**Adenosine kinase inhibition therapy for radiation-induced cognitive dysfunction**

Clinical radiation therapy for the treatment of CNS cancers leads to unintended and debilitating impairment in cognition that adversely impacts quality of life. Pediatric cases are of particular concern, as children treated with cranial radiotherapy can lose up to 3 IQ points/year and often live long lives post-cancer. Therefore, with the exception of survival, cognitive impairment resulting from the clinical management of brain and other cancers may well be the most critical criterion for evaluating therapeutic outcome and for determining long-term quality of life. Early onset or more severe cognitive dysfunction involves a range of neurodegenerative effects including a decline in neurogenesis, oxidative stress, compromised neuronal structure and astrogliosis. However, the molecular and cellular mechanisms underlying radiation-induced cognitive decline have not been resolved.

Astrocytic networks in the brain provide metabolic clearance of surplus neurotransmitters and signaling metabolites such as adenosine. Extracellular adenosine is tightly regulated by astrocytic adenosine kinase (ADK). ADK overexpression is linked to astrocyte activation and depletes extracellular adenosine. Adenosine deficiency in turn limits endogenous neuroprotection in the brain and has causally been linked with cognitive impairment. Even a subtle change in ADK expression can rapidly translate into major changes in adenosine that may significantly impact neuronal function. However, the impact and consequences of radiation therapy on adenosine homeostasis are currently largely unknown. Our immunohistochemical analyses of irradiated rat brains showed significant elevation of ADK levels with corresponding increases in astrogliosis in the hippocampus. We therefore hypothesize that *altered adenosine / ADK dynamics play important roles in the perpetuation of radiation-induced cognitive dysfunction*. Importantly, transient pharmacological inhibition of ADK activity via systemic injection of 5-iodotubercidin prior to irradiation can ameliorate cognitive impairments in rats exposed to a single dose (10 Gy) of cranial irradiation long-term, providing the ***first evidence*** that therapeutic manipulation of adenosine homeostasis can be used effectively to improve the effects of radiation-induced tissue damage in the brain.

To understand better the mechanistic regulation of astrocyte-mediated adenosine/ADK modulation, we propose to utilize pharmacologic ADK-inhibitor (ABT-702, oral route) to study the CNS-radiation response and its impact on cognitive function. Correspondence of elevated ADK expression and astrogliosis post-irradiation, indicate a critical role of the astrocytic compartment in the regulation of the extracellular adenosine pool. Our translational approach provides useful and selective tool to mechanistically dissect the importance of adenosine/ADK in the neuropathology of radiation-induced cognitive dysfunction.

**Specific Aim 1:** Ascertain the effectiveness of pharmacologic ADK inhibition (ABT-702, oral route) to mitigate radiation-induced cognitive dysfunction.

**Specific Aim 2:** Determine the impact of cranial irradiation and ADK inhibition therapy on astrogliosis, neuroinflammation, and ADK, adenosinergic receptor protein and gene expression.

Our proposal represents a critical *unexplored link* between radiation-induced modulation of adenosine metabolism and cognitive dysfunction. The expected outcome of this translational study will lay the foundation for novel astrocyte-specific therapeutic interventions to curtail cranial radiation-induced cognitive dysfunction.