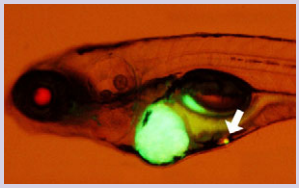

Inducible zebrafish model of hepatocellular carcinoma

Pharmacological inhibition of the Ras pathway in patients with hepatocellular carcinoma (HCC) has shown promising results, supporting the development of additional treatment strategies that target this pathway. Nguyen et al. previously reported a transgenic zebrafish model constitutively expressing *krasV12*; now, they improve on this system by developing a model that allows *krasv12* to be inducibly expressed, giving 100% tumour incidence that can be temporally controlled. They use this system to show that the Raf-MEK-ERK and PI3K-AKT-mTOR signalling pathways are involved in HCC, and that inhibitors of these pathways might be promising therapeutics. **Page 63**

Dicty provides clues about anti-seizure agent

Valproic acid (VPA) is used to treat epilepsy, bipolar disorder and migraine, but its mechanism of action is not well understood. Chang et al. use *Dictyostelium* to uncover a previously unidentified ability of VPA to decrease cellular phosphoinositide levels. Testing related compounds identifies several medium-chain fatty acids that have a more potent effect. Two of these are more effective than VPA at suppressing a correlate of seizure in an in vitro assay involving rat hippocampal slices. These new data might help to develop improved therapies for conditions that VPA is currently used to treat. **Page 115**

Effects of γ-secretase inhibitors in mouse colon

γ-secretase inhibitors (GSIs) block Notch pathway activation, which is thought to contribute to various epithelial cancers. Previous studies in the Apc^{min} mouse model of colon cancer suggest that GSIs inhibit intestinal neoplasia by converting proliferating cells into terminally differentiated goblet cells. Droy-Dupré et al. now assess the effects of a GSI called dibenzazepine (DBZ) in the intestines of healthy mice. They show that DBZ induces a homogenous goblet-cell conversion throughout the intestine, but that effects on intestinal-crypt-cell proliferation are heterogeneous. The authors propose that the effects of GSIs cannot be determined by goblet-cell conversion alone and encourage caution in the use of DBZ as a therapy. **Page 107**

Peroxisomal biogenesis disorders: role for oxidative stress?

Peroxisome biogenesis disorders (PBDs), thought to be inherited in an autosomal recessive manner, are caused by mutation in one of several PEX genes. Ahlemeyer et al. study the effects in mice of homozygous versus heterozygous deletion of *Pex11b*, which has a known role in peroxisome proliferation. Surprisingly, heterozygotes show signs of neuronal cell death, delayed neuronal differentiation and increased levels of oxidative stress, although to a lesser extent than homozygotes. These data suggest that mutation of a single Pex allele can cause neurological defects, and represent one of the first reports of oxidative stress being involved in the pathology of PBDs. **Page 125**

TNFα: role in post-dieting weight gain?

Re-gain of weight lost during dieting – known as post-restriction hyperphagia (PRH) – is commonly observed but not well understood. Hambly et al. study this phenomenon in mice and find that a decrease in fat mass, and the signals produced by fat mass, are partly to blame. Mice on a restricted diet have decreased circulating levels of leptin and tumour necrosis factor-α (TNFα), and supplementation of these factors to non-restriction levels suppresses PRH. These data might help to develop targeted therapies that improve the outcome of dieting in obese individuals. **Page 83**

Androgens in spinal and bulbar muscular atrophy

Spinal and bulbar muscular atrophy (SBMA) is a rare neurodegenerative disorder caused by polyglutamine expansion in the androgen receptor. Before the disorder was found to be androgen-dependent, many patients with SBMA were treated with testosterone. Chevalier-Larsen and Merry now use a mouse model of SBMA to test whether androgen treatment might have exacerbated the disease in these patients. Surprisingly, testosterone treatment did not have any effect on the mice, suggesting that patients that received this treatment did not suffer ill effects, and that the pathological mechanism of SBMA saturates at near-endogenous hormone levels. **Page 141**

Ewing's sarcoma: transgenic zebrafish provide new clues

Ewing's sarcoma is a malignant bone tumour often found in children and young adults. It is commonly caused by a chromosomal translocation resulting in the fusion protein EWS-FLI1, which is unique to tumour cells and therefore a candidate for targeted therapy. Leacock et al. are the first to report EWS-FLI1 transgenic zebrafish lines, which they use to shed new light on the function of this oncogenic fusion protein. Adult zebrafish with mosaic EWS-FLI1 expression develop tumours similar to human Ewing's sarcoma, but zebrafish embryos expressing EWS-FLI1 exhibit developmental defects suggesting that EWS-FLI1 acts in part by suppressing non-canonical Wnt signalling. **Page 95**

Studying disc degeneration with a *Noto-cre* mouse

Low back pain is a common clinical problem that is attributed to degeneration of the intervertebral disc (IVD), and specifically the inner nucleus pulposus. Treatments are limited owing to lack of knowledge about disc development, maintenance and degeneration. McCann et al. now report a mouse model that allows lineage-tracing experiments of cells of the IVD, and show that all cells in the nucleus pulposus are derived from the embryonic notochord. These mice can be used to investigate mechanisms regulating the transition from notochord to nucleus pulposus cells, which might aid the development of regenerative therapies for IVD degeneration. **Page 73**

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