Figure S1. Classification of Adhesion GPCR Ligands. Adhesion GPCRs recognize three types of extracellular ligands that target the NTFs to regulate G protein signaling. Trans-cell presented proteins (red) are ligands that form inter-cell connections with AGPCRs. They allow for direct cell-to-cell messaging and are well characterized in ADGRE and ADGRL subfamilies in immune cells and neurons, respectively. They are predicted to activate AGPCRs via either allosteric modulation or tethered agonism (via forced dissociation of the NTF). Extracellular matrix components (blue) are anchored ligands that may also activate AGPCRs by tethered agonist and allosteric activation modes. Integrins and collagen subtypes are currently well characterized examples of ECM or ECM-associated ligands for specific receptors. Lipids, soluble proteins, and small molecules (green) are unanchored ligands that are expected to regulate signaling via allosteric modulation. 16 adhesion GPCRs have no reported ligand and thus remain classified as orphans (gray). This figure accompanies Table 2 in which the specific ligands are referenced.