Figure Legends

Figure 1. Pseudokinase as allosteric modulators.

Janus kinases (JAKs) act downstream of cytokine receptors to recruit and activate STAT transcription factors (represented as a star). The pseudokinase domain of JAKs generally negatively regulates the tyrosine kinase domain (blue), and is also important for signal transduction after activation. CASK associates with ion channels and other membrane complexes, and allosterically modulates activity of the active kinase CaMKII. FAM20A (green) controls both the activity and secretion of the kinase FAM20C (green). STRADA and STRADB are both able to allosterically regulate the kinase activity of LKB1/STK11, with help of the adapter protein MO25/CAB39. PAN3 associates with, and is important for activity of, the deadenylase PAN2. The pseudokinase domain of GCN2/EIF2AK4, a protein involved in control of translation, is required for the activity of its kinase domain. VRK3 associates with, and allosterically regulates, the Erk phosphatase DUSP3. The pseudokinase domains are drawn throughout in green; active kinase domains are shown in light blue (in proteins containing a pseudokinase domain) or dark purple.

Figure 2. Transmembrane pseudokinases.

The pseudokinase domains of receptor guanylyl cyclases (RGCs) are responsible for controlling the activity of their guanylyl cyclase domains (shown in dark blue). NRP1, NRP2, and GUCY2C all bind extracellular ligands, however the retinal RGCs (GUCY2D and GUCY2F) are activated by the binding of guanylyl cyclase activating proteins (GCAPs; shown in black) to their pseudokinase domains. Both EPHB6 and EPHA10 are able to bind ephrins. The functional role of EPHA10 is unclear, but EPHB6 can form heterodimeric associations with other EPH receptors and influence signalling pathways. ERBB3 can associate with, and allosterically regulate, other ERBB family members, and can act as a scaffold for other signalling components. Additionally, RYK, ROR1, ROR2, and PTK7 all bind non-canonical Wnt ligands, and can also recruit other proteins, such as kinases (shown purple) or transcription factors (shown as a star), to these complexes. They can also form interactions with a number of other RTKs. STYK1 is believed to act as a scaffold to facilitate the phosphorylation of GSK3-β by PI3Ks. Pseudokinase domains are drawn throughout in green; kinase domains are drawn in purple or orange.

Figure 3. Pseudokinases involved in signalling in the cytoplasm and nucleus.

A number of pseudokinases are important for signalling downstream of receptor complexes: KSR1 or KSR2, PEAK1/SgK269, ILK, IRAK2 and IRAK3. NRBP1 is a small adapter protein that is predicted to have roles in a number of cellular compartments, including scaffolding ubiquitin ligase complexes to negatively regulate Wnt signalling. The lesser-known relative, NRBP2, is believed to influence PKB/AKT signalling through an association with annexin 2A at membranes.

Several pseudokinases located in the cytoplasm perform various protein interaction functions: MLKL, RNaseL, PRAG1/SgK223 and TTN. The MLKL pseudokinase domain is thought to restrain the cell killing activity of its N-terminal domain until phosphorylated by RIPK3, when membrane translocation and permeabilisation ensues. The RNaseL pseudokinase domain mediates dimerisation, which enables the decay of cytoplasmic RNA. TTN is a large polypeptide found in muscle sarcomeres, whose pseudokinase domain recruits the E3 ligases Murf1 and Murf2.

In the nucleus, TRRAP scaffolds histone acetyltransferase complex assembly, and the TRIBs assemble complexes between E3 ligases, such as COP-1, and its various transcription factor

substrates (depicted as a star). STK40 also binds COP-1, and does affect transcription factor function, however direct binding to transcription factors has not been shown. TEX14 and STK31 have also been implicated in cell cycle control. Lastly, BUBR1/BUB1B is an important scaffold for the APC/C^{Cdc20} ubiquitylation complex and acts as a mechanosensor to modulate kinetochore/microtubule tension. Pseudokinase domains are drawn throughout in green; active kinases are drawn in purple, orange, or brown.

Figure 4. Pseudokinases involved in cellular trafficking and maintenance of cilia/flagella.

The NME proteins all possess pseudo-nucleoside diphosphate kinase (NDPK) domains (light green) rather than a conventional protein kinase domains, which act as scaffolds with cilia (NME7, RP2) or flagella (NME8, NME5). NME7 also has an active NDPK domain (shown in light blue). Similar to RP2, which associates with Arl GTPases, the pseudokinase ULK4 associates with cilia and influences GTPase activity through the binding of regulatory proteins.

PXK is a pseudokinase associated with receptor internalisation, and is believed to facilitate interactions between endosomes and actin. RPS6KC1 is proposed to act as an adapter to recruit a number of proteins, including kinases (shown in orange), to early endosomes. FJX1 and CXorf36/DIAR1 are poorly understood, but are thought to be localised to the Golgi and endoplasmic reticulum, respectively. CAMKV is a vesicle associated pseudokinase involved in dendrite physiology at synapses, while SCYLs are a group of vesicle-associated pseudokinases thought to be involved with intracellular transport. Pseudokinase domains are drawn throughout in dark green.