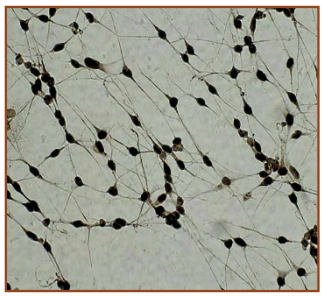
## Must migrate



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Individuals with neurofibromatosis type 1 (NF-1) develop benign tumors composed mainly of fibroblasts and Schwann cells (shown here in culture). These neurofibromas are heavily infiltrated by mast cells, which normally mediate wound healing and tissue repair.

In the December 15 *Journal of Clinical Investigation,* Wade Clapp and colleagues report that neurofibromas may form when molecularly deviant Schwann cells beckon corrupted mast cells. This distressing behavior is caused by alterations in the dose of *NF1*, which encodes neurofibromin, a GTPase-activating protein for Ras. NF-1 afflicts one in 3,500 individuals, who are heterozygous for *NF1*.

In cell culture assays, the investigators found that mouse Schwann cells lacking *NF1* secreted substantial amounts of soluble Kit ligand. This activator of c-Kit acted as a potent chemotactic stimulus for mast cells-but only if the mast cells were heterozygous for *NF1*.

The data are in line with the notion that loss of the second allele of *NF1* in Schwann cells initiates tumor formation. Exactly how such loss leads to increased output of Kit ligand is unknown. But similar events may happen in humans, where neurofibromas pump out excessof Kit-ligand transcripts. The authors speculate that mast cells—and possibly other cells in the milieu—may alter the local environment to promote tumor formation. The findings point to possible therapies for NF-1, including c-Kit inhibitors and other drugs that target mast cell migration, some of which are already in clinical trials.

## Phage power

New antibiotic drug candidates have emerged from bacteriophages. Bacteriophages interfere with critical cellular processes to transform their hosts into factories of phage reproduction. Jing Liu *et al.* took advantage of this subversive trait to identify phage polypeptides that inhibited growth of *Staphylococcus aureus*. Resistance of this microbe to last-resort antibiotics like vancomycin is growing fast.

The investigators sequenced 26 *S. aureus* phages and identified 31 phage peptide families that inhibited growth when expressed in the bacterium. They then used this information to identify two compounds that potently inhibited microbe growth, as reported in the February *Nature Biotechnology*. These compounds were identified by screening 125,000 small-molecules for their ability to block the interaction of a phage peptide with its target. Both compounds blocked DNA synthesis in bacteria but were not toxic to human cells in culture.

The study emerges against a backdrop of other work that co-opts phages to treat bacterial diseases. Other groups have recently shown that whole phages or phage proteins that lyse bacteria can act as effective antibiotics in various experimental systems. Whether these two new compounds will make it through the pipeline is unclear. If not, the raw materials for new drugs are not yet exhausted: by some estimates there are about 100 million phage species on the planet.

Charlotte Schubert and Pierrette Lo

## Too much excitement

Stroke, trauma and other insults can unleash a deadly cascade in neuronal cells. Glutamate receptors are nudged into overdrive, permitting a massive and toxic influx of calcium into neurons. In cell culture, anti-excitotoxicity therapies that block these receptors rescue neurons that would otherwise have died, but clinical trials generally have failed to benefit patients. In the 26 December 2003 *Cell*, Michelle Aarts *et al.* uncover another mechanism that prompts calcium inrush.

The investigators exposed neurons in culture to oxygen-glucose deprivation, which results in glutamate receptor activation and neuronal death. They identified a lethal cation current in this system mediated by TRPM-7, a member of the transient receptor potential cation channel superfamily. Blocking or suppressing TRPM-7 expression prevented anoxic cell death—even in the absence of excitotoxic therapy. Although many events contribute to neuronal death after injury, the investigators speculate that TRPM-7 activation could explain the failure of excitotoxic therapy.

## Mighty microRNAs

**The growing influence of microRNAs (miRNAs)—small noncoding RNAs of about 22 nucleotides—has extended now to hematopoietic cell differentiation in mammals. Humans have between 200 and 255 genes that encode miRNAs, some of which are found at sites of DNA breaks or deletions linked to leukemia. In the 2 January *Science*, Chang-Zheng Chen *et al.* assign a function to three mammalian miRNA genes.**

**The investigators cloned 100 unique miRNAs from mouse bone marrow and homed in on those preferentially expressed in hematopoietic tissues. Three miRNAs were expressed at low levels in undifferentiated hematopoietic cells, and at high levels in various distinct lineages. For instance, one miRNA, miR-181, was preferentially expressed in the B-lymphoid cells of mouse bone marrow. The investigators found that miR-181 regulated B-cell differentiation: ectopic expression of miR-181 in hematopoietic precursors in cell culture and in whole animals boosted B-cell production.**

**How do these little RNAs pack such a punch? In invertebrate systems, miRNAs repress translation of RNA targets during development. The authors note that uncommitted hematopoietic progenitor cells promiscuously express a range of RNAs, and speculate that translational repression by miRNAs might occur as cells gain their identities.**

## Bone holes

Hyperactive bone-resorbing cells drill painful holes in the bones of patients with multiple myeloma, an incurable B-cell cancer. The immunoglobulin-secreting cancer cells migrate to bone and release factors that upset the balance between resorption and formation that keeps normal bones healthy. In the 25 December *NEJM*, Erming Tian *et al.* uncover one such factor contributing to bone destruction.

The authors provide evidence that in humans, expression of the dickkopf-1 (*DKK1*) gene by multiple myeloma cells exacerbates lesions by blocking the differentiation of osteoblasts, which lay down new bone. This prevents repair of lesions initiated by osteoclasts, the bone-resorbing cells. The investigators found that in culture, recombinant human DKK-1 or bone marrow serum containing an elevated level of DKK-1 inhibited the differentiation of osteoblast precursor cells. Targeting the DKK-1 protein might be one way to provide relief to patients with weakened bones.