The coagulation pathway serine proteinases, like thrombin, Factor VIIa/Xa, and activated Protein C (APC) are now known to regulate cell signaling by cleaving and activating a novel family of G-protein-coupled Proteinase-activated Receptors (PARs 1 to 4) via exposure of a ‘tethered’ receptor-triggering ligand (Adams et al., 2011). On their own, short synthetic peptides based on the ‘tethered ligand’ sequences of the PARs (PAR-APs) can, in the absence of receptor proteolysis, selectively activate PARs 1, 2 and 4 and cause physiological responses both in vitro and in vivo. Using the PAR-APs as probes in vivo, it has been found that PAR activation can affect the vascular, renal, respiratory, gastrointestinal, musculoskeletal and nervous systems (both central and peripheral) and can promote cancer metastasis and invasion (Ramachandran & Holleenberg, 2008). The responses triggered by PARs 1, 2 and 4 are in keeping with an innate immune inflammatory response, ranging from vasodilatation to intestinal inflammation, increased cytokine production and increased nociception. Further, PARs have been implicated in a number of disease states including cancer and inflammation of the cardiovascular, respiratory, musculoskeletal, gastrointestinal and nervous systems. Moreover, PAR-regulating proteinases have been implicated in pathogen-induced inflammation. The seminar will provide an overview of the molecular pharmacology of the PARs, their potential role in a variety of inflammatory diseases and their likelihood as therapeutic targets for inflammatory disease and cancer (Ramachandran et al., 2011).