Over the last 10 years, the wnt signaling pathway has emerged as a critical signaling pathway involved in development, axial and planar differentiation, and cell-cell communication. Dysfunction in the pathway is causative in several human diseases including cancer, especially colon and breast cancer. Part of the difficulty in understanding this pathway is its very complexity: the family of wnt ligands is comprised of 19 gene products in humans, there are 10 frizzled receptors for these ligands, and there are at least 5 extracellular physiological antagonists that interfere with wnt-frizzled interaction. The interaction of a wnt with a cognate receptor can elicit a response in three distinct signaling pathways. The “canonical” pathway involves wnt-mediated stabilization of β-catenin, translocation of β-catenin into the nucleus and changes in specific gene transcription mediated by the TCF/LEF transcription factors. The planar polarization pathway is mediated by alteration in jun-kinase levels and changes in gene expression mediated mostly by the AP-1 family members. The “Ca²⁺ -pathway” involves frizzled interaction with a G-protein, including but not limited to Gαt2 and Gαo. These G-proteins in turn are coupled to changes in IP3 hydrolysis and release of intracellular calcium and changes in transcription mediated by NF-AT. This very complexity makes this pathway an attractive target of drug discovery. Clearly agents that interfere with the canonical pathway could have a role in cancer treatment and perhaps prevention. Current drug discovery targeting this pathway are focused on interfering with terminal events in the signaling pathway, specifically with the interaction of β-catenin with TCF and related transcription factors. We have developed a novel, high throughput protein complementation assay that will allow us to screen for molecules that are either agonists or antagonists of this pathway. Our assay “readout” is the activation of the frizzled receptor and we believe it a completely novel strategy to screen for molecules that modulate the activity of this pathway.