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RESEARCH CONNECTION

Targeting high-grade brain tumors using rational drug design

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Why this research is important

Malignant glioma is a lethal cancer of the central nervous system. The most biologically aggressive subtype, glioblastoma multiforme (GBM), is a World Health Organization grade IV astrocytoma associated with a 3-year survival of less than 3%, and a median survival of 12 -15 months. The current standard of care encompasses surgical resection, chemotherapy (temozolamide) and radiation therapy. Although >95% of the tumor can be removed with surgery, glioma cells moving away from the core leads to the formation of tumors at secondary sites within the brain. By understanding biochemical mechanisms of these cells, the overall goal of our work is to improve the lives of patients with GBM through the design and the preclinical testing of novel therapeutics.

What you need to know

We are working towards understanding glioma cell migration with the purpose of developing novel therapeutics to combat the disease. Little is known about the molecular mechanisms of cancer cell invasion. Our research works towards understanding the matrix metalloproteinase, a family of enzymes that are involved with clearing a path for cancer cells to invade. The overall goal of this work is to develop therapeutic agents to prevent the migration of human glioma cells.

How the research is being done

Areas of scientific expertise within our group include biochemistry, glioma biology, proteomics, bioinformatics, organic and medicinal chemistry. Using an established model of glioma cell migration, we have observed that highly motile gliomas will promote movement by releasing enzymes into their environment. Associated with glioma invasiveness, we have identified more than 100 proteins for further characterization. Amongst these, members of the matrix metalloproteinase family were observed. The matrix metalloproteinases are proteases involved with normal development and tissue remodeling. The extracellular matrix is a complex network of proteins and polysaccharides that make up structural elements of tissue. In glioma (and other forms of cancers), the matrix metalloproteinases are implicated in

disease progression. Using this information, we are now developing novel small molecules and peptide-based inhibitors. Using a 'lock and key' approach, compounds are designed to specifically bind and inhibit these enzymes with the hope they will obstruct the movement of GBM cells. Signaling pathways downstream of drug inhibition will be further characterized to identify additional targets for therapeutic development. Ongoing collaborations include BU researchers Dr. Eric Bushnell (Dept. of Chemistry) and Mousumi Majumder (Dept. of Biology).

How this research can be used

GBM is most common type of primary malignant brain tumor. Average survival, even with aggressive treatment, is less than one year. Therapeutic agents and research within this area is urgently needed. To address these needs our work has four principal aims: (1) The design, development, and preclinical testing of therapeutic agents; (2) Knowledge transfer and collaboration; (3) The promotion of brain tumor research and training in Manitoba; and (4) Technology development.

About the researchers

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Alisha Poole and Emmanuel Ojefua are graduate students in the Master's of Environment and Life Sciences at Brandon University.

Publications based on the research

Aftab, A., Mesnil, M., Noordenbos, J., Stoynov, N., Strale, P.-O., Naus, C. C., Chey, W., & Chen, V. C. (2017). *Conditioned Media from Cx43-expressing Cells Enhances Migration of C6 Glioma*. Manuscript submitted for publication.

Keywords

Glioma; cancer invasion; glioblastoma multiforme (GBM); drug design; proteomics; chemistry; biochemistry; cancer cell biology

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This research project has been approved by the Brandon University Research Ethics Committee.