Vesicle transport and membrane trafficking in eukaryotic cells is highly regulated and depends on the function of more than 60 Rab GTPases, which play pivotal roles in these processes. Rabs control vesicle budding, membrane localization, and recruitment of effectors to direct cargo to their correct destination. It is for this reason that several pathogenic bacteria manipulate these proteins to establish a replicative niche for themselves. The focus of our laboratory is to elucidate how intracellular bacterial pathogens manipulate Rab function to promote their virulence and to uncover fundamental principles of membrane traffic. To accomplish this, we will utilize the intracellular pathogen Legionella pneumophila as a model. Legionella pneumophila is responsible for a severe pneumonia called Legionnaire’s disease and cause infection via inhalation of contaminated aerosols. Following phagocytosis by host alveolar macrophages, L. pneumophila avoids fusion with endo-lysosomes and instead hijacks the host transport machinery to establish an endoplasmic reticulum (ER)-derived Legionella containing vacuole (LCV) that does not acidify and facilitates bacterial replication. Essential to Legionella’s pathogenicity is a type IV secretion system called the Dot/Icm system that functions to translocate bacterial effector proteins directly into infected host cells. Dot/Icm secreted effectors usurp many host cell processes and are essential for the establishment of the LCV.

Several L. pneumophila effector proteins subvert host vesicular traffic by directly manipulating the host GTPases Arf1 and Rab1. Our research has demonstrated that during infection, the Legionella effectors DrrA and AnkX perform novel posttranslational modifications on Rab1 and Rab35 via covalent addition of an adenosine monophosphate nucleotide (AMPylation) and a phosphocholine moiety (phosphocholination), respectively, to adjacent residues in the class II switch region. AnkX-mediated phosphocholination inhibits Rab35 from binding its guanine nucleotide exchange factor (GEF), connecenn (CD). Although other pathogens employ virulence factors to modify GTPases via AMP addition; thus far, only the Legionella effector AnkX has been shown to cause phosphocholination via its FIC domain, a domain that is conserved amongst proteins found in most pathogenic bacteria. Understanding the downstream signaling of post-translationally modified Rabs will provide critical clues towards answering many interesting questions in cell biology. We expect that our future studies will enable the discovery of novel mechanisms used by Legionella to manipulate host vesicular transport.