Medicine

Cancer-killing virus on a drip

Cancer Cell **4,** 263–275 (2003)

There is a new virus on the block that kills tumours but not their host, according to David F. Stojdl and colleagues.

Budding tumours switch off from many signals around them; for example, they often become indifferent to interferon, a major regulator of cell growth and death. But this so-called cytokine also coordinates a cell's antiviral response, making tumour cells with disabled interferon signalling vulnerable to a viral attack. It is thus feasible — in theory — to eliminate tumours by unleashing a virus. But it's no good if the patient then succumbs to a raging viral infection.

Stojdl *et al.* have now identified variant strains of the vesicular stomatitis virus (VSV) that kill the tumour and spare the host. Following simple intravenous delivery in mice, the virus destroyed tumours — even metastases — and was rapidly cleared by the mice thereafter. What's the secret?

To evade an antiviral attack by immune cells, ordinary VSV also tampers with interferon signalling in the cell. Stojdl *et al.* show that their mutant strains lack the capacity to do so. Thus, they induce a powerful 'cytokine cloud' wherever they go, and a proper antiviral response in healthy cells. Tumour cells are oblivious to this cloud and are eliminated one by one by the virus. **Marie-Thérèse Heemels**

Physiology

Hotter equals smaller

Proc. R. Soc. Lond. B doi:10.1098/rspb.2003.2538 (2003)

Cold-blooded animals such as fish show an inverse relationship between the temperature at which they are reared and their final body size — something known as the temperature–size rule. Now David Atkinson *et al.* show that single-celled organisms called protists follow a similar rule.

The researchers carried out a meta-analysis of published data on water-dwelling protists, including amoebae, ciliates, diatoms, dinoflagellates and flagellates. By combining 65 data sets, they found that the organisms' average size decreases by 2.5% for every 1 °C boost in temperature above 15 °C.

The team proposes two hypotheses to explain the size trend. The availability of respiratory gases such as oxygen and carbon dioxide could limit growth as the temperature rises, because the amount of gases dissolved in water decreases, whereas the organisms' demand for such gases rises because of their increased metabolic rate. Alternatively, the organisms may gain a competitive edge by dividing earlier as population growth increases.

The equation can be used to better estimate how the number or biomass of protists changes with temperature, and this might be useful in modelling aquatic ecosystems. **Helen Pearson**

Glaciology

Thin ice

Science **302,** 856–859 (2003)

In two abrupt episodes during the past ten years, the Larsen Ice Shelf on the Antarctic Peninsula lost its northern-most sections — Larsen A and Larsen B — when they fragmented into icebergs. What caused the break-up, and what does it imply for the much larger Larsen C shelf that makes up the rest of this sea-ice sheet? Andrew Shepherd and colleagues say that the Larsen Ice Shelf has been thinning steadily since at

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least 1992, and suspect that this contributed to the weakening of Larsen A and B, which together had an area of more than 5,000 km^2.

The authors studied nine years' worth of satellite altimeter measurements of the ice sheet's surface height, and find that, since 1992, Larsen B and C have decreased in height at annual rates of about 0.17 and 0.08 metres, respectively. These decreases do not necessarily imply melting-induced mass loss: some of the change might have come from increased densification of the ice. Yet that alone is unlikely to account for all of the thinning; the researchers say that there has also been melting of basal ice. If their estimate of the ice erosion rate is correct, within 100 years Larsen C will be close to the thickness at which Larsen B broke up. **Philip Ball**

Prion diseases

Untangling toxicity

Science **302,** 871–874 (2003)

Giovanna Mallucci *et al.* have found a way to reverse the first signs of brain destruction in a mouse model of prion disease.

The disease-associated prion protein causes normal versions of the protein to change shape and stick together in the brain. As the prion clumps accumulate, neurons die, leaving the brain riddled with holes like a sponge. But what kills the neurons? To investigate this, Mallucci *et al.* created genetically engineered mice that produce the normal prion protein in neurons during the first 10–11 weeks of life only. Older mice continue to produce this protein in other brain cells.

The authors injected abnormal prions into the brains of the mice at 1 week old. By 8 weeks, all the mice had developed early signs of 'spongiform' disease. Remarkably, these signs disappeared in 12-week-old mice, when neurons were no longer making the normal protein. And the animals remained disease-free for at least 48 weeks, even though prion clumps were still being produced by other brain cells.

Mallucci *et al.* suggest that conversion of the normal protein to the disease-related form is toxic only if it occurs within neurons. It remains to be seen whether eliminating normal prion proteins in human neurons could be equally beneficial. **Clare Thomas**

Cell biology

Arrested replication

J. Cell Biol. **163,** 245–255 (2003)

Cells use several mechanisms to ensure that, when DNA is damaged, it is repaired before it can be replicated and produce mutations in daughter cells. Matthew P. Stokes and W. Matthew Michael now describe a previously unsuspected pathway that prevents global DNA replication when damage is present.

DNA damage is known to activate factors called checkpoint proteins, which prevent new replication from being initiated. But it was unclear whether damaged DNA itself is sensed by checkpoint proteins, or whether ongoing replication stalls at the site of damage, forming abnormal 'replication intermediates' that are recognized by the checkpoint machinery. Using frog extracts, Stokes and Michael find that the presence of damaged plasmids (circular DNA molecules) causes replication to stall on separate, undamaged chromosomes. This suggests that the damaged DNA activates a diffusible replication inhibitor that can act on other DNA molecules. The inhibitor prevents DNA from binding to PCNA, a complex that tethers DNA-replicating enzymes to chromosomes. Unexpectedly, activation of the inhibitor is independent of the DNA-damage checkpoint, but causes checkpoint activation on undamaged DNA.

The nature of the inhibitor is unknown, but preliminary data suggest that it does not bind to PCNA directly. Instead, it may bind 'factor X' — a hypothetical protein that loads PCNA onto DNA. **Angela K. Eggleston**