Clathrin mediated endocytosis is the major process by which many transmembrane proteins of a huge variety of types and functions are internalised from the cell's limiting membrane into the endosomal system. From here these cargo proteins can be trafficked to their required destination. Thus endocytosis plays important roles in cell signaling, nutrient uptake, cellular homeostasis and the interaction of the cell with its external environment. The formation of clathrin coated endocytic vesicles (CCVs), which requires the complex interplay of many proteins with each other and with the membrane itself, serves as a paradigm for formation of all types of transport vesicle. CCVs possess three layers: the inner membrane layer, in which the transmembrane cargo is embedded, that is linked to the outer clathrin lattice by a layer of cargo binding adaptors and proteins that aid and regulate in vesicle formation.

We have used a combination of protein X-ray crystallography with biochemical, biophysical and cell biological assays to understand the structure and function of some of the proteins that make up the middle layer of CCVs. These proteins are modular in nature consisting of folded domains joined by long unstructured linkers. Within these linkers are short motifs that interact with the folded domains of other components of the CCV formation machinery. Many of these folded domains also bind directly to the membrane. These interactions, whose molecular basis we have studied, have Kds in the low micromolar range, making them readily reversible and easily regulated, properties that are necessary for establishing dynamic networks of interacting partners found in processes such as transport vesicle formation.