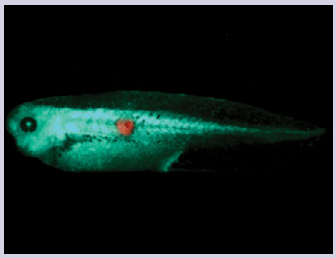


Bioelectric signals: a diagnostic marker for cancer

Cancer is widely regarded as a developmental disorder. Endogenous bioelectric signals (patterns of transmembrane voltage gradients in tissues) underlie a conserved set of mechanisms that regulate development and might, therefore, be involved in tumorigenesis. Chernet and Levin investigated this possibility by testing the role of transmembrane potential in tumorigenesis in *Xenopus*. Using a fluorescent voltage reporter dye, they show that oncogene overexpression in *Xenopus* induces the formation of tumour-like structures that are characterised by a depolarised membrane potential. Importantly, this bioelectric signature can be detected before the tumours become apparent and, remarkably, hyperpolarisation of oncogene-bearing cells by expression of various ion channels reduces tumour formation. These data implicate bioelectric signalling in tumorigenesis and suggest new approaches for the early detection of tumours and for the development of anti-cancer therapies. *J.B.* **Page 595**

Respiratory failure in myotonic dystrophy 1

Respiratory failure is a life-threatening complication of myotonic dystrophy type 1 (DM1), a disorder caused by abnormal expansion of CTG trinucleotide repeats in the 3′ untranslated region of the DM1 protein kinase gene. But does respiratory failure in DM1 involve the diaphragm muscle only or is the neuronal network that controls the respiratory rhythm also involved? To find out, Panaite et al. analysed DMSXL transgenic mice, an established animal model for congenital DM1. They report that DMSXL mice have impaired respiratory function, pathological changes in their muscle fibres and diaphragmatic neuromuscular junctions, and reduced numbers of unmyelinated phrenic afferents. These results suggest that, although failed communication between the diaphragmatic muscle fibres and nerve endings might be the main cause of respiratory failure in DMSXL mice, altered regulation of breathing could also be involved. *J.B.* **Page 622**

New mouse model for Parkinson's disease

Age-dependent degeneration of midbrain dopaminergic (mDA) neurons underlies the cognitive and motor symptoms of Parkinson's disease. Havrda et al. previously reported that mice that lack the transcription factor Id2, which is expressed in the developing CNS, have fewer dopaminergic neurons in the olfactory bulb and reduced olfactory discrimination, a preclinical marker of Parkinson's disease. Now, the researchers report that *Id2*$^{-/-}$ mice exhibit age-dependent degeneration of mDA neurons that is associated with changes in locomotor activity. Young *Id2*$^{-/-}$ mice had reduced dopamine transporter (DAT) expression, a biomarker of Parkinson's disease. Moreover, DAT expression was found to be dependent on Id2 expression in an *in vitro* dopaminergic neuron differentiation model. Thus, the *Id2*$^{-/-}$ mouse represents a new model in which to study the progression and treatment of neurodegenerative disorders that involve the dopamine system. *J.B.* **Page 819**

Innate immunity: clues from zebrafish

Signalling from Toll-like receptors (TLRs) initiates the innate immune response, the body's first line of defence against invading microbes. Because the adaptor molecule myeloid differentiation factor 88 (MYD88) is required for TLR signalling, MYD88 deficiency causes a human primary immunodeficiency syndrome. Here, van der Vaart et al. characterise a zebrafish line that expresses truncated Myd88. Zebrafish *myd88* mutants, they report, are more susceptible to infection by bacterial pathogens than are wild-type fish. Moreover, expression of many (but not all) of the transcription factors, signalling factors and effector molecules that are central to innate immunity is dependent on Myd88 signalling during bacterial infections. These and other results establish the zebrafish *myd88* mutant as a valuable tool for studying the role of TLR signalling in innate immune processes underlying infectious disease and disorders associated with immune dysregulation, such as cancer. *J.B.* **Page 841**

