**Supplemental Figure 1.** Polarized IR spectrum of the TpoR transmembrane domain. Polarized IR spectroscopy can be used to establish the global secondary structure of peptides reconstituted into membrane bilayers. Polarized IR spectra of the mouse TpoR exhibit an amide I vibration at 1,657 cm\(^{-1}\), a frequency characteristic of \(\alpha\)-helical structure. The dichroic ratio of the amide I band is sensitive to the orientation of the TM helix relative to the plane of membrane. The observed dichroic ratio of 2.7 corresponds to a helix orientation of 33° relative to the membrane normal. Peptides corresponding to the TM and JM domains of TpoR (amino acids 481-522) were synthesized by solid-phase chemistry. Three arginine residues were added to the N-terminus for solubility, and the C-terminus was amidated. The synthetic peptides were purified by reverse-phase high-performance liquid chromatography (HPLC) on a C4 column with an acetonitrile-water gradient and lyophilized. The purity was confirmed by matrix-assisted laser desorption/ionization (MALDI) mass spectrometry and HPLC. The reconstitution was carried out by dialysis after co-mixing peptide, lipid (DMPC, DMPG in a 10:3 molar ratio), and detergent (octyl-\(\beta\)-glucoside). The peptide-to-lipid molar ration 1:50. Polarized attenuated total reflection (ATR) FTIR spectra were obtained on a Bruker IFS 66V/S spectrometer.
Supplemental Figure 2. Transcriptional activity via FoxO transcription factors was assessed in γ2A cells co-transfected with one of the seven cc-TpoRs, pRLTK-luc and with the 6xDBE-Luc reporter, which is known to be activated by FoxO family members. Shown are averages of triplicate values +/- S.D. of one representative experiment out of two independent experiments. PI-3-K/Akt signaling is inversely correlated with 6xDBE-Luc reporter activity.
Supplemental Figure 3. (A) The mutation W_{515}K found in ET and PMF patient was introduced at the corresponding W_{508} position in the seven murine ccTpoRs. (B) STAT5 transcriptional activity via JAK2 was measured in γ2A cells transiently transfected with reporter plasmids, cc-TpoRs W508K and JAK2. The results shown reflect averages of triplicate values +/- S.D. similar results were obtained performing two independent experiments.
**Supplemental Figure 4.** Helical wheel representation of *cc-TpoRs* and their weakest (in blue) or strongest (in red) signaling dimeric interfaces for JAK2/STATs, PI-3-kinase and MAP-kinase signaling (A), TYK2/STATs signaling (B). The broad helical face exhibiting high JAK signaling (red) also induces high levels of Ba/F3 proliferation (C). *cc-TpoR*-II adopts a completely inactive interface.