

Abstract: Approximately 45% of prescription drugs are targeted at members of the **G-protein-coupled receptor** (GPCR) superfamily. Originally believed to function as monomeric units, GPCRs are now known to associate as dimers. Constitutive GPCR homodimerization is considered to be a universal event. **Heterodimerization** has been described for several GPCR with significant alterations in the pharmacological characteristics of the individual partners. Targeting GPCR heterodimers has untapped therapeutic potential, exemplified by the potent analgesic effects of an agonist that selectively activates the δ/κ opioid receptor heterodimer.

Prostacyclin (PGI₂) and **thromboxane** (TxA₂) are vasoactive mediators with opposing roles in cardiovascular disease. Through elevation of cAMP, activation of the PGI₂ receptor (**IP**) inhibits cell proliferation and platelet activity in models of atherosclerosis and vascular injury. Conversely, TxA₂ receptor (**TP**) activation elevates cellular calcium promoting these biological processes. A dramatic change in TP signaling follows **IPTP heterodimerization** - when complexed with the IP, an uncharacteristic anti-proliferative, anti-thrombotic TP-dependent signaling event, elevation of cellular cAMP, occurs. IPTP-dependent cAMP generation is a distinguishable readout of heterodimer activation. This proposal aims to use this readout to screen the PCMD chemical library for **selective IPTP ligands**.

IP and TP are frequently co-expressed in the cardiovascular system but the role of the IPTP heterodimer in cardiovascular disease has not been examined. An IPTP heterodimer-specific agonist is critical for such explorations. Further, selective activation of the “PGI₂-like” function of the IPTP heterodimer may provide a novel therapeutic strategy in cardiovascular disease.