Technical Abstract

Blood-Brain Barrier Transport of Uranium

**Background**: Recent studies of Gulf War veterans with depleted uranium (DU) embedded fragments in their soft tissues point to DU-induced effects on neurobehavioral and cognitive function (McDiarid et al., 2000). These observations are corroborated by electrophysiological changes in hippocampal slices isolated from rats embedded with DU fragments (Pellmar et al., 1999a; Pellmar et al., 1999b). Notably studies from the same group also suggest, for the first time, that uranium accumulates within brain tissue (Pellmar et al., 1999a). It is presently unknown how uranium is transported into the brain, and there are no pharmacological modalities to reduce its accumulation within the central nervous system (CNS).

**Objective/Hypothesis**: The proposal will assess the substrate specificity of uranium transport into the CNS, testing the hypothesis that the divalent metalcation, 1 (DMT1), which has an unusually broad substrate range that includes Fe 2+, Zn 2+, Mn 2+, Co 2+, Cd 2+, Cu 2+, Ni 2+ and Pb 2+ is also mediating uranium transport into the CNS.

**Study Design**: As a first step in testing this hypothesis, we will characterize uranium transport in cultured bovine and rat brain endothelium models of the blood-brain barrier (BBB) (Technical Objective 1.0). Correlative in vivo microdialysis studies will delineate the pharmacokinetics of uranium transport across the BBB in rats embedded with DU fragments (Technical Objective 2.0).

**Relevance**: The studies will test the hypothesis that a relationship exists between blood and brain uranium concentrations, determining whether rats with the highest blood uranium concentrations also accumulate the highest uranium concentrations in the CNS. As such, the studies will facilitate risk assessment in Gulf War veterans, and will determine whether veterans with high uranium blood levels are more prone to accumulate uranium in the CNS compared to veterans with low blood uranium levels.