Identification of ligands for orphan GPCRs and analyses for their functions

○Shuji Hinuma (Takeda Pharmaceutical Company Ltd)

GPCRs are the largest family of receptors encoded on the human genome and function to regulate a variety of cellular responses. In human genome, there are numerous genes encoding 'orphan' GPCRs – so called because their ligands remain unknown. The identification of their ligands is indispensable to clarify their functions. In addition, as many medical drugs currently on the market have been designed to act on GPCRs, identifying ligands for orphan GPCRs would provide new drug targets. Research on orphan GPCRs is therefore important for both basic and applied science. We have developed a method applicable to identify ligands for a wide range of orphan GPCRs by detecting specific signal transductions induced in cells expressing orphan GPCRs. That is, a sample is determined to contain a ligand or not by detecting responses accompanied by changes in intracellular Ca^{2+} or cAMP. Applying this method, we have succeeded in identifying various orphan GPCR ligands including peptides and small molecule compounds (1,2). We believe that the identification of orphan GPCR ligands will contribute to revealing the regulatory mechanisms behind various physiological phenomena and will provide opportunities for developing novel drugs.

1. Fukusumi S, Fujii R, Hinuma S. Recent advances in mammalian RFamide peptides: the discovery and functional analyses of PrRP, RFRPs and QRFP. Peptides. 27:1073-86 (2006)
2. Itoh Y, et al. Free fatty acids regulate insulin secretion from pancreatic beta cells through GPR40. Nature. 422:173-6 (2003).