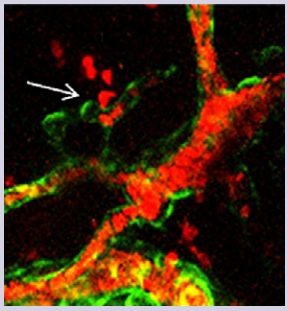

Venous malformations: TIEing genotype to phenotype in zebrafish

Cutaneomucosal venous malformations (VMCMs) are rare inherited disorders caused by mutations in the tyrosine receptor kinase TIE-2. Although thought to function in vascular development and stability, exactly how TIE-2 mutations cause VMCMs is unclear, partly because *Tie-2*$^{-/-}$ mice are embryonic lethal owing to heart defects. Gjini et al. now report that a *tie-2* loss-of-function zebrafish mutant is viable into adulthood. Unlike mice, the function of Tie-2 in zebrafish seems to be redundant to that of Tie-1 during early heart development, although both proteins are required for endocardial-myocardial interactions at later stages. In addition, testing of statins in the *tie-2* zebrafish mutant suggests that these drugs act by reducing endothelial cell-cell contacts in newly forming brain vessels. *S.A.* **Page 57**

Partial inhibition of Akt activity might be enough to beat cancer

Hyperactivation of the growth-promoting Akt signalling pathway is common in many human tumours, and studies in mice indicate that ablation of Akt activity reduces tumour initiation and progression in vivo. However, it is unlikely that complete Akt inhibition can be tolerated in a clinical setting, so it is unclear whether drugs that partially inhibit the Akt pathway will have a therapeutic effect. Wullschleger et al. now show that a moderate (~twofold) decrease in Akt activity delays the development of tumours in cancer-prone *PTEN*$^{+/-}$ mice, providing hope that Akt inhibitors that are currently under development will benefit cancer patients. *S.A.* **Page 95**

Insight into metastasis through studying *Drosophila* haemocyte migration

Understanding the molecular events that underlie metastasis is a major goal of cancer research. In line with the involvement of the cytoskeleton in cell motility and invasion, the Ena/VASP family of actin-regulatory proteins is implicated in metastasis; for example, Mena is upregulated in several human cancers. To investigate the potential role of this protein family in metastasis, Tucker et al. address how Ena, the *Drosophila* homologue of Mena, influences the migration of embryonic macrophages (haemocytes) in the fly embryo. In contrast to reported observations of mammalian fibroblasts in vitro, Ena overexpression increases macrophage migration speed in vivo. *S.A.* **Page 126**

PEX13-knockout mice model Zellweger syndrome

Zellweger syndrome (ZS), a fatal autosomal recessive disorder, is caused by defects in peroxisome biogenesis. Using a conditional knockout targeted to mouse brain, Müller et al. show that loss of *PEX13*, one of the genes mutated in ZS, recapitulates the symptoms of the disease, and results in mitochondrial-mediated oxidative stress, neuronal cell death and impaired cerebellar development. PEX13-deficient mice will be valuable for investigating the molecular basis and treatment of ZS cerebellar pathology. *K.W.* **Page 104**

Shock therapy: modulating stem cells

Understanding mechanisms of stem cell regulation is crucial for regenerative medicine as well as for new therapies for developmental defects and cancer. Using *Xenopus laevis* neural crest, an embryonic stem cell population, as a model system, Blackiston et al. show that modulating the bioelectrical state of a population of 'instructor' cells expressing the native glycine receptor chloride channel can trigger a neoplastic phenotype in other cells, an effect that is mediated by long-range serotonergic signalling. Modulating membrane voltage is therefore a potentially powerful therapeutic approach for manipulating stem cells. *K.W.* **Page 67**

pH-dependent regulation of Batten disease protein

Juvenile Batten disease is a fatal neurodegenerative disorder caused by mutations in the *CLN3* gene, whose function is unknown. CLN3 has a yeast orthologue, Btn1p, the function of which can be complemented by its human counterpart, indicating some conservation of CLN3 function between the two organisms. Wolfe et al. show that both the level and the subcellular location of yeast Btn1p is pH-dependent, suggesting that human CLN3 might share this complexity of regulation and shedding light on the pathology of Batten disease. *K.W.* **Page 120**

Announcing a xenograft model of *E. coli* O157:H7

Enterohemorrhagic *Escherichia coli* (EHEC) O157:H7 infects only humans (causing acute gastroenteritis and hemorrhagic colitis) and calves. Because EHEC does not infect mice, simplified models that allow investigation of EHEC virulence mechanisms are urgently needed. Golan et al. now report a xenograft model involving transplantation of human and bovine intestinal segments into SCID mice that recapitulates several aspects of natural EHEC infection, including tissue tropism and typical histopathology. This model should allow further molecular studies of this important pathogen's virulence. *S.A.* **Page 86**

Mapping mutations in a mouse model of Meckel-Gruber syndrome

Meckel-Gruber syndrome (MKS) is a lethal recessive disorder characterised by multiple severe birth defects. The disease is associated with mutations in genes that are required for the generation of cilia, which are cellular structures with multiple roles ranging from motility to sensation. Cui et al. recover a mouse mutant with developmental defects similar to those seen in humans with MKS, including polycystic kidneys and laterality defects. The authors map the mutation in these mice to a previously uncharacterised, highly conserved domain of a centrosome-localised protein called Mks1. They show that the mutation disrupts Mks1's function in late-stage ciliogenesis. These results clarify mechanisms underlying birth defects in MKS and provide molecular insight into how ciliogenesis occurs. *S.A.* **Page 43**