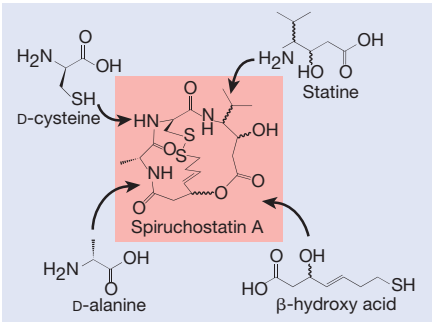

Synthetic chemistry

Spiruchostatin from scratch

J. Am. Chem. Soc. doi:10.1021/ja039258q (2004)

Histone deacetylases are enzymes involved in regulating DNA transcription, and several molecules that inhibit their activity are being investigated as potential anticancer drugs. In particular, the natural product FK228, derived from *Chromobacterium violaceum*, is currently in phase II clinical trials.

To understand exactly how FK228 works in the body, and to discover whether nature's own anticancer agents can be improved on, chemists need a range of analogues of FK228 to work with. But FK228 has proved very resistant to any structural modifications. One solution is to build the molecule from scratch, using a method that is flexible enough to produce a variety of similar molecules with the same core structure.

Alexander Yurek-George and colleagues have developed the first total synthesis of spiruchostatin A, a close analogue of FK228 that was originally isolated from an extract of the bacterium *Pseudomonas*. At a crucial stage of the synthesis, the authors introduce a Nagao chiral auxiliary — a chemical that attacks only one side of the substrate molecule, preferentially forming a product that is easily separated from trace amounts of an unwanted mirror-image compound. This not only puts them on the road to obtaining the correct form of spiruchostatin A, but also activates a key intermediate so that the two halves of the final product come together with ease. **Mark Peplow**

Cancer

Assisted suicide for tumours

Cancer Cell **5,** 25–35 (2004)

Defective cells eliminate themselves by a process called apoptosis — tumours may arise if they fail to do so. Aaron D. Schimmer and colleagues have screened nearly one million compounds to find a handful that jump-start the apoptosis programme in a wide variety of tumour cells.

The effectors of the cell's death programme are the caspases. These cellular knives cut specific proteins with precision to bring about the systematic collapse of a cell. In normal cells, caspases lie dormant and their activation indicates that the cell's end is near. Like sharp tools fitted with safety caps, caspases are physically kept in check by 'inhibitor of apoptosis' proteins — IAPs. But these safety caps may also help tumour cells to survive and defy chemotherapy. For example, one IAP, called XIAP, is present at high levels in various cancers and strongly inhibits caspase-3 and caspase-7.

Schimmer *et al.* found a few small compounds that could release XIAP from caspase-3 and unleash the latter's cutting activity. These compounds induced apoptosis of tumour cell lines and sensitized them to anticancer drugs. Moreover, they limited tumour growth in mice, showing surprisingly little toxicity to normal tissues. The authors suggest that in cancer cells caspases might no longer be dormant, so that the simple removal of IAPs allows apoptosis to proceed. **Marie-Thérèse Heemels**

Microelectronics

Keep the beat

Phys. Rev. Lett. **92,** 027201 (2004)

On-chip clocks for synchronizing the timing of electronic circuits could result from a device created by W. H. Rippard and colleagues. The group induced oscillations at microwave frequencies (about 5–40 gigahertz) in a structure built from stacked layers of metals and alloys each just a few nanometres thick.

In the presence of a magnetic field, passing a current through the device causes the direction of magnetization of a ferromagnetic film of nickel–iron alloy to rotate periodically relative to the magnetization of a cobalt–iron alloy separated by a thin layer of copper. This results in a periodic change in the voltage across the layered structure at microwave frequencies.

The device is much smaller than the cumbersome quartz crystals currently used as clocks or frequency standards in information processing and telecommunications, but has comparable stability. It could conceivably be fabricated at the nanoscale directly onto chips. **Philip Ball**

Structural biology

Parasite protein probed

Structure **12,** 41–53 (2004)

Chagas disease, an incurable and sometimes fatal condition, affects an estimated 18 million people in the Americas. As the disease progresses, the heart, oesophagus, colon and peripheral nervous system suffer irreparable damage, and death can occur suddenly.

The disease is caused by a parasite, *Trypanosoma cruzi*, which passes to humans through infected blood transfusions or the faeces of some blood-sucking insects. Maria Harkiolaki *et al.* now unveil the X-ray structure of a protein that is essential to the parasite's survival.

The protein, dUTPase, is found in most organisms and is an enzyme involved in ensuring the integrity of DNA. Without it, cells die. Harkiolaki *et al.* show that the structure of *T. cruzi* dUTPase has a novel protein fold, making it very different from the human form. The finding may help in designing drugs that kill the parasite by turning the *T. cruzi* enzyme off, while leaving the human enzyme unharmed. **Helen R. Pilcher**

TALI KIMCHI

Animal behaviour

Dead reckoning in the dark

Proc. Natl Acad. Sci. USA **101,** 1105–1109 (2004)

Tali Kimchi and colleagues show that the blind mole rat (*Spalax ehrenbergi*) uses the Earth's magnetic field to guide its subterranean excursions. The researchers found that when the animals were placed in an artificially skewed magnetic field, the mole rats quickly lost their bearings.

Like all animals, blind mole rats need to navigate efficiently. In the absence of visual landmarks, they require a reliable compass to verify that they're moving in the direction they think they are (a process called path integration, or dead reckoning).

Kimchi *et al.* tested the rodents' navigational ability by presenting them with a wheel-shaped maze that had eight spokes, one of which led straight to the home nest. Mole rats left at the maze's hub, after a long walk around its perimeter, made straight for the nest. But when an artificial magnetic field was applied at 90° to the Earth's field, the animals made off in a correspondingly different direction.

The mole rats also used the Earth's magnetic field to find short-cuts in a rectangular grid, much like the streets in a US city. When faced with a zig-zag route to a food source, they subsequently devised a much shorter path, with less than half as many twists and turns. But when the magnetic field was rotated, the mole rats were less sure of themselves and frequently doubled back. **Michael Hopkin**