SS03-5 Nuclear receptor and protease as a drug target

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Three-dimensional structure of the protein, which is a drug target, allows us to logically design the drug molecule. We have been continuing to investigate the development of ligands for vitamin D receptor (VDR) and peroxisome proliferator-activated receptor (PPAR) by using methods of structure based drug design, synthesis, activity evaluation and X-ray crystal structure analysis. Both VDR and PPAR are the members of the nuclear receptor superfamily. In addition, we recently started design and synthesis of an inhibitor of thrombin-activatable fibrinolysis inhibitor (TAFI) which is one of proteases. In VDR ligand research, we identified a new class of ligands that work as an agonist, a partial agonist or an antagonist and modulate the ligand binding pocket structure of the VDR (*J. Med. Chem.* **52**, 1438–1449, 2009). In PPAR ligand research, we found that oxidized derivatives of natural polyunsaturated fatty acids activate PPARg. X-ray crystal structures of their complex with the ligand binding domain of PPARg showed that oxidized fatty acid derivatives are accommodated into PPARg with the various binding modes including covalent bond (*Nat Struct Mol Biol.* **15**, 924-931, 2008). In this presentation, I will show those recent research results.