With an estimated two billion people globally chronically infected, *Toxoplasma gondii* is one of the most infective parasites in the world. This neurotropic protozoan is the 2nd leading cause of death due to foodborne illness in the US, and has been designated as one of five Neglected Parasitic Infections targeted by the CDC for public health action. Toxoplasma-associated illnesses are responsible for symptoms such as pregnancy loss (miscarriage or stillbirth), encephalitis, blindness, and death. Chronic infection has also been correlated to several mental illnesses including schizophrenia, bipolar disorder, and OCD. Currently, there is no efficacious *T. gondii* therapeutic capable of treating the chronic dormant-phase toxoplasmosis infection in the central nervous system. As such, there is a critical need for the development of a treatment capable of eliminating the *T. gondii* neural cysts.

Recently, we demonstrated that *T. gondii* cathepsin protease L (tgCPL) is critical to the parasite’s survival ([Fig. 1A&B](#)). Inhibition of tgCPL in tissue culture, by the irreversible inhibitor LHVS, kills *T. gondii* cysts, further implicating CPL as a viable target for treatment of the chronic stage infection ([Fig. 1C](#)). However, LHVS is unable to reduce neural cysts in infected mice due to suboptimal ADME properties and its lack of CNS permeability. Confirmation that tgCPL inhibition can eliminate neuronal cysts in a mouse with chronic toxoplasmosis is a crucial step in demonstrating that CPL is a valid target for the treatment of chronic toxoplasmosis.

We set out to identify alternative tgCPL inhibitors with optimal properties for diffusion into the brain. Through a broad literature search and analysis of calculated BBB permeability, we selected a hsCPL selective inhibitor (CCG:232877) with encouraging potential for the development of a selective and BBB permeable inhibitor.

Initial SAR studies have focused on shifting selectivity toward the inhibition of tgCPL over the human isoforms, while simultaneously altering physicochemical properties (MW, tPSA, HBA) to be more favorable for CNS permeability. Initially, our lead compound was approximately 100-fold selective for hsCPL, over tgCPL. Examination of the hsCPL and tgCPL crystal structures revealed several non-conserved residues and topological differences that can potentially be targeted for Tg selectivity. Chiefly among these, tgCPL has a smaller S2 pocket that bears a non-conserved Asp-218, offering an excellent opportunity to pick up selective interactions. We have begun to elucidate the pharmacophore necessary for tgCPL selective inhibition, increased potency against the parasitic cathepsin, and improved upon the calculated CNS access score. Current endeavors focus primarily on advancing this series toward proof-of-concept that pharmacological inhibition of tgCPL is an effective method of treating chronic *T. gondii* infection in the CNS.