathways downstream of the M2 mAChR activated by APE or N8, focusing on the possible interaction between M2 and β1-arrestin and the possible implication in glioblastoma cell proliferation and migration.

**Lavori pubblicati negli ultimi 5 anni dal docente richiedente la borsa**

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