IN BRIEF

BIOCHEMICAL ENGINEERING

Ta da! A way to add fluorine to natural products

Adding fluorine to small molecules can improve their properties, such as preventing enzymatic breakdown and increasing membrane permeation, but it is hard to add fluorine to natural products. Walker *et al.* engineered polyketide synthase enzymes, which are normally involved in acetate-based biosynthesis, to incorporate fluoroacetate: the primary product of the only biological fluorination route. In *Escherichia coli* cells, this process was used as a building block to introduce fluorine substituents in a site-selective manner into polyketide-based natural product scaffolds.

ORIGINAL RESEARCH PAPER Walker, M. C. *et al.* Expanding the fluorine chemistry of living systems using engineered polyketide synthase pathways. *Science* **341**, 1089–1094 (2013)

INFECTIOUS DISEASE

Combating visceral leishmaniasis

Visceral leishmaniasis is often fatal, yet current drugs are very toxic and incur resistance. Because *Leishmania spp.* require exogenous haem for growth, Guha *et al.* investigated whether haem acquisition could be a potential target. They found that the haemoglobin receptor (HbR) was conserved across several strains of *Leishmania*, and a HbR-specific antibody was detected in patients with visceral leishmaniasis. Immunization of mice and hamsters with HbR DNA completely protected against virulent *Leishmania donovani* infection and stimulated the production of protective cytokines as well as $CD4^+$ and $CD8^+$ T cells, which suggests that HbR is a target for vaccine development.

ORIGINAL RESEARCH PAPER Guha, R. *et al.* Vaccination with *Leishmania* hemoglobin receptor-encoding DNA protects against visceral leishmanias. *Sci. Transl. Med.* **5**, 202ra121 (2013)

G PROTEIN-COUPLED RECEPTORS

Crystal structures aid ligand mechanistics

Two new papers on G protein-coupled receptor (GPCR) structure shed new light on how different ligands interact with their cognate GPCRs. The study by Tan *et al.* determined the crystal structure of a stabilized CCR5 chemokine receptor — which acts as a co-receptor for HIV-1 viral entry — bound to the HIV drug maraviroc. A comparison of CCR5 with the crystal structure of the chemokine receptor CXCR4 bound to an antagonist suggested that different charge distributions and steric hindrances caused by different residue substitutions determine HIV-1 co-receptor selectivity. For example, maraviroc penetrated deeply into an open binding pocket, whereas the CXCR4 inhibitor inserted less deeply into a more closed binding pocket. The authors note that these insights could aid HIV-1 structure-based drug discovery. The study by Ring *et al.* determined the first crystal structure of an active state GPCR bound to its native ligand. The structure of the adrenaline-bound, nanobody-stabilized human β_2-adrenergic receptor, as well as the receptor bound to other agonists, showed that the adrenaline-bound structure is similar to that bound to other ligands (despite diverse chemical structures with different affinities), but substantial rearrangements occur in extracellular loop 3 and the extracellular tip of transmembrane helix 6. The authors note that these results offer new insight into how diverse agonists can activate a specific GPCR.

ORIGINAL RESEARCH PAPERS Tan, Q. *et al.* Structure of the CCR5 chemokine receptor–HIV entry inhibitor maraviroc complex. *Science* **341**, 1387–1390 (2013) | Ring, A. M. *et al.* Adrenaline-activated structure of β_2-adrenoceptor stabilized by an engineered nanobody. *Nature* http://dx.doi.org/doi:10.1038/nature12572 (2013)