Cryptococcus neoformans is an encapsulated fungal pathogen responsible for 15% of AIDS-related deaths around the world. Although there are several classes of antifungals in clinical settings, the widespread use of these drugs in medical and agricultural applications have caused emergence of resistance that threatens current therapies. A new strategy to combat fungal infections is to disarm the pathogen using an anti-virulence approach. Extracellular peptidases constitute promising targets, as they are associated with virulence and antifungal drug resistance but are not directly involved in growth. Disruption of peptidase activity by peptidase inhibitors (PIs) perturbs fungal proliferation or virulence, suggesting an important opportunity to combat the pathogen. Notably, mollusks possess PIs with antimicrobial applications but are underexplored in their usage against fungal pathogens. In this proposal, I will screen mollusks from Ontario against standard peptidases of the same family as those identified in C. neoformans for strong inhibitory activity using enzymology approaches. Next, anti-cryptococcal activity will be assessed by monitoring PI effects on wild type and mutant strains lacking peptidases of interest using a combination of phenotypic and mass spectrometry-based proteomics approaches. My aim is to discover new PI with anti-fungal properties against C. neoformans that are less prone to develop resistance. Preliminary results indicate that protein extracts from Planorbella pilsbryi and Cepaea nemoralis have reversible strong inhibitory activity against S8 serine peptidases and moderate activity against M4 metallopeptidases. Furthermore, these extracts seem to possess a fungistatic effect on the growth of C. neoformans. While more experiments are underway, these results highlight the potential of mollusks as promising sources of new PIs with anti-cryptococcal properties.