**Background:**

Diffuse astrocytomas are classified by the World Health Organization (WHO) as a grade ii glioma accounting for 10-15% of all astrocytic brain tumours and 25% of all gliomas.$^{[14,15]}$ These low-grade gliomas are relatively slow growing with a median survival time of 5-7 years and their current standard of care is primarily maximal surgery resection follow by radiation and/or chemotherapy.$^{[16,17]}$ However, due to the infiltrative nature into the surrounding cerebral tissue of these astrocytic tumours, total resection is difficult to achieve and in many cases recurrence and malignant transformation into higher grade gliomas are observed.$^{[17,18]}$ Thus, controversy remains pertaining to the best therapeutic management for grade ii gliomas.

A significant challenge for developing effective treatments for astrocytomas, as with other cancers, is the blood-brain barrier (BBB). Formed of endothelial cells lining the cerebral microvasculature, it controls the movement of substances and regulates the volume and composition of fluid surrounding the brain restricting the passage to only fat-soluble substances. The BBB is the main reason behind the complexity in treating brain tumours, as it prevents many drugs from crossing into the brain parenchyma.

Due to the lack of success previous techniques have experienced in bypassing the BBB, a non-invasive intranasal delivery of medication for brain tumour treatment proves to be an interesting alternative for circumventing said barrier. This intranasal technique is a remarkable adjuvant treatment to surgery and allows for the precise targeting of the gliomas without affecting healthy tissue.$^{[9]}$ Thus, the following proposal addresses intranasal administration of medication that could provide a potential solution to the treatment of diffuse astrocytomas.

**Hypothesis:**

Intranasal administration of telomerase inhibitor GRN163 will be effective in delaying the growth of Connie’s diffuse astrocytoma, and perhaps treating it.

**Specific Aims:**

I. Finding an effective and non-invasive method of bypassing the BBB by using intranasal delivery of telomerase inhibitor GRN163 to treat diffuse astrocytomas.$^{[9]}$

II. Providing Connie with viable clinical trials using the intranasal administration of GRN163 as treatment for her astrocytoma thus addressing Connie and her family’s concerns about current clinical trials for which she may be eligible.$^{[9]}$

**Research Question:**

The inconclusive struggle of bypassing the BBB: Although transmembrane diffusion has proven somewhat conclusive, many variables affect the efficiency of this method: blood flow in the cerebrum, protein binding within the blood, the BBB itself disallowing substances from entering and the similar behaviour of surrounding tissue, et cetera.$^{[6]}$ Pharmacokinetics and the creation of lipid soluble carriers for medication have been attempted, yet have been ineffective for the transport of substances across the BBB.$^{[5]}$

Circumventing the BBB intranasally and its benefits: The circumvention of the BBB intranasally is owed to the anatomical connections of the olfactory nerve fibers of the olfactory bulb and trigeminal nerves.$^{[9,13]}$ Through this passageway, therapeutic agents
do not require modification or a carrier to transport them across the BBB, for intranasal administration allows all substances to bypass the BBB, small molecules and macromolecules alike.\textsuperscript{13} The nasal mucosa, which is susceptible to leakage due to the constant replacement of olfactory receptor neurons, and the central nervous system (CNS) quickly become available through this passageway, due to their connections with the prior mentioned nerves.\textsuperscript{9,13} After only a few minutes, the intranasally delivered drugs reach the brain parenchyma, spinal cord, and cerebrospinal fluid (CSF), through an extracellular route found within the perineural and/or perivascular channels along the above mentioned nerves.\textsuperscript{9} This provides the simple benefits of self-administration and painlessness; thus, this is therapeutically relevant and provides patients with an even wider range of solutions for their brain tumours.\textsuperscript{9}

Contrary to chemotherapeutic agents, an oligonucleotide telomerase inhibitor / antagonist, as with GRN163, can target tumour tissue while leaving healthy tissue unscathed.\textsuperscript{3,9} In prior studies, not only was the delivery of GRN163 precise, it also inhibited the growth of the brain tumours in humans, for telomerase forms one of the enzymes most found within the brain tumour cells.\textsuperscript{9} Telomerase inhibitors, including GRN163, as the above mentioned, are currently found in clinical trials.\textsuperscript{9}

**Methodologies:**

GRN163 should be observed within the brain for a period of 24 hours, as in past studies with human intracerebral glioblastoma xenografts, in a clinical trial setting.\textsuperscript{10} After 4 hours of administration into the nasal cavity, the concentration of GRN163 is at its highest which shows considerable retention, perhaps due to the efficiency with which GRN163 binds with the telomerase enzyme.\textsuperscript{10} The treatment that should be used is the maximum dosage of GRN163 that can be dissolved in saline solution for intranasal administration, at 0.65 μmol / 65 μl.\textsuperscript{10} However, a proper dosing schedule has yet to be created, and this will be affected by the type and size of the tumour.

**Hypothesized Results:**

Hypothesized is the effective intranasal administration of GRN163 in a post-surgical adjuvant treatment to treat patients with diffuse astrocytoma. It can be believed that Connie, and other patients with low-grade gliomas, would consider this clinical trial appropriate to her condition, for it is non-invasive and has proven to leave healthy tissue untouched. Thus, through the dissolvable maximum dosage of GRN163 in a saline solution, intranasally delivered, this substance would reduce telomerase activity and combat the enzymatic component of the astrocytoma.

**Rationale for Proposed Research / Therapeutic Relevance:**

This particular study is innovative and supportive on the goals of brain tumour research for it addresses a non-invasive method of medication administration to the brain, one that does not require to bypass the BBB. In this way, it also provides a safer alternative for patients suffering from brain tumours, and provides them with more treatment options depending on the type and placement of the tumour. This study would allow for further studies to be conducted, for this more modern approach to tumour treatment has only been briefly experimented with in the history of brain tumour research, and thus many more ailments could be treated using intranasal administration. This should thus be considered for it would allow for new branches of both research and therapy to be at the disposal of patients, as it became for Connie.
References:

2. “Angiogenesis.” CancerQuest, Emory Winship Cancer Institute, www.cancerquest.org/cancer-biology/angiogenesis?gclid=CjwKCAjw14rbBRB3EiwAKeoG_DWj--svlgiQvTvb9N2NsPpVTNaQyr2XqT5Sj95YOqhWE5HrlYY3RoCJX0QAyvD_BwE.
