Proteins that reside in the cell membrane are among the most important of all proteins, as they play key roles in almost every cellular process, and represent over a third of all proteins, yet they represent one of the most difficult challenges for expression and isolation, because they are partially hydrophobic, flexible, and unstable in isolation. The adenosine receptor subfamily of G-protein coupled receptors is important in modulating blood pressure, and more recently has been implicated in cancer, neurodegenerative diseases, and diabetes. Our laboratory has had great success expressing the human adenosine A2a receptor (A2aR) in yeast, and I will describe computational and experimental studies to understand the role of cholesterol on the protein stability and function. In particular, our data support a model of receptor state-dependent binding between cholesterol and a conserved binding motif, which could facilitate both G-protein coupling and downstream signaling of A2aR.