Research Proposal Description – NIH F32 Fellowship Application

Cell migration describes the directed movement of cells to a particular location in the body. This process is an essential step in tissue formation and the development of multicellular organisms. Furthermore, cell migration is required for maintenance of the body's immune system and wound healing. Disruptions in cell migration can lead to medical problems such as vascular disease and the progression of cancer. The germ cells of the fruit fly *Drosophila melanogaster* undergo a stereotypic and genetically regulated migration process and thus provide an ideal model system to study cell migration. Genetic studies have identified a conserved family of lipid phosphate phosphatases (LPPs), the Wunens, as important regulators of germ cell migration in the Drosophila embryo. The Wunens function as germ cell repellants and are required for directing germ cells along a proper route to the embryonic gonad. In the absence of Wunen function in somatic cells such as the midgut and central nervous system, germ cell migration is abnormal, with germ cells found scattered throughout the embryo. Furthermore, Wunen function is required within the germ cells for survival and proper migration. Similar to other LPPs, the Wunens are thought to function by dephosphorylation of extracellular phospholipid substrates. However, the mechanisms by which Wunens regulate germ cell migration are not well understood. The goal of this proposal is to identify and characterize these mechanisms. We hypothesize that Wunens hydrolyze and uptake a secreted phospholipid that acts as a chemoattractant and regulator of membrane dynamics required for germ cell migration and survival. Localized Wunen activity in somatic cells creates a phospholipid gradient, directing the proper migration of germ cells to the developing gonad. To address this model, germ cells will first be isolated from the embryo by cell sorting techniques, allowing us to study them in a simplified environment. Sorted germ cells will be used in an *ex vivo* migration assay, allowing us to recapitulate Wunen chemorepellent activity and identify Wunen-regulated phospholipids with chemoattractant activity. The role of Wunen in germ cell membrane dynamics will be determined by a detailed phenotypic analysis of sorted cells lacking Wunen function. Finally, the mechanism of Wunen-mediated lipid uptake will be clarified by a cell-based screen for additional mediators of this process. Further studies will be focused on those genes predicted to have roles in the regulation of membrane dynamics. Taken together, these data will provide insight into the mechanisms by which lipid regulation promotes an essential cell migration process.