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Exploration of Novel, CNS Penetrant Inhibitors of *T. Gondii* Cathepsin L

Toxoplasma gondii is a neurotropic protozoan that chronically infects about a third of the world's population and is the second leading cause of death due to foodborne illness in the US. Currently, there is no efficacious *T. gondii* therapeutic capable of treating the dormant phase toxoplasmosis infection in the CNS. It has been shown that inhibition of *T. gondii* cathepsin L (TgCPL) can eliminate neuronal cysts in a mouse with chronic toxoplasmosis, validating CPL as a promising target for treating chronic toxoplasmosis. A series of dipeptide nitrile inhibitors and triazine nitrile inhibitors were developed as potent inhibitors of CPL. The dipeptide series included a few compounds capable of penetrating the BBB, however were rapidly cleared. The triazine series have better predicted BBB penetrant properties as well as PK properties. The triazine nitrile analogs developed improved metabolic stability, selectivity over human isoforms of CPL, and potency to as low as 5nM. More importantly, it was shown that CNS penetrance was achieved (up to Brain/Plasma = 1.4) and treatment of chronic stage bradyzoite cysts with triazine nitrile inhibitors reduces parasite viability comparable to a TgCPL genetic knockout. Currently, we are exploring other scaffolds that will reduce rotatable bonds, reduce nitrile reactivity to avoid potential side-effects as well as improve selectivity, and stabilize the thioimidate transition state through intramolecular interactions. Also, we plan to advance toward *in vivo* proof-of-concept that pharmacological inhibition of TgCPL is an effective method of treating chronic *T. gondii* infection in the CNS.