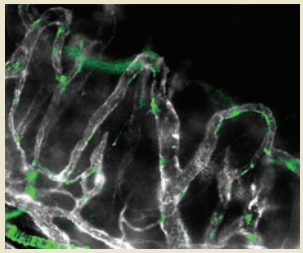
Wound healing by force



It has long been assumed that the repair of blood vessels in wounds occurs through the recapitulation of developmental angiogenesis, involving capillary sprouting, intussusception from smooth muscle and vasculogenesis from progenitor cells. Now Kilarski and colleagues have shown that in the earliest stages, vessels are formed not *de novo* but rather by the expansion of preexisting vessels into the wound area, initiated by fibroblast-mediated wound contraction. In two model systems—chick chorioallantoic membranes (CAM) implanted with a collagen matrix and injured mouse cornea—the researchers observed vascular loops protruding from vessels in the periphery of the region undergoing repair. They find that using a rigid matrix that abolishes contraction in the CAM system prevents revascularization, indicating that this action is dependent on biomechanical forces. In addition, they show that growth factors are not required for the early stage; antibody directed against vascular endothelial growth factor does not interfere with revascularization until several days into the process, after vascular loops have appeared. Although this so-called 'looping angiogenesis' seems to be important in wound healing, the molecular mechanisms are unknown and the importance of this process in the vascularization of tumors or other tissues remains to be seen. (*Nat. Med.* **15**, 657–665, 2009) *LD*

Awakening parasitic nematodes

A key stage in the life cycle of the model worm *Caenorhabditis elegans* is also shared by parasitic nematodes, opening the way toward new leads for drugs to treat worm infestations, which affect more than 1 billion people and are the primary cause of anemia worldwide. Previously, Mangelsdorf and colleagues identified a *C. elegans* signaling pathway that initiates or ends a hibernation-like state called the dauer diapause, showing that a steroid hormone called dafachronic acid promotes dauer recovery. They now provide *in vitro* evidence that the same pathway is conserved in several parasitic nematodes, including hookworms, and that dafachronic acid–like molecules can interrupt the infectious cycle by tricking these parasites into maturing before they are in the host environment needed for them to complete the life cycle. As current anthelminthics target only adult, nondormant forms of parasitic nematodes, this approach may be more effective in eliminating persistent autoinfection *in vivo*. X-ray crystallographic analysis of the steroid hormone nuclear receptor for dafachronic acid in one of the most problematic parasitic nematodes, *Strongyloides stercoralis*, provides mechanistic insight into the receptor's activation and may be useful in identifying species-selective ligands based on dafachronic acid. (*Proc. Natl. Acad. Sci. USA* **106**, 9138–9143) *PH*

Making cells count

Synthetic networks that can count the number of specific events experienced by cells would be useful in such applications as gene therapy vectors that replicate a finite number of times or cell therapies with limited proliferative potential. Friedland *et al.* now present two genetic networks that have the ability to count chemical cues and trigger the expression of a reporter gene in *Escherichia coli* after a requisite number of events have occurred. Their first counter design comprises a cascade of genes under both translational and transcriptional control; the number of events is recorded by the presence of different expressed proteins. The transcriptional control is provided by promoter-specific RNA polymerases with long half-lives, whereas translational control is mediated by transactivating small RNAs with a very short half life. The chemical cue activates the production of the transactivating RNA, which allows the production of the RNA polymerase specific for the next gene in the cascade, but because of RNA turnover, the mRNA of the next gene can be translated only after the next event occurs. In a second counter design, the authors 'hardwire' the counter into the DNA itself. Each counting unit comprises an inducible promoter, an inverted promoter and a DNA flipase that can invert the counter DNA sequence. The whole unit is placed between the recognition sites of the flipase. When expression of the flipase is triggered, it inverts the counting unit, terminating the production of the flipase. This primes the next counting unit for transcription by bringing the inverted promoter into the correct orientation. (*Science* **324**, 1199–1202, 2009) *ME*

Written by Kathy Aschheim, Laura De Francesco, Markus Elsner & Peter Hare

Stuck on glioma stem cells

The theory that tumors contain only a small subset of cells, called cancer stem cells, that uniquely have the ability to initiate a tumor *de novo* has received increased attention in recent years. Even so, the study of cancer stem cells has been hampered by the difficulty of isolating cells with high enough efficiency and of expanding them *in vitro* for functional studies. Pollard *et al.* present a method for isolating and expanding cancer stem cells derived from malignant gliomas and show that these cells can be used for transcriptional profiling and drug screening applications. Their method makes use of established procedures for cultivating adherent neural stem cells. Individualized primary tumor cells are added to laminin-coated culture dishes containing optimized neural stem cell medium. The resulting cell population can be readily expanded, expresses several markers for neural stem cells and is highly tumorigenic. Glioma stem cell lines from different patients showed expression profiles closer to those of neuronal stem cells than to those of adult brain tissue cells, but showed significant interpatient variations. (*Cell Stem Cell* **4**, 568–580, 2009) *ME*

Targeting age-related macular degeneration

Inhibitors of vascular endothelial growth factor (VEGF)-A are used clinically to treat wet age-related macular degeneration (AMD), a blinding disease characterized by the growth of new blood vessels in the choroid layer of the eye. But VEGF-A antagonists fail to help a large fraction of patients, and alternative treatments are needed. A recent study by Takeda *et al.* reveals a new potential drug target for AMD. The authors first determine that the chemokine CC-motif receptor 3 (CCR3) is expressed on choroidal endothelial cells only in individuals with AMD. Using a mouse laser-injury model of choroidal neovascularization, they show that an anti-CCR3 antibody is therapeutically effective and slightly more potent than an anti-VEGF-A antibody. Thus far, CCR3 has been known as a component of inflammatory rather than angiogenic processes, but the authors find that the effects of CCR3 targeting in their model are mediated by angiogenic and not inflammatory pathways. Moreover, the angiogenic pathway involved seems to be independent of the VEGF-A pathway. Initial toxicity studies suggest that CCR3 inhibition is safer than VEGF-A inhibition. (*Nature*, published online 14 June 2009; doi:10.1038/nature08151) *KA*