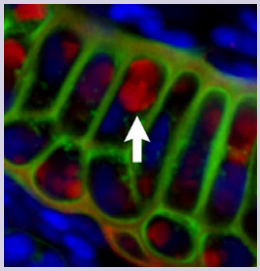

Linked defects in secretory pathways and skeletal morphogenesis

Craniofacial and skeletal mutations are the most common human birth defects, but little is known about their aetiology. Melville et al. show that the zebrafish *feelgood* mutation, which causes severe skeletal malformation, is a partial loss-of-function allele of the transcription factor Creb3l2. *feelgood* mutant fish have selective defects in protein secretion, as Creb3l2 regulates a subset of secretory pathway proteins. The data underline the importance of intracellular transport in skeletal morphogenesis, and provide proof of principle that this link can be probed in the zebrafish model. *K.W.* **Page 763**

Validating mouse model of Beckwith-Wiedemann syndrome

Mutations in the *CDKN1C* gene are associated with the childhood developmental disorder Beckwith-Wiedemann syndrome (BWS), whose main symptom is overgrowth of body and organ size. *Cdkn1c*-knockout mice do not show overgrowth at birth, casting doubt on the validity of mice as an appropriate BWS model. Now, Tunster et al. show that CDKN1C-deficient mouse foetuses do overgrow, but the effect is lost shortly before birth if the knockout foetuses are part of a large litter. This might have important implications for BWS underdiagnosis in non-singleton pregnancies in humans. *K.W.* **Page 814**

Feeding frenzy: *Drosophila* model of type 2 diabetes

Type 2 diabetes (T2D) and obesity are co-morbid metabolic disorders with increasing prevalence. Disease is linked to genetics in some individuals, but how dietary excess leads to the development of T2D is unclear. Musselman et al. report a new *Drosophila* model that permits close examination of factors linking a high-sugar diet with the development of obesity and insulin resistance. Fly larvae reared on excess sugars – but not those reared on excess fats or proteins – developed metabolic phenotypes resembling T2D. Many of the genes and pathways implicated in T2D in humans are also differentially expressed in flies reared on excess sugar. This system will be useful for high-throughput screens to identify genes and drug candidates that influence diet-induced insulin resistance. *S.A.* **Page 842**

Zebrafish model for IBD

Crohn's disease is a debilitating chronic inflammatory disorder of the bowel caused by inappropriate activation of the innate immune system in response to normal gut flora. The interplay between host gut factors and microbiota is challenging to study in humans, so little progress has been made in developing treatments. Using two of the best-studied susceptibility genes, encoding the bacterial detector proteins NOD1 and NOD2, Oehlers et al. demonstrate that the zebrafish is a tractable model for modelling Crohn's disease. These findings establish an efficient system for testing genotype-phenotype associations relevant to intestinal inflammatory diseases. *K.W.* **Page 832**

Modelling liver cancer in transgenic zebrafish

Liver cancer, of which hepatocellular carcinoma (HCC) is the most common type, is a leading cause of cancer death. HCCs have a complex aetiology, but the fact that the Ras-ERK pathway is upregulated in nearly all HCCs makes this pathway a promising therapeutic target. Nguyen et al. characterise a transgenic zebrafish model of human HCC in which an EGFP-tagged form of oncogenic $KRAS^{V12}$ is expressed in the liver. This model enables analysis of tumorigenesis in liver using imaging and genetic approaches, and reveals two conserved gene signatures associated with HCC. *S.A.* **Page 801**

Yeast-based screen for inhibitors of Aβ oligomerisation

Research on Alzheimer's disease (AD) indicates that oligomers of amyloid β_{42} ($A\beta_{42}$) contribute to neuropathology. Park et al. designed a yeast-based high-throughput screen for compounds that inhibit aggregation of $A\beta_{42}$ oligomers. Their pilot screen of 12,800 compounds identifies two molecules that are promising candidates for development into drugs appropriate for use in the CNS. These data put forward two new compounds worthy of testing in preclinical models of AD and establish a system to screen for new inhibitors of $A\beta_{42}$ oligomerisation. *S.A.* **Page 822**

Usher syndrome: a developmental disease of vision?

Usher syndrome is a recessively inherited disease of combined deafness and blindness that can be caused by a mutation in several genes. Phillips et al. investigate the genotype-phenotype link for one of these genes, *USHC1*, by studying the effects of *ush1c* deficiency in zebrafish. *ush1c* mutant or morphant fish have early-onset defects in vision, hearing and balance, associated with defects in sensory cell structure and, in particular, in Müller glia, suggesting that this retinal cell type might be involved in the pathology of Usher syndrome in humans. *S.A.* **Page 786**

Investigating heritable skin disorders in zebrafish

Ichthyosis comprises a group of heritable skin disorders of varying severity. Among these are Harlequin ichthyosis (HI), which is associated with *ABCA12* mutations and is fatal soon after birth, and CEDNIK syndrome (involving cerebral dysgenesis, neuropathy, ichthyosis and keratoderma), which is associated with *SNAP29* mutations. $Abca1^{-/-}$ mice have provided some clues about HI, but there is no model for CEDNIK. Li et al. use zebrafish to investigate the effects of disrupting *abca12* or *snap29* expression during development. Different lipid-transport pathways are impaired upon *abca12* versus *snap29* knockdown, but both cause epidermal defects similar to those seen in individuals with ichthyosis, providing new insight into the pathology of these disorders. *S.A.* **Page 777**