contain measurably different amounts of ^{15}N in their nitrogen pools. They found that, in the forest growing on nitrogen-rich sedimentary rock, the ^{15}N-content in both plants and soils matched that of the bedrock; this was not true for forests growing on the nitrogen-poor igneous rock, ruling out the possibility of significant nitrogen contribution from this rock.

Although the nitrogen-isotope measurements helped build the case for sedimentary bedrock as a nitrogen source for forests, they alone were not a smoking gun. To extend the findings beyond the carefully matched forest stands, the authors carried out a regional analysis of similar conifer forests in California. Sure enough, they found that the above-ground biomass of forests growing on nitrogen-rich sedimentary bedrock was almost 50% bigger by mass than that of forests on igneous bedrock, after accounting for differing ages of tree stands.

The 'imprint' of nitrogen from bedrock on streams[5] and soils[6] has previously been reported for isolated sites in the same general region as the current study[3], and so Morford and colleagues' analysis makes the case for this as a regional pattern. But less than 2% of conifer-forest soils in that same region have a nitrogen capital as high as the sedimentary-bedrock forest that has been intensively studied by the authors (see Supplementary Information for ref. 3). This means that the high input of nitrogen from bedrock beneath that forest — which is equivalent to atmospheric nitrogen inputs — probably represents an upper estimate for the extent of this phenomenon. With 75% of Earth covered by sedimentary and related rock types[7], there is a real need to explore the phenomenon beyond this region to determine what more common levels of bedrock-nitrogen inputs are for ecosystems elsewhere. ■

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CANCER

Tumour-fighting virus homes in

An early clinical trial demonstrates the delivery and replication of a cancer-killing virus in metastasized tumour tissue. These promising results could provide a foundation for systemic virotherapy for patients with cancer. SEE LETTER P.99

EVANTHIA GALANIS

Clinical advances in cancer research are often slow to materialize, in part because the efficacy of a treatment has to be balanced against its potential toxicity to normal tissues. Infection of tumours with oncolytic (cancer-killing) viruses has been explored as a new type of treatment that is not cross-resistant with approved cancer therapies and, being target-specific, may have fewer toxic side effects. On page 99 of this issue, Breitbach *et al.*[1] describe a phase I clinical trial in which an intravenously delivered oncolytic poxvirus was capable of replicating selectively in metastasized tumours. This is a milestone in the development of an effective oncolytic agent for systemic administration.

Oncolytic viruses became a focus of attention for cancer therapy following observations that natural viral infection or vaccination can lead to spontaneous regression of malignancies[2]. Unhindered by interferon-mediated antiviral defence, which is compromised in many tumours[3], these viruses specifically attack cancer cells by gaining entry through receptors that are overexpressed in these cells and/or by exploiting molecular pathways associated with malignant transformation for their replication[4,5]. As the virus starts to replicate at the tumour site, its destructive effect increases. Strategies are being devised to make this process even more efficient by deploying genetically engineered oncolytic viruses that carry therapeutic or immunomodulatory transgenes.

In advanced cancer, systemic dissemination of solid tumours is linked with a poor prognosis. Before oncolytic viruses can be used to treat such metastases, they must be able to reach and replicate in metastatic sites following intravenous administration. But there are obstacles to be overcome, including the antiviral immune response, and the uptake and destruction of the virus by the endothelial reticulum system in the liver and spleen.

Breitbach *et al.*[1] take up the challenge using a genetically engineered oncolytic poxvirus known as JX-594. This is a smallpox-vaccine derivative of Wyeth-strain vaccinia virus carrying an inactivated thymidine kinase gene to increase tumour specificity, and expressing two transgenes: one encoding human granulocyte–macrophage colony-stimulating factor (GM-CSF) to stimulate anti-tumour immunity and the other β-galactosidase, a surrogate marker for detecting viral gene expression.

The authors tracked the virus in 23 cancer patients, all with advanced solid tumours that were resistant to other treatments. Patients were each given one dose of JX-594 at one of six different dosage levels by intravenous injection; these were all well tolerated. The maximum feasible dose was 3×10^7 plaque-forming units (PFU) per kilogram of body weight (corresponding to a total dose of about 2×10^9 PFU). This dosage is in line with doses of other oncolytic viruses that can safely be given intravenously, including adenovirus, reovirus, paramyxovirus (Newcastle disease virus and measles) and Seneca Valley virus.

Breitbach *et al.* demonstrated such dose-dependent delivery of the virus (at 8–10 days after intravenous administration) to metastatic tumour deposits from a variety of tumour types, including leiomyosarcoma, mesothelioma, and lung, ovarian and colorectal cancers. In eight patients who had received 10^9 PFU or more per dose, delivery and replication were confirmed by quantitative polymerase chain reaction in five patients and by immunohistochemistry using a polyclonal anti-vaccinia antibody in six patients: granular cytoplasmic staining evident in tumour tissue was indicative of replicating virus (viral factories; Fig. 1).

Although JX-594 administration seemed to result in disease control in a dose-dependent way, with patients treated with the higher doses benefitting the most, viral infection and replication in metastatic deposits did not consistently affect clinical outcome. Some patients experienced clinical benefit — defined as disease stabilization for more than ten weeks — even when there was no evidence of viral replication in their tumour biopsies. By contrast, two out of six patients who were JX-594-positive by immunohistochemistry had progressive disease at first evaluation, even though replicating virus was detected in their metastatic tumours.

