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### The Novel Role of GABAB and CXCR4 in Medulloblastoma

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## **The Colocalization of GABA<sub>B</sub> and CXCR4 in Medulloblastoma**

Philip Habashy, Dorota Lubanska, Lisa A. Porter, Huiming Zhang

Medulloblastoma (MB) is the most common malignant pediatric brain tumor and it occurs in 16-25% of diagnosed cases, with a higher incidence in children aged 1 to 9 years old. The current standard of care consists of multiple stages of therapy including surgery, irradiation, and chemotherapy. However, a subset of tumors with a still devastating prognosis remains.

Metabotropic receptors are G-protein coupled receptors (GPCRs) that act as second messengers.  $\Gamma$ -aminobutyric acid B receptors (GABAB) and C-X-C chemokine receptor type 4 (CXCR4) are metabotropic receptors that belong to the C-family of GPCRs and are activated by the neurotransmitters,  $\gamma$ -aminobutyrate (GABA) and stromal-cell derived factor; SDF-1 (CXCL12), respectively. GABAB receptors are heterodimers where GABA binds to a B1 subunit, and the B2 subunit is coupled to G-proteins regulating activities of the Ca<sup>2+</sup> channels, K<sup>+</sup> channels, and adenylyl cyclase (AC).

Previous studies showed that CXCR4 is highly expressed by glial and neuronal cells in the central nervous system (CNS) and GABAergic neurons. Evidence shows that CXCR4 is overexpressed in MB and upon administration of a CXCR4 antagonist significantly decreased the cell proliferation rate in Type II MB. Evidence also proved that CXCR4 and GABA<sub>B</sub> can crosstalk and GABA<sub>B</sub> was found to be highly expressed in Type II – MB showing increased Ca<sup>2+</sup> levels and protein receptor localization. Current results show that upon administration of the GABA<sub>B</sub> agonist; baclofen increased cell proliferation in Type II MB cells. Moreover, immunofluorescence showed increased levels of GABA<sub>B</sub> during mitotic division. In conclusion, by administering the antagonist; phaclofen would enhance the efficacy of chemotherapeutic treatments on MB patients by decreasing the proliferation rate of the aggressive tumors.