Project Title: Targeting complement signaling in glioblastoma
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In the U.S., approximately 200,000 patients per year will receive radiation- and chemotherapy for brain cancer. Studies have shown the adverse side effects of these therapies on cognition that badly impact the quality of life (learning, memory, attention, multi-tasking, planning). This is a particularly serious problem for survivors of childhood cancer who frequently live long lives but experience reductions in I.Q. by as much as 3 points per year. Unfortunately, few if any effective treatments exist for radiation therapy-related cognitive deficits, making this an unmet medical need for millions of cancer survivors. Our study will provide novel insights into the mechanisms by which radiation therapy impacts brain function and leads to cognitive impairments. Using a mouse model, we will determine how radiation disrupts inflammatory communication for brain's immune cell - microglia - by a series of unfortunate molecular events. Our recent experiments found that radiation exposure activates signaling proteins termed as the complement system. This system comprised of about 30 proteins in the body and play important roles in the prevention of viral or bacterial infections. In the brain, complement system helps in maintaining memory units (synapses) of neurons - that forms memory. Radiation exposure to the brain leads to uncontrolled activation of microglia and complement proteins (such as complement C5a) that eventually forms an inflammatory complex called anaphylotoxin. Our studies using a drug (PMX205) targeting C5a receptors on microglia found that disruption of complement signaling is neuro-protective against radiation injury. This drug can be taken orally and it has shown beneficial effects on cognition and inflammation in Alzheimer's disease mouse models. In the current study we propose to determine if combined treatment with radiation and PMX205 will provide an efficient solution to kill cancer as well as preserve normal brain function. This drug is currently being tested in other human neurological conditions and showed very good safety profile. Thus, if successful, our project will lay the foundation for novel therapeutic interventions designed to thwart cancer without damaging the brain.