Rediscovering penicillin

β-lactam antibiotics such as penicillin protect neurons from death by upregulating expression of the glutamate transporter GLT1, report Jeffrey Rothstein *et al.* in the 6 January *Nature* (**433**, 73–77; 2005).

GLT1 mediates activity at the neuronal synapse, and in experimental models upregulation of the molecule can stave off neuronal damage. Such findings have prompted the fierce pursuit for a molecule that can positively modulate GLT1. To find such a molecule, the researchers screened a library of 1,040 FDA-approved compounds for their ability to increase GLT1 expression in cultured slices of spinal cord. A single class of compounds, the β-lactam antibiotics, came to the top.

β-lactam antibiotics kill bacteria by inhibiting synthesis of the cell wall. In neurons, the researchers found that the drugs upregulated the transcription of the gene encoding GLT1, through an as yet unexamined pathway. Both in culture and in mice, the drugs boosted expression of GLT1 threefold. In a model of spinal cord injury, treatment with penicillin and ceftriaxone prevented motor neuron loss. What's more, ceftriaxone could slow progression of symptoms in a mouse model of amyotrophic lateral sclerosis (ALS) which involves altered expression of glutamate transporters. The drug delayed loss of muscle strength and body weight in the mice and had a modest effect on prolonging lifespan.

Moving out

Strategies that promote movement of stem cells from the marrow to the bloodstream are used during hematopoietic stem cell transplantation. A key player in this mobilization process emerges from work in the 1 January *Journal of Clinical Investigation* (115, 168–176; 2005).

Previous studies have shown that the chemokine SDF-1 regulates aspects of stem cell behavior, such as homing to the bone marrow and adherence to bone marrow stromal cells. SDF-1 interacts with the CXCR4 receptor, which is expressed on a variety of hematopoietic cells—but the exact molecular events that occur after this interaction have remained murky. Isabelle Petit *et al.* found that SDF-1 triggered the activation of PKC-ζ. PKC-ζ was required for multiple SDF-1 mediated events, including cell polarization and adhesion to bone marrow stromal cells; conversely, overexpression of PKC-ζ enhanced motility of cells *in vitro* in response to SDF-1.

In transplantation experiments in mice, PKC-ζ was required for the engraftment of hematopoietic stem cells. What's more, injection of mice with inhibitory peptides that act as a pseudosubstrate for PKC-ζ resulted in the movement of hematopoietic progenitor cells away from the bone marrow into the blood. The results should spur research into harnessing PKC-ζ to improve mobilization regimes in stem cell transplantation.

Obedient virus

Measles virus induces cell fusion, which makes it particularly efficient at maiming tumors. But barriers to the clinical use of the virus to treat cancer remain, such as infection of non-target cells, and efforts to retarget viruses to cancer cells have encountered the problem of reduced efficiency of viral entry. In the March *Nature Biotechnology*, Takafumi Nakamura *et al.* make the measles virus leaner and meaner (*Nat. Biotech.* **23**, 209–214; 2005). Using a technique they had perfected with adenovirus to induce targeted cell fusion (*Nat. Biotech.* **22**, 331–336; 2004) the researchers created measles viruses that no longer bind to their native targets and instead efficiently infect tumor cells. To target tumor cells, the engineered viruses expressed single-chain antibody fragments against CD38, epidermal growth factor receptor (EGFR) or a mutant EGFR, proteins expressed on the surface of many tumors. When administered to mice with tumors bearing such surface proteins, the viruses killed the tumors or shrank them. The targeted treatment also prolonged survival in a mouse model of metastatic cancer.

The approach could be harnessed to engineer cancer-killing viruses aimed at a variety of molecular targets, an area of intensive research. For instance, Ira Bergman *et al.* recently souped up another tumor-killing virus, vesicular stomatitis virus (*Virology* **330**, 24–33; 2004). The virus steered clear of its native cellular target, expressed a single-chain antibody against Her2/neu and killed Her2/neu-expressing cancer cells in culture.

Written by Charlotte Schubert

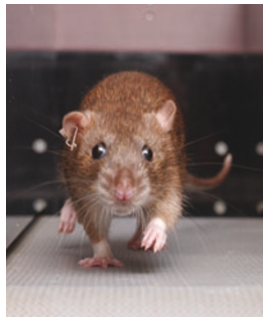
Morning madness

The incidence of heart attacks, stroke and cardiac arrythmias peaks at 10 a.m. That is a well-known fact long attributed to morning behaviors—such as starting work. A study in the 28 December *Proceedings of the National Academy of Sciences* (**101**, 18223–18227; 2004) explores another explanation for the pattern. Kun Hu *et al.* show that subtle fluctuations in the heart beat peak at ten a.m., and suggest that this is under control by the circadian clock.

To show this, the researchers examined five individuals cloistered over eight days in a controlled environment. The researchers first measured baseline heartbeat when subjects were kept on a 24-hour cycle of sleeping and waking; they found that the incidence of heartbeat fluctuations peaked at about 10 a.m. At 10 a.m. the beat of a healthy heart more closely resembles that of an unhealthy heart than at any other hour.

The researchers then shifted the subjects' sleep-wake pattern to a 28-hour cycle for several days. Independent of when the subjects woke up, or their level of activity, heartbeat fluctuation still peaked at around 10 a.m. Exactly how endogenous circadian rhythms influence heartbeat and whether the circadian rhythm can explain the morning spike in the incidence of adverse cardiovascular events remains to be determined.

Bred to run



University of Michigan Photo Services, Martin Vloet

Rats genetically selected to tire quickly on treadmills score high on tests for cardiovascular risk factors compared to rats bred to run without tiring. The rats selected for low aerobic capacity—who could run for 14 minutes—had higher levels of insulin resistance, blood pressure and obesity than rats with high aerobic capacity—who could run for 42 minutes. Even when they were young, and not yet fat, the low-capacity rats scored high on such measures. The findings, by Ulrik Wisløff *et al.* in the 21 January *Science* (307, 418–420; 2005), suggest that the low-capacity rats had metabolic syndrome, physical changes that often precede cardiovascular disease and diabetes.

The underlying defect in the low-capacity rats might originate with the mitochondria, as these rats had decreases in the levels of transcription factors that promote mitochondrial growth, such as PGC1-α. The results are in line with studies in people and animals suggesting that impaired regulation of oxidative pathways in mitochondria may contribute to cardiovascular and metabolic disease. The animals should also prove useful as badly needed models to study metabolic syndrome and cardiovascular disease.