A tumor is not just an assembly of cancer cells but an entire microenvironment composed of many different cell types that communicate with one another. These cells help the tumor grow, form new blood vessels, and weaken the immune system, which normally protects us from the disease. This complex system is highly dynamic and changes in response to therapy, often reducing treatment effectiveness and promoting disease recurrence. Targeting such mechanisms is particularly important in malignant gliomas, the most common and incurable primary brain tumors. As they develop in an organ essential for life, they can rarely be completely surgically removed. The glioma cells that remain after surgery give rise to tumor regrowth, and recurring tumors are even more difficult to treat. Standard therapy, which includes surgical resection and radiotherapy (usually combined with temozolomide chemotherapy), extends patient survival by only a few months, and less than 20% of patients survive longer than one year after diagnosis. Immunotherapies, which help the body fight disease using its own immune system, and have been a breakthrough in other types of cancer, have so far been ineffective in gliomas due to the profoundly suppressed immune responses within the tumor.

We showed that macrophages and microglia, the first-line defenders of the immune system that accumulate within the brain tumor, play a key role in this process. In gliomas, these cells become “reprogrammed” and, instead of helping to eliminate the tumor, send signals that suppress immunity. We have recently discovered the way to redirect them onto the correct path and restore their anti-tumor immune activity. We developed a synthetic peptide (7aaRGD) that blocks receptors called integrins, important mediators of communication between cells in the tumor microenvironment. **The goal** of this project is to determine whether 7aaRGD will function as an immune “switch” in mouse models of glioma that closely resemble human disease and are resistant to immunotherapy. We will examine the effects of 7aaRGD on immune cells within the tumor, assess whether irradiation (radiotherapy) alters its activity, and test whether combining the peptide with other therapies improves treatment outcomes. We will analyze both tumor size in experimental animals and thoroughly characterize immune responses and other changes occurring within the tumor microenvironment. By targeting a root-cause of the disease, we expect to demonstrate that integrin blockade can enhance the efficacy of immunotherapy and/or radiotherapy. We believe that advancing our understanding of these processes, together with validating the activity of the 7aaRGD peptide activity, will help pave the way toward more effective treatment strategies for gliomas. This project may represent an important step toward developing new, more successful therapies for patients facing this highly challenging malignancy.