



In vivo model for modulators of CFTR^{ΔF508} misfolding

Cystic fibrosis (CF) is most commonly caused by deletion of a single amino acid ($\Delta F508$) in the cystic fibrosis transmembrane conductance regulator (CFTR) protein. This mutation causes protein misfolding and disrupts many cellular functions. Many models of CFTR^{ΔF508} misfolding exist, but none are amenable to rapid genetic dissection of the pathways that are disrupted by the mutation. He et al. now report a fluorescence-based *C. elegans* model that will enable such studies. They show that expressing the $\Delta F508$ mutation in P-glycoprotein-3 (PGP-3), which is similar to mammalian CFTR, disrupts protein folding and prevents CFTR trafficking to the apical membrane of epithelial cells; this resembles the effects of the CFTR^{ΔF508} mutation, and is rescued by the same treatments as in mammalian cells. This model will enable unbiased genetic screens for modulators of CFTR misfolding and hopefully uncover new therapeutic targets. **Page 930**

Exploring long-term outcomes of galactosemia in flies

Despite lifelong restriction of dietary galactose, individuals with classic galactosemia suffer from various long-term complications, including speech, cognitive and movement problems. The underlying mechanisms are unknown, and treatments are limited. To shed light on this issue, Ryan et al. investigated long-term disease outcomes using a *GALT*-null *Drosophila* model of galactosemia that they developed previously. They report that, similar to patients, mutant flies develop a long-term movement defect that worsens rapidly with age. As little as 2.5% residual expression of the missing enzyme, *GALT*, is sufficient to improve long-term outcomes, whereas low-level exposure to galactose during development had no effect. These findings challenge current theories about long-term complications of galactosemia and confirm that this fly model will be useful for further studies of the disease. **Page 796**

Haem-driven IL-1 in acute brain injury

Subarachnoid haemorrhage (SAH) is a form of stroke that can occur spontaneously or as a result of head injury. Treatment options are limited, and few experimental models recapitulate the key features of the condition. Using a recently developed rat model that closely mimics human SAH, Greenhalgh et al. now show that blocking the IL-1 pathway using its endogenous receptor antagonist, IL-1Ra, lessens CNS pathology. They also show that haem, a breakdown product of haemoglobin derived from lysed erythrocytes in the subarachnoid space, drives IL-1 production and neuronal death. These results suggest that haem acts as a danger signal driving CNS inflammation,

and that IL-1Ra – a therapy already approved for other indications – might be a promising treatment for SAH. **Page 823**

Disease-associated CNVs: zebrafish provide clues

Copy number variants (CNVs) – intervals of DNA in which one genomic copy is duplicated or deleted – are associated with many different human disorders. CNVs of 16p11.2 are associated with problems including intellectual disability disorder (IDD) and autism spectrum disorders (ASDs). The 16p11.2 interval contains 25 genes, but which genes are important for its association with brain disorders is unclear. Blaker-Lee, Gupta, McCammon et al. identified zebrafish homologs of 22 of these genes, 20 of which were important for normal brain development. Two genes – encoding glycolytic enzyme aldolase A (*Aldoa*) and microtubule motor kinesin family member 22 (*Kif22*) – caused a phenotype at 50% expression levels, suggesting that their function is dosage-sensitive. These data will guide future studies of the association between 16p11.2 and brain disorders in mammals, and indicate that zebrafish are an effective tool for investigating other disease-associated CNVs. **Page 834**

Zebrafish model of neurofibromatosis type 1

Neurofibromatosis type 1 (NF1), a common inherited disorder, causes skin-pigmentation and CNS abnormalities, and increases the risk of developing several types of cancer. It varies widely in clinical presentation, even in family members carrying an identical mutation at the *NF1* locus, suggesting genetic or environmental modifiers. To probe underlying mechanisms, Shin, Padmanabhan et al.

studied the zebrafish homologues of human *NF1* – *nf1a* and *nf1b* – and used targeted approaches to create *nf1*-null zebrafish, which showed melanophore defects and a range of CNS abnormalities at the larval stage. As hypothesised for human *NF1*, zebrafish *nf1* genes also act as tumour suppressors: *nf1*-null larvae showed hyperactivation of Ras in the spinal cord, and combined loss of *nf1* and *p53* accelerated tumorigenesis. These data indicate that zebrafish *nf1a* and *nf1b* are tumour suppressors with crucial roles in CNS development. This is also the first animal model of NF1 in which pigmentation defects – an important feature of the human disease – have been documented. **Page 881**

New zebrafish model of seizure

Epilepsy affects millions of people worldwide, but many patients do not respond well to treatment or develop drug-resistant seizures. Many animal models of seizure exist, but additional, more economical systems are required for high-throughput drug testing and basic research. Lee et al. report a new model involving exposure of zebrafish larvae to ginkgotoxin, which induces seizure-like swimming behaviour that is reversed by commonly used anti-epileptic drugs. In addition, the phenotype is reversed by the inhibitory neurotransmitter GABA or PLP, an upstream enzyme in the GABA synthesis pathway. This model provides a system for addressing a proposed mechanism of seizure involving GABA, and introduces a relatively simple new platform for high-throughput drug screening. **Page 785**

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