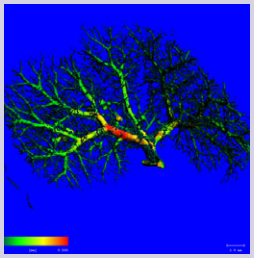

Clarifying roles for Notch signalling in liver

Alagille syndrome (AGS) is a developmental disorder affecting multiple organs, including the liver, in which bile duct paucity is observed. Clinical presentation varies widely, but nearly all AGS patients have altered Notch signalling. By studying the 3D structure of the liver in conditional mouse strains, Sparks et al. show that altered Notch signalling not only disrupts normal development of bile ducts, as previously reported, but also causes a progressive obstruction of the bile duct network with age. These results provide new clues about the complex mechanisms of liver dysfunction in AGS, and may help to manage AGS patients that present with evolving bile duct obstruction. *S.A.* **Page 359**

Flies for cardiovascular research: seeing is believing

At first glance, the human and *Drosophila* heart appear to have little in common. However, Choma et al. now provide evidence that flies can be used to model aspects of complex cardiovascular disease. Using an innovative optical imaging technique to visualise *Drosophila* during the semi-transparent pre-pupal stage of development, they show that numerous baseline physiological measurements of cardiovascular function are remarkably similar in the *Drosophila* heart and in closed vertebrate cardiovascular systems, including that of humans. They also report a subtle functional heart defect caused by mutation in troponin I, which is associated with heart dysfunction in vertebrates. *K.W.* **Page 411**

Finding HPE modifier genes in mice

Holoprosencephaly (HPE) is a common human birth defect caused by failure to properly form the midline of the midface and/or forebrain, and is frequently associated with mutations in genes that encode sonic hedgehog (SHH) signalling pathway components. The wide spectrum of clinical defects suggests the existence of silent modifier genes that influence the phenotype. Zhang et al. show, using a mouse model lacking the SHH pathway regulator *Cdo*, that a related gene, *Boc*, modifies the HPE phenotype, providing a framework to identify additional modifiers of HPE. *K.W.* **Page 368**

Fishing for answers: MBNL2 in myotonic dystrophy

Myotonic dystrophy (DM) is a disorder of progressive muscle weakness and wasting caused by repeat expansion in genes encoding DM1 or DM2. The mutated protein becomes trapped in the nuclei of mutant cells, where it associates with RNA-binding factors, including muscleblind-like (MBNL) proteins, disrupting splicing. Sequestration of MBNL proteins is thought to be central to the pathology of DM. Machuca-Tzili et al. explore this hypothesis using a zebrafish model and show that deficiency for *mbnl2* recapitulates several features of human DM. The finding that *mbnl2* is also important for zebrafish brain development opens up new questions about cognitive function in DM patients. *S.A.* **Page 381**

How hypertrophic cardiomyopathy manifests: clues from development

Hypertrophic cardiomyopathy (HCM) is a monogenic cardiovascular disorder that is caused mainly by mutations in sarcomeric contractile proteins such as cardiac troponin T (TNNT2). Becker et al. create a *tnnt2* zebrafish morphant to study basic mechanisms of HCM pathology and to identify modifiers of the HCM phenotype. Their findings indicate that *tnnt2* deficiency initiates cardiac defects at early developmental stages, including abnormalities in cardiomyocyte calcium handling. These findings suggest that the pathology of HCM might arise during development, before the onset of symptoms. *S.A.* **Page 400**

Improved mouse model of invasive lobular carcinoma

Similar to other metastatic cancers, loss of E-cadherin is a feature of invasive lobular carcinoma (ILC), a common form of breast cancer that is often not detected until late stages because the invasive cells are not mass-forming. How E-cadherin loss is linked to tumour development in ILC and in other cancers is still unclear. Derksen et al. report a new mouse model of human ILC in which E-cadherin and p53 are conditionally inactivated in mammary epithelial cells. These mice exhibit several features of human ILC, including invasive, metastatic mammary tumours that develop in a lactation-independent manner. *S.A.* **Page 347**

Figuring out FAS in fruit flies

Consumption of excess alcohol during pregnancy can cause fetal alcohol syndrome (FAS), but exactly how alcohol disrupts normal development is unclear. McClure et al. now report that fruit flies reared on ethanol show several characteristics of human FAS, including reduced viability, and abnormal development and behaviour. These changes are caused largely by reduced *Drosophila* insulin-like peptide and insulin receptor expression. This model can now be used to screen for modifiers of FAS that might help to prevent or treat the syndrome in humans. *S.A.* **Page 335**

Investigating a new Noonan syndrome mutation in zebrafish

Noonan syndrome is a congenital disorder characterised by a range of clinical problems, including heart defects. It is associated with mutations in components of the RAS-MAPK signalling pathway, most recently N-RAS. Runtuwene et al. now report a newly identified activating N-RAS mutation (I24N) in a patient with features of Noonan syndrome, and explore the effect of this and other activating N-RAS mutations on embryonic development in zebrafish. Their results validate the use of zebrafish for studying mutations associated with Noonan syndrome, and provide support that the developmental defects are caused exclusively by hyperactivation of the RAS-MAPK pathway. *S.A.* **Page 393**