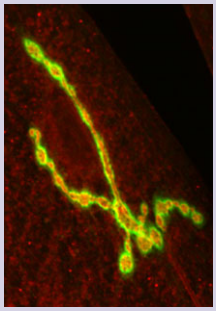

Minocycline and MMPs: towards treatment for Fragile X syndrome

Fragile X syndrome (FXS) causes behavioural symptoms including hyperactivity, disrupted circadian patterns, and impaired learning and memory. It results from loss of the fragile X mental retardation 1 protein product (FMRP). A recent study in mice showed that the tetracycline derivative minocycline alleviates FXS symptoms by inhibiting matrix metalloproteinases (MMPs). Siller and Broadie now follow this up with new findings that minocycline treatment restores multiple synaptic connectivity defects in the well-characterised *dfmr1*-null *Drosophila* model of FXS. Overexpressing TIMP (an inhibitor of MMP activity) prevents the synaptic connectivity defects in *dfmr1*-null flies, as does deleting the single MMP present in *Drosophila*. These data support minocycline as a promising FXS therapy and suggest that the FMRP and MMP pathways interact. **Page 673**

HADP1: new regulator of cardiac contractility

Congenital heart disease is a common inherited birth defect. Much is known about electrical conduction and Ca^{2+} handling in the adult heart, but not about how these characteristics are established during embryogenesis. Wythe et al. use a zebrafish embryo screen to identify a highly conserved gene encoding heart adaptor protein 1 (HADP1), a membrane-bound factor that interacts with phosphatidylinositol (PI) derivatives. Pharmacological experiments implicate PI4-kinase (PI4K) as an upstream regulator of HADP1 function, indicating that interaction between PI4K and Ca^{2+} signalling might regulate heart morphogenesis, function and disease. **Page 607**

Regulating IGF1 bioavailability is crucial for normal development

Insulin-like growth factor-1 (IGF1) has numerous biological roles. Its bioactivity is modulated by binding to IGF-binding proteins (IGFBPs) present in serum and tissues. Elis et al. studied the role of unbound (bioavailable) IGF1 in mouse strains expressing forms of IGF1 with low affinity for IGFBPs. They find that the mutant mice have increased body weight, length and relative lean mass, enlarged organs and enhanced mammary gland complexity. These data underscore the importance of tightly regulated IGF1 bioactivity for normal growth and development. **Page 649**

Balancing Ca^{2+} levels in Alzheimer's

Drugs that maintain homeostatic Ca^{2+} levels might be a promising therapy for Alzheimer's disease (AD), but systems to test them efficiently are lacking. Copenhaver et al. now report a 'translational suite' comprising four bioassays relevant to AD pathology – including in vitro screening, *Drosophila*, *Manduca* and the 3×Tg mouse model of AD – to test the therapeutic potential of dihydropyridines (DHPs), which target low-voltage-gated Ca^{2+} channels. One compound, isradipine, provides neuroprotection and minimal toxicity in all four assays, supporting this compound as a candidate drug for AD and validating this multi-pronged approach for drug development. **Page 634**

A closer look at the *SOD1*^{G93Adl} mouse model of ALS

Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disorder with no cure. Of mouse models used to study ALS, the *SOD1*^{G93A} mouse is the most common, although its use is limited owing to a short lifespan (~16 weeks). Acevedo-Arozena et al. now characterise in detail the more recently reported *SOD1*^{G93Adl} low-copy transgenic, which lives for ~34 weeks. They find that genetic background and gender both influence lifespan and disease course. In addition, *SOD1*^{G93Adl} mice are abnormal in the startle-response test, which the authors introduce as a new assay for use in *SOD1* transgenic mice. The data support wider use of the *SOD1*^{G93Adl} strain, as it is well suited for studying early-stage ALS. **Page 686**

Pleurocidin peptides: a new class of anti-cancer agents?

Some families of host-defense peptides exhibit selective cytotoxicity towards cancer cells and therefore might be promising as a new type of anti-cancer therapy. Morash et al. now report on a screen of 26 naturally occurring cationic antimicrobial peptides of the pleurocidin family, carried out using in vitro testing and an in vivo zebrafish embryo model. Specific members of this family selectively induce death of cancer cells, leaving non-cancerous cells unharmed, indicating that certain pleurocidin variants might be promising anti-cancer agents. **Page 622**

Fly model of peroxisome biogenesis disorders

Individuals with peroxisome biogenesis disorders (PBDs) suffer from various symptoms, such as deafness, hepatic disease and mental disability. The range of symptoms indicates the importance of peroxisomes for normal physiology, but exactly how peroxisome defects cause these disorders is unclear. Mast et al. now show that *Drosophila* is a relevant model for addressing this issue by characterising flies carrying mutant *Pex1* (the fly homologue of the gene most commonly mutated in humans with PBDs). *Pex1* mutant flies have characteristics similar to patients with PBDs, and genetic profiling indicates that peroxisomal function is important for neuronal development, innate immunity, lipid and protein metabolism, and gamete formation. **Page 659**

Neuroprotection by Nrf2 in Parkinson's disease model

Oxidative stress is thought to be central to the pathogenesis of Parkinson's disease (PD). Nrf2, which regulates cellular antioxidant responses, has previously been implicated as neuroprotective in PD. Barone et al. now show that upregulation of the Nrf2 pathway, or inhibition of its negative regulator, Keap1, is sufficient to restore defective locomotor activity in a fly model of PD. Moreover, the loss of dopaminergic neurons (a hallmark of PD pathology) is inhibited when the Nrf2 pathway is upregulated. Therefore, the neuroprotective potential of Nrf2 pathway components in PD warrants further study. **Page 701**