Title: The *C. elegans* L-AChR as a model for studying Helminth ion channels

Abstract: Pentameric ligand-gated ion channels represent an ancient, fundamental signaling mechanism. These receptors at the Helminth neuromuscular junction are of particular interest as anthelmintic drug targets. The response of specific receptors depends on the composition and arrangement of their subunits. The nematodes have an expanded family of pLGIC subunits that allows for receptor subunit diversity. The levamisole-sensitive acetylcholine receptor (L-AChR) from *C. elegans* is used as a model to study Helminth receptors due to high structure conservation across subunit orthologs. The *C. elegans* L-AChR requires subunits encoded by five different genes; two non-alpha subunits LEV-1 and UNC-29*,* and three alpha subunits ACR-13, UNC-38, and UNC-63. In *Haemonchus contortus* the L-AChR does not require LEV-1, suggesting it is replaced by one of the other subunits. The appearance of new subunits through gene duplication reveals a pair of alpha-type subunits (*acr*-8 and *acr*-13) and a pair of non-alpha type subunits (*unc*-29.1 and *unc*-29.2). Interaction between these regulates whether the non-alpha subunit can occupy multiple positions within the receptor. The non-alpha UNC-29.1 and the alpha ACR-8 do not require the presence of LEV-1 to form a functional channel. Chimera subunits were made by exchanging the intracellular parts between unc-29.1 and unc-29.2, and between acr-8 and acr-13. Expression of the ion channels in *Xenopus* oocytes and characterization by two-electrode voltage-clamp electrophysiology shows different regions contributing to subunit positioning between alpha and non-alpha subunits. The intracellular loop mediates non-alpha UNC-29.1 to function without LEV-1, whereas the extracellular domain of ACR-8 allows it to function without LEV-1. Future studies will use subunit concatemers to identify the subunit that replaces LEV-1.