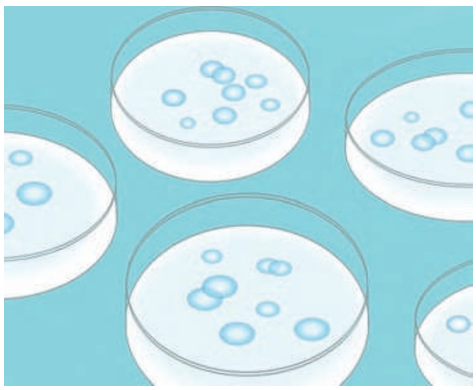
IN BRIEF



ANTIBACTERIAL DRUGS

The RNA polymerase "switch region" is a target for inhibitors.

Mukhopadhyay, J. *et al. Cell* **155**, 295–307 (2008)

The antibiotic myxopyronin inhibits bacterial RNA polymerase (RNAP). This paper shows that myxopyronin interacts with the RNAP switch region — the hinge that mediates opening and closing of the RNAP active centre cleft — to prevent the interaction of RNAP with promoter DNA. The switch region is distant from targets of previously characterized RNAP inhibitors, and myxopyronin and other functionally analogous antibiotics did not exhibit cross-resistance with previously characterized RNAP inhibitors. So, the RNAP switch region is an attractive target for the identification of new broad-spectrum antibacterial agents.

G-PROTEIN-COUPLED RECEPTORS

The 2.6 Angstrom crystal structure of a human A_{2A} adenosine receptor bound to an antagonist.

Jaakola, V.- P. *et al. Science* 2 Oct 2008 (doi:10.1126/science.1164772)

Jaakola and colleagues have determined the crystal structure of the human A_{2A} adenosine receptor. Features distinct from previously reported GPCR structures were shown, including a distinct antagonist binding pocket defined by disulphide bridges in the extracellular domain, combined with a subtle repacking of the transmembrane helices relative to the adrenergic and rhodopsin receptor structures. Knowledge of the A_{2A} receptor structure should aid in the design of new compounds with increased selectivity for this drug target.

ANALGESIA

Prostatic acid phosphatase is an ectonucleotidase and suppresses pain by generating adenosine.

Zylka, M. J. *et al. Neuron* **60**, 111–122 (2008)

This paper showed that thiamine monophosphatase — a marker of small-diameter dorsal root ganglia neurons — and the transmembrane form of prostatic acid phosphatase (PAP) — an enzyme with previously unknown functions — are identical molecules. The authors showed that PAP-knockout mice have enhanced inflammatory and neuropathic pain sensitivity, and that injection of PAP protein in mouse pain models had potent antinociceptive, antihyperalgesic and anti-allodynic effects. PAP suppressed pain by dephosphorylating extracellular AMP to adenosine and activating A_1 adenosine receptors in dorsal spinal cord.

RENAL DISEASE

Combination therapy with AT1 blocker and vitamin D analog markedly ameliorates diabetic nephropathy: blockade of compensatory renin increase.

Zhang, Z. *et al. Proc. Natl Acad. Sci. USA* **105**,15896–15901 (2008)

The renin–angiotensin system (RAS) plays a critical role in the development of diabetic nephropathy, but blockade of RAS induces compensatory renin increases, which reduce the efficacy of this treatment. Zhang and colleagues demonstrated that combination therapy with an angiotensin 1 receptor blocker and a vitamin D analogue ameliorated renal injury in a rodent diabetes model owing to the blockade of the compensatory renin rise by the vitamin D analogue, leading to more effective RAS inhibition.