E64d is a Translational Opportunity for Traumatic Brain Injury (TBI) Drug Development

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Entirely new pharmaceutical approaches need to be tried in treating traumatic brain injury (TBI) because the compounds clinically tested to date have all failed. Gene knockout data strongly argue that the cysteine proteases cathepsin B and calpain are effective TBI drug targets but no cathepsin B/calpain inhibitor has yet been clinically evaluated in TBI. This presentation makes the case that the epoxysuccinyl compound E64d, which is a potent cysteine cathepsin and calpain inhibitor, is an excellent scaffold from which to develop a TBI cysteine protease inhibitor clinical candidate. That is because there are extensive data in TBI and TBI-related animal models showing that E64d treatment is efficacious. Moreover, there is detailed biodistribution, pharmacokinetic, toxicologic, mutagenic, teratogenic and, most important, clinical data on E64d. Oral E64d treatment post-TBI in a mouse model significantly improves neuromotor deficits, reduces brain tissue loss, neuronal cell death and apoptotic cell death protein Bax. Intravenous (iv) E64c administration after ischemic injury prevents 85% of the hippocampal neuronal cell death that occurs without treatment. In an epilepsy model, intraperitoneal (ip) prophylactic E64d treatment completely prevents hippocampal mossy fiber pathology. E64d iv administration after spinal cord injury significantly reduces apoptotic Bax protein. Feeding (oral) E64d to transgenic Alzheimer's disease mice expressing APP containing the wild-type β-secretase site sequence and the London mutation, reduces memory deficits and neurotoxic amyloid-β. E64d ip treatment in a rat rheumatoid arthritis model dramatically reduces inflammation. E64d completed years of Phase 3 trials in pediatric muscular dystrophy patients without significant adverse events but did not advance as a drug due to insufficient efficacy. In man, E64d has no effect on blood/urine chemistry and cardiac function, has a half-life of about 1.5 hours, forms two metabolites, and does not accumulate. There is a wide acute and subacute toxicity window although low-dose species-specific liver toxicity occurred in rats but not hamsters that was attributed to the rat's unique liver chemistry. E64d did not cause *in vitro* or *in vivo* mutagenesis but did have teratogenic effects when given to pregnant animals. In summary, beneficial outcomes obtained from many pathological animal models and extensive pre-clincial and clinical pharmacological data support E64d as an excellent translational opportunity for developing a new TBI clinical therapeutic.