**G PROTEIN-COUPL ED RECEPTORS**

Crystal structure of the \( \beta_2 \) adrenergic receptor–Gs protein complex

Rasmussen, S. G. F. et al. *Nature* 19 Jul 2011 (doi:10.1038/nature10361)

Agonist binding to G protein-coupled receptors (GPCRs) leads to the activation of G proteins and subsequent downstream signalling. Here, the authors present the first high-resolution crystal structure of a GPCR in its active state: namely, agonist-bound \( \beta_2 \)-adrenergic receptor (\( \beta_2 \)-AR) in complex with the stimulatory G protein G\(_s\). Interactions between \( \beta_2 \)-AR and G\(_s\) involved the amino- and carboxy-terminal \( \alpha \)-helices of G\(_s\) and, surprisingly, a major displacement of the \( \alpha \)-helical domain of G\(_{\alpha}\) relative to the Ras-like GTPase domain was observed. Knowledge of this structure will aid the understanding of GPCR activation and signalling.

**ANTICANCER DRUGS**

Selective killing of mixed lineage leukemia cells by a potent small-molecule DOT1L inhibitor

Daigle, S. R. et al. *Cell* 20, 53–65 (2011)

In mixed-lineage leukaemia (MLL), chromosomal translocations of the MLL gene result in recruitment of the histone methyltransferase DOT1L to aberrant gene locations, which results in increased expression of genes that are involved in leukaemogenesis. This paper describes the development of a potent, selective inhibitor of DOT1L. The compound blocked methylation (of Lys79 on histone 3), inhibited expression of leukaemogenic genes, selectively killed cultured cells that expressed MLL translocations and had antitumour activity in a mouse model of MLL.

**ANTIBACTERIAL DRUGS**

Small-molecule inhibitor binding to an \( N \)-acylhomoserine lactone synthase

Chung, J. et al. *Proc. Natl Acad. Sci. USA* 108, 12089–12094 (2011)

Quorum sensing is a process that influences the virulence of many pathogenic bacteria. In the rice bacterium *Burkholderia glumae*, quorum sensing is mediated by the binding of \( N \)-octanoyl-L-homoserine lactone (C8-HSL) — which is synthesized by TofI — to its cognate receptor, TofR. This study identified two inhibitors of quorum sensing: a TofI inhibitor and an inhibitor of the binding of C8-HSL to TofR. Analysis of X-ray crystal structures identified respective binding sites for the inhibitors. Such information may facilitate the design of a new class of therapeutic inhibitors of quorum sensing.

**ANTICANCER DRUGS**

Chemical genetics identify elf2\( \alpha \) kinase heme-regulated inhibitor as an anticancer target

Chen, T. et al. *Nature Chem. Biol.* 17 Jul 2011 (doi:10.1038/ncmbio.613)

An increase in the abundance of the translation initiation complex elf2\( \alpha \)-GTP–tRNA\(_{iMet}\) is involved in the malignant transformation of cells. Using a cell-based assay, Chen et al. identified a series of \( N,N' \)-diarylureas that inhibited the accumulation of this ternary complex. The compounds selectively activated haem-regulated inhibitor kinase, thereby phosphorylating elf2\( \alpha \) and reducing the abundance of elf2\( \alpha \)-GTP–tRNA\(_{iMet}\). Several compounds inhibited the growth of cancer cells, and one inhibited growth in a breast cancer xenograft model without causing toxicity.