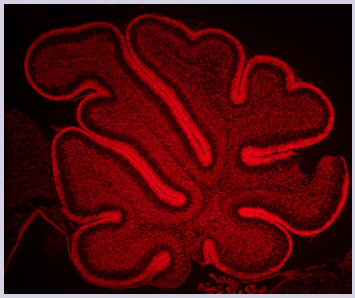

Bmi1, medulloblastoma and regenerative therapy

The epigenetic gene regulator BMI1 induces neural stem cell self-renewal in vitro and in vivo, a function that could be useful in regenerative medicine. However, increased expression of BMI1 in medulloblastoma, a brain tumour that can arise from cerebellar granule cell progenitors (CGPs), suggests that BMI1 is oncogenic in some circumstances. Behesti et al. investigated this possibility by generating transgenic mice that overexpress *Bmi1* in the granule cell lineage. *Bmi1* overexpression in CGPs decreased cerebellar size by decreasing CGP proliferation, whereas its overexpression in postmitotic granule cells improved cell survival under stress. No medulloblastomas developed in the transgenic mice, but *Bmi1* overexpression in a *Trp53*$^{-/-}$ background produced a low incidence of medulloblastomas. Thus, BMI1 overexpression is not sufficient to induce neoplastic transformation but can improve neuronal survival under stress. These results have implications for regenerative therapies. **Page 49**

Multipurpose cell-based fascin bioassay

The actin-bundling protein fascin is involved in tumour invasion and metastasis, whereas fascin deficiency is implicated in some developmental brain disorders. Because this association with diverse clinical problems makes the fascin pathway a desirable drug target, Kraft et al. devised an assay for fascin function that is based on the characteristic 'filagree' phenotype of cultured fascin-deficient mutant *Drosophila* neurons. When used to screen 1040 known compounds, the assay identified 34 fascin-pathway blockers (potential anti-metastasic agents) and 48 fascin-pathway enhancers (potential cognition-enhancing agents). The screen also revealed neurotoxic effects of other drugs. Notably, statins induced a unique morphological disruption of the cultured neurons. These results suggest that this cell-based fascin bioassay should be useful for drug discovery and identifies primary cultures of *Drosophila* neurons as a promising neurotoxicity screening platform. **Page 217**

Ang-1, lung development and congenital diaphragmatic hernia

Children with congenital diaphragmatic hernia (CDH), a condition characterised by herniation of the abdominal contents into the thoracic cavity, also develop pulmonary hypertension. Angiopoietin-1 (Ang-1), a central mediator of angiogenesis, is involved in the development of non-familial pulmonary hypertension, but its role in CDH-associated pulmonary hypertension is unclear. Grzenda et al. now examine the expression patterns of Ang-1 and its receptor Tie-2 during lung development in normal mice and in a nitrofen-based murine model of CDH. Their results suggest that the Ang-1–Tie-2 pathway is important during normal lung development and that alterations in the pathway might be responsible for the development of pulmonary hypertension in CDH. Investigation of the role of other components of the Ang-1 pathway during normal and pathological lung development is therefore warranted. **Page 106**

Zebrafish model for diseases caused by ER stress

Mutations in human *SEC63* cause polycystic liver disease (PCLD). Because Sec63 is a component of the endoplasmic reticulum (ER) translocon machinery, it has been proposed that SEC63 mutations cause PCLD by triggering ER stress, activation of which is also linked to myelin disorders. Monk et al. now describe a zebrafish mutant that was isolated in a screen for mutations affecting the development of myelinated axons. The mutant carries *sec63*^{st67}, a missense mutation in the zebrafish ortholog of Sec63. The researchers report that liver cells and nervous system cells in *sec63*^{st67} mutants show a swollen and fragmented ER, and express molecular markers of ER stress. *sec63*^{st67} mutants could therefore serve as a model for studying the role of ER stress in PCLD and in myelin disorders. **Page 135**

Myotonic dystrophy: new clues from flies

Myotonic dystrophy type 1 (DM1), the commonest type of muscular dystrophy in adults, is caused by expansion of CTG repeats in the 3′UTR of the *DMPK* gene. Sequestration of the alternative splicing regulator MBNL1 (muscleblind-like protein 1) by CUG expansions in *DMPK* transcripts is associated with some of the pathogenic features of DM1. Llamusi et al. now identify two RNA-binding proteins, BSF and TBPH, as modifiers of CTG toxicity in a *Drosophila* model of DM1. They report that these proteins and Muscleblind (the fly orthologue of MBNL1) are present in the sarcomeres of normal flight muscle, and that CTG expansion disrupts this expression pattern. Importantly, TBPH silencing improves the dystrophic muscle phenotype. These results provide new clues about DM1 and identify TBPH as a potential therapeutic target. **Page 184**

Left-right patterning: where and when serotonin acts

The left-right (LR) asymmetry of internal organs is established during embryogenesis. Failure of LR patterning causes serious birth defects, so it is important to understand how it is initiated. Vandenberg et al. performed experiments in *Xenopus* embryos to distinguish between two theoretical models explaining the initiation of LR patterning – the EARLY model, which proposes that serotonin acts in right-side blastomeres to initiate the cascade of asymmetric gene expression, and the LATE model, which proposes that, during neurulation, serotonin induces cilia that later break embryonic symmetry. The researchers show that preventing serotonin signalling in blastomeres that do not contribute to cilia randomises asymmetry, and that asymmetric genes become expressed even in explants without cilia. Their results uniformly support the EARLY model, a finding that could affect our understanding of the aetiology of several birth defects. **Page 261**

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