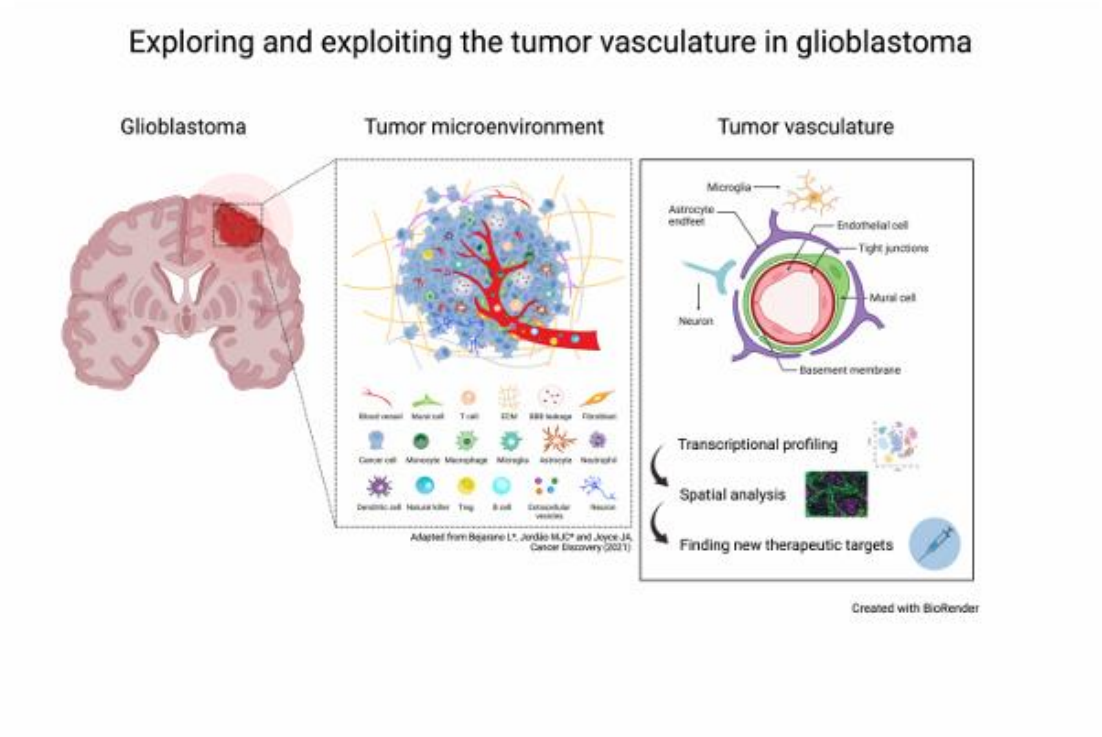
Integrated analysis of tumor vessels and immune cells in glioblastoma



Glioblastoma (GBM) is the most common and deadliest type of primary brain tumor, with an average survival of just over one year following diagnosis. Traditional approaches to treating GBM have mainly focused on targeting and removing the cancer cells through surgery, radiation, and chemotherapy. However, despite these combined treatments, GBM almost always recurs. To combat this, we need to broaden our understanding and consider the role of other cell types that are found in these aggressive tumors – not just the cancer cells themselves. These include various immune cells and blood vessels that the GBM exploits to support its growth and aggressiveness. Collectively, this can be thought of as a complex interconnected cancer ecosystem – which we call the tumor microenvironment (TME). Our lab's research has centered on studying the TME, which offers a fresh perspective in the field of GBM research. By deeply investigating the diverse cells in the TME, we aim to develop novel and effective treatments that specifically target these deadly cancers.

Recent studies, including from our lab, have revealed the importance of the brain TME, including different types of immune cells, in regulating the progression of primary brain tumors, as well as tumors that have spread to the brain from other organs – known as brain metastases. The blood-brain barrier (BBB) is another crucial component of the TME, unique to the brain. It is formed by several cell types including endothelial cells, mural cells, astrocytes, and microglia. The BBB acts as a protective shield, guarding the brain against infections and preventing the entry of harmful substances. However, GBMs can hijack the BBB and employ various mechanisms to augment the blood supply that nourishes the growing tumor. This results in the formation of a twisted and dysfunctional network of vessels known as the blood-tumor barrier. This abnormal vasculature plays a key role in promoting the progression of GBM and its invasion into healthy brain tissue.
An exciting new approach is to combine strategies that target blood vessels with immunotherapy, which aims to activate the immune system to detect and fight cancer. This approach is based on the observation that the tumor vasculature can specifically control the infiltration of distinct immune cell populations into tumors - for example, as reported in ovarian and colorectal cancers. However, to date, this perspective has not been extensively explored in brain tumors.

In this project, our goal is to explore the mechanisms underlying tumor vascularization in GBM. To achieve this, we will perform a comprehensive analysis of the key components of the tumor blood vessels using state-of-the-art techniques. We will examine the gene expression of endothelial and mural cells isolated from human GBM and non-tumor samples through sequencing, and we will also analyze the spatial relationship between immune cells and the tumor vessels using imaging methods. Additionally, we will use data recently generated in our lab for brain metastasis (BrM) samples to understand the similarities and differences between primary and metastatic brain tumors. This project will be critical for deepening our understanding of how blood vessels form in different tumor types within the brain and for exploring novel therapeutic approaches to combat these devastating tumors.