EPO pre-treatment for haemorrhagic shock

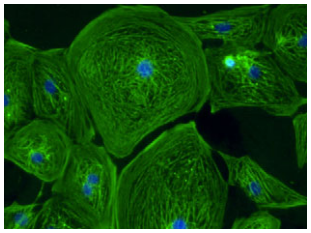
Blood loss (haemorrhage) is responsible for nearly 2.5 million trauma-related deaths annually. Haemorrhage can be managed with fluid resuscitation and blood transfusions but, because this treatment combination can lead to haemorrhagic shock and life-threatening organ damage, pharmaceutical interventions that limit this damage are urgently needed. Nandra et al. investigated one possible intervention – pre-treatment with erythropoietin (EPO), a hormone that regulates erythroid progenitor cell proliferation in bone marrow. They show that daily treatment of rats with EPO before induction of haemorrhagic shock attenuates organ injury, mobilises endothelial progenitor cells and activates the Akt-eNOS pro-survival pathway. These results provide new insights into how EPO pre-treatment protects against haemorrhagic shock and suggest that its use before foreseeable haemorrhage (for example, before surgery) could limit the tissue injury associated with haemorrhage and fluid resuscitation. *J.B.* **Page 701**

Role of CagA in *H. pylori* gastric cancer

Infection with *Helicobacter pylori* is linked to a wide range of gastric disorders, including stomach cancer. Although only a small proportion of infected individuals develop cancer, most cases of gastric cancer are attributed to *H. pylori*. Several virulence factors have been implicated in *H. pylori*-associated carcinogenesis, particularly the effector protein CagA. Here, Neal and colleagues use a novel transgenic zebrafish model to investigate the effects of CagA on

digestive tract epithelial cells. They demonstrate that CagA induces proliferation of the zebrafish intestinal epithelium via activation of the canonical Wnt signalling pathway. In addition, they provide the first *in vivo* evidence for cooperation between CagA and the tumour suppressor p53 in oncogenesis. The study highlights the potential of the zebrafish system for exploring genetic interactions between pathogen virulence effectors and host cell signalling proteins. *P.D.* **Page 802**

Patient-derived iPSCs: a new model for Friedreich's ataxia



Friedreich's ataxia (FRDA), which is characterised by neurodegeneration and cardiomyopathy, is caused by expanded GAA repeats within the gene encoding frataxin, a conserved mitochondrial protein. This mutation reduces frataxin expression, but the lack of good models has hampered attempts to understand the pathogenesis of FRDA. Hick et al. now describe the derivation of induced pluripotent stem cells (iPSCs) from two patients with FRDA, and differentiation of these iPSCs into neurons and cardiomyocytes. They show that, compared with control iPSC-derived cells, FRDA iPSC-derived neurons and cardiomyocytes exhibit some mitochondrial defects. Furthermore, the expanded GAA repeats show high instability in FRDA iPSCs compared with the differentiated cells. Because the patient-derived differentiated cells described here recapitulate the genetic aspects of FRDA and express measurable phenotypes, these cells should facilitate research into FRDA pathogenesis and treatment. *J.B.* **Page 608**

Biomaterial promotes muscle cell regeneration *in vivo*

Duchenne's muscular dystrophy (DMD) is a recessive, X-linked skeletal muscle disorder that is characterised by muscle tissue weakness and wasting. In DMD, muscle cells lose the ability to regenerate in response to injury, and ultimately undergo necrosis. Amyotrophic lateral sclerosis is another condition in which the regenerative capacity of skeletal muscle cells is impaired, but, in this case, muscle loss occurs via atrophy. In light of recent evidence that biomaterials mimicking healthy extracellular matrix can enhance regeneration, Kuraitis et al. explored the therapeutic potential of a collagen-based matrix in mice. Treatment with the matrix promoted skeletal muscle regeneration *in vivo* and *in vitro*; however, the positive effects were observed only in a necrotic environment. This study provides a promising new therapy for skeletal muscle disorders that involve active necrosis, such as DMD. *P.D.* **Page 793**

An inducible knockout mouse model for *PTEN* cancers

Mutations in *PTEN*, a tumour suppressor gene, occur at a high frequency in human cancer. The gene encodes a phosphatase that acts in signalling pathways to negatively regulate cell growth. Inactivation of *PTEN* leads to increased cell proliferation and reduced cell death, resulting in tumour formation. Until now, it has proven difficult to induce complete PTEN loss in different tissues simultaneously because of the protein's crucial role in development. Here, Mirantes and colleagues describe an inducible *PTEN* knockout mouse model. Tamoxifen-induced *PTEN* deletion resulted in the rapid development of hyperplasias and neoplasias in endometrial, prostrate and thyroid tissue and administration of a known anti-tumoral drug, everolimus, hindered carcinogenesis. These data validate the model as a valuable tool for investigating PTEN-negative cancers and for testing the efficacy of new therapies. *P.D.* **Page 710**