Structure of the human $P2Y_{12}$ receptor in complex with an antithrombotic drug

With the support by the National Natural Science Foundation of China and the Ministry of Science and Technology of China, Prof. Zhao Qiang's laboratory at Shanghai Institute of Materia Medica, Chinese Academy of Sciences, reported the crystal structure of the human $P2Y_{12}$ receptor in complex with an antithrombotic drug, which was published in *Nature* (**2014**, 509(7498): 115—8).

P2Y receptors (P2YRs), a family of purinergic G-protein-coupled receptors (GPCRs), are activated by extracellular nucleotides. Their ligands are generally charged molecules with relatively low bioavailability and stability *in vivo*, which limits our understanding of this receptor family. $P2Y_{12}R$ regulates platelet activation and thrombus formation, and several antithrombotic drugs targeting $P2Y_{12}R$ have been approved for the prevention of stroke and myocardial infarction. However, limitations of these drugs (for example, a very long half-life of clopidogrel action and a characteristic adverse effect profile of ticagrelor) suggest that there is an unfulfilled medical need for developing a new generation of $P2Y_{12}R$ inhibitors. The 2.6 Å resolution crystal structure of human $P2Y_{12}R$ in complex with a non-nucleotide reversible antagonist, AZD1283, reveals a distinct straight conformation of helix V, which sets $P2Y_{12}R$ apart from all other known class A GPCR structures. With AZD1283 bound, the highly conserved disulphide bridge in GPCRs between helix III and extracellular loop 2 is not observed and appears to be dynamic. Along with the details of the AZD1283-binding site, analysis of the extracellular interface reveals an adjacent ligand-binding region and suggests that both pockets could be required for dinucleotide binding. The structure provides essential insights for the development of improved $P2Y_{12}R$ ligands and allosteric modulators as drug candidates.

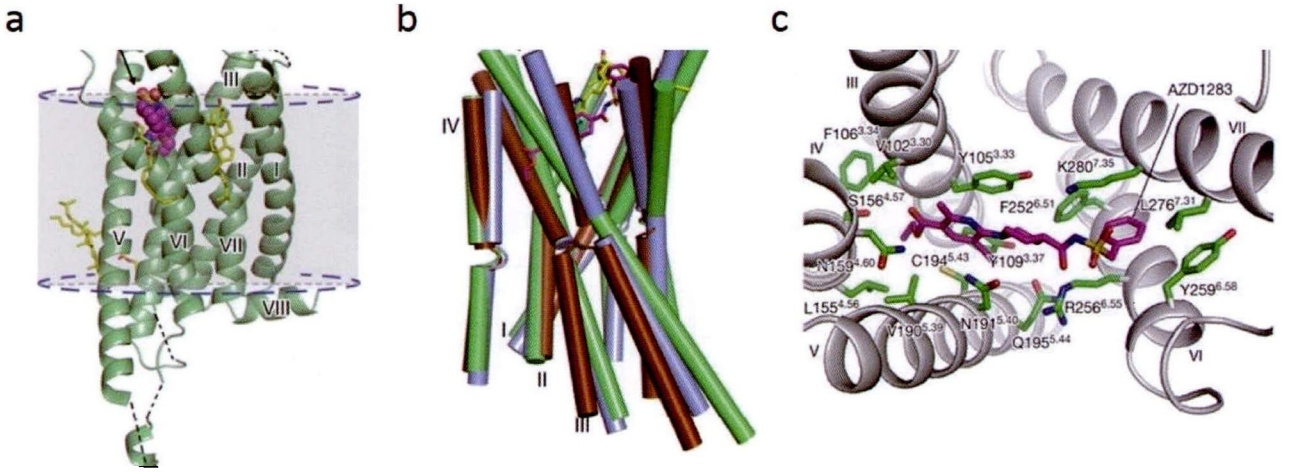

Figure The crystal structure of $P2Y_{12}$ receptor in complex with the antagonist AZD1283. a, Cartoon representation of $P2Y_{12}R$. $P2Y_{12}R$ is coloured green. AZD1283 is shown as magenta spheres. Cholesterol and lipids have yellow carbons. The disulphide bridge is shown as lime sticks. Missing loops and membrane boundaries are indicated as black and blue dashed lines, respectively. b, Side views of $P2Y_{12}R$ (green cylinders) compared with β_2AR (PDB accession 2RH1, brown) and PAR1 (PDB accession 3VW7, blue). The ligands AZD1283, carazolol and vorapaxar are shown as sticks with magenta, cyan and yellow carbons, respectively. c, Key residues in $P2Y_{12}R$ for AZD1283 binding. AZD1283 (magenta carbons) and receptor residues (green carbons) involved in ligand binding are shown in stick representation.