The explanation for these discrepancies may be down to several factors. For example, patients were allowed only one viral dose and treatment cycle: as with other cancer therapies, it is unlikely that a single round of treatment would be enough to stop tumour growth. Sampling variability in patients, whether

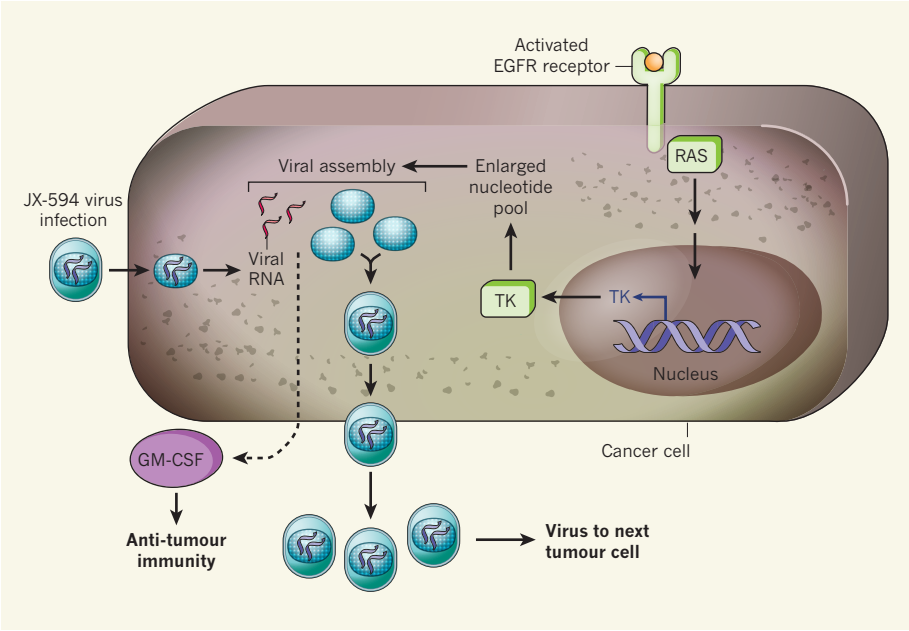

Figure 1 | Common oncogenic mutations in cancer cells encourage replication of the genetically engineered oncolytic JX-594 virus[1]. The virus takes advantage of a cancer cell's uncontrolled epidermal growth factor receptor (EGFR)–RAS signalling pathway. To replicate, this thymidine kinase (TK)-deficient virus relies on expression of TK by cancer cells. The newly assembled viruses then leave the cell to infect other tumour cells. These viruses also secrete GM-CSF, a factor that stimulates anti-tumour immunity. In normal cells, however, viral replication is blocked because this virus cannot efficiently exploit the cell's replication machinery.

positive or negative for JX-594, may also have confounded the results. Reassuringly, the normal tissue of patients in whom replication was detected was negative for replication by immunohistochemistry.

The limitations notwithstanding, these results convincingly demonstrate successful dose-dependent delivery and replication of an oncolytic virus in metastatic disease sites, following intravenous administration in patients with primary solid tumours. Although oncolytic viral replication in metastatic disease sites after systemic administration has been reported before, those studies are undermined by detectable replication only in isolated patients or by methodology unable to distinguish properly between input and progeny virus. Promising preclinical data, however, point to several strategies for enhancing systemic delivery of oncolytic viruses, including the use of cell carriers, cationic liposomes and polymers.

Large randomized trials to test oncolytic viruses in cancer treatment are ongoing or soon to be activated. These will investigate the potential synergistic cytotoxicity between oncolytic viruses and more conventional therapeutic approaches such as chemotherapy, small-molecule cell-cycle inhibitors, radiation therapy and anti-angiogenesis agents[6–9]. In addition, they will exploit induction of a systemic anti-tumour immune response in association with oncolytic tumour-cell death and expression of immunomodulatory transgenes[10].

Examples of such trials include the soon-to-be-completed phase III trial of an attenuated strain of herpes simplex virus-1 that encodes GM-CSF in patients with metastatic melanoma; the recently activated phase III trial testing addition of reovirus to paclitaxel/carboplatin chemotherapy in patients with recurrent head and neck cancer; and a randomized phase II trial comparing JX-594 with the best supportive care in patients with hepatocellular carcinoma for whom treatment with the drug sorafenib has failed.

In contrast to Asian countries, no virotherapy agent has so far been approved in the United States or Europe. The outcome of these trials may change this, generating additional valuable clinical tools for oncologists. ■

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AGEING

Blood ties

The brain's ability to generate new neurons declines with age. This reduction is mediated by increased levels of an inflammatory factor in the blood of ageing mice and is associated with deficits in learning and memory. SEE LETTER P.90

RICHARD M. RANSOHOFF

On the face of it, the production of new neurons in the adult mammalian brain[1,2] sounds like a good thing. Interventions that reduce neurogenesis in adulthood can be associated with impaired brain function (in particular, with deficits in learning and memory), and the formation of neurons from neural stem cells declines with age. Understanding neurogenesis is therefore a major research goal, and neural stem cells are a tantalizing target for attempts to treat damaged brains by stimulating the production of neurons and other brain cells. On page 90 of this issue, Villeda and colleagues[3] report a crucial advance in this direction by identifying a blood-borne factor that affects neurogenesis and cognitive function in ageing mice.

With age, not only might the activity of neural stem cells (NSCs) deteriorate, but their immediate environment (the neurogenic niche) might also become compromised. The NSC niches lie near blood vessels, and factors that alter neurogenesis, such as exercise or systemic inflammation[4,5], might act by modifying blood cells or the abundance of signalling proteins in the blood plasma. Villeda *et al.* proposed, therefore, that agents present in the blood might affect neurogenesis.

To test this possibility, the authors[3] used a surgical procedure called parabiosis to connect the flank tissues of pairs of mice so that the animals developed a shared circulation. In mouse pairs of the same age (young–young or old–old), parabiosis alone did not affect neurogenesis. In the old–young pairs, however, the older animal showed enhanced neurogenesis, and in younger