Mending a broken heart in zebrafish

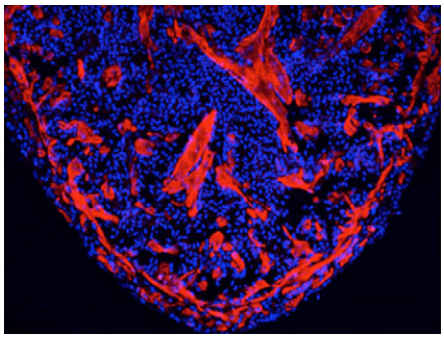

Image reproduced from Wang et al. (2011).

The ultimate goal in heart failure treatment is to stimulate the heart's natural regenerative capacity and replace damaged tissue. Previous work has shown that lower vertebrates such as zebrafish can efficiently regenerate cardiac cells after injury. However, current methods to induce injury in an experimental setting are invasive, making it difficult to assess the maximum regenerative potential of cardiomyocytes. Wang et al. minimised this problem by creating a zebrafish model in which cardiomyocytes could be inducibly depleted. The authors used a tamoxifen-inducible promoter to drive expression of cytotoxic diphtheria toxin A (DTA) specifically in cardiomyocytes. On exposure to tamoxifen, death of a high proportion of cardiomyocytes resulted in cardiac failure. After several days, ablated cardiomyocytes fully regenerated from highly proliferative neighbouring cardiomyocytes that had not been ablated, replacing the structure and function of the damaged tissue. This model system should provide new insight into heart-regenerative mechanisms. *M.R.*

Wang, J., Panáková, D., Kikuchi, K., Holdway, J. E., Gemberling, M., Burris, J. S., Singh, S. P., Dickson, A. L., Lin, Y. F., Sabeh, M. K. et al. (2011). The regenerative capacity of zebrafish reverses cardiac failure caused by genetic cardiomyocyte depletion. *Development* **138**, 3421-3430.

Understanding epilepsy in a canine model

Genetic epilepsies generally present in children aged 2-10 years, during the developmental phase when the neural network undergoes 'pruning', and often spontaneously remit. Idiopathic epilepsies are common in dogs and in some breeds are ten times more common than in humans. It was previously reported that the *Lagotto romagnolo* breed exhibits an epileptic disorder with onset at ~7 weeks (equivalent to age 2 years in humans) and remit at ~4 months (age 8 years in humans). Seppälä et al. now report the genetic defect and affected neurological pathways underlying this phenotype. Mapping studies showed that the genetic defect results in truncation of the secreted neuronal protein LGI2, preventing its secretion and interaction with three ADAM-family neuronal membrane receptors. LGI2 mutations have not been associated with human epilepsy, but autosomal dominant lateral temporal lobe epilepsy (ADLTE) is associated with mutations in LGI1, which interacts with the same ADAM-family receptors. These interactions are thought to stabilize synapses, and LGI1 seems to protect the brain against seizures during and/or after the pruning phase. By contrast, the authors propose, based on LGI gene expression data, that LGI2 might be important for preventing seizures early during development of the neural network, before pruning. These results suggest that *LGI2* should be considered as a candidate gene in childhood epilepsies. *S.A.*

Seppälä, E. H., Jokinen, T. S., Fukata, M., Fukata, Y., Webster, M. T., Karlsson, E. K., Kilpinen, S. K., Steffen, F., Dietschi, E., Leeb, T. et al. (2011). LGI2 truncation causes a remitting focal epilepsy in dogs. *PLoS Genet*. **7**, e1002194.

Defective α-tubulin acetylation in models of Charcot-Marie-Tooth

Charcot-Marie-Tooth (CMT) disease is a common disorder of the peripheral nervous system characterised by progressive weakness and atrophy of distal muscles, sensory loss and foot deformities. Depending on the predominant neurological defect, it is classified as Type 1 CMT (demyelination), Type 2 CMT (axonal loss) or distal hereditary motor neuropathy (HMN; mainly affecting motor axons). Among the ~40 genes linked to the disease is *HSPB1*, which can cause Type 2 CMT or distal HMN, depending on the mutation. To investigate the underlying mechanisms, d'Ydewalle et al. created two transgenic mouse strains expressing CMT-associated mutant forms of *HSPB1* specifically in neurons: S135F, causing symptoms resembling Type 2 CMT, and P182L, causing symptoms resembling distal HMN. In addition to neurological defects, both strains displayed axonal transport deficits caused by decreased α-tubulin acetylation (a cue for anchoring of molecular motors) in peripheral nerves. Inhibiting the histone deacetylase HDAC6, the primary enzyme that deacetylates α-tubulin, restored axonal transport and abrogated disease symptoms in $HSPB1^{S135F}$-expressing mice. So, dysregulated α-tubulin acetylation might play a role in the pathology of CMT and other heritable peripheral neuropathies, opening up new avenues for treatment. *S.A.*

d'Ydewalle, C., Krishnan, J., Chiheb, D. M., Van Damme, P., Irobi, J., Kozikowski, A. P., Vanden Berghe, P., Timmerman, V., Robberecht, W. and Van Den Bosch, L. (2011). HDAC6 inhibitors reverse axonal loss in a mouse model of mutant HSPB1-induced Charcot-Marie-Tooth disease. *Nat. Med.* **17**, 968-974.

Serotonergic neurons in regulating homeostasis

Serotonin-producing neurons are implicated in regulating crucial physiological processes such as breathing and body temperature. Defective serotonin networks are associated with disorders such as sudden infant death syndrome (SIDS) and depression. To assess the involvement of serotonergic neurons in respiration and thermoregulation, Ray et al. developed a system to acutely and specifically inhibit these neurons. The authors engineered mice that express a synthetic G-protein coupled receptor (Di) almost exclusively in serotogenic neurons; Di is activated only by a synthetic, biologically inert and reversible ligand called clozapine-*N*-oxide (CNO). Following administration of CNO, serotonergic neuronal activity was rapidly inhibited by Di. In mice, CNO triggering of Di resulted in an impaired respiratory response to tissue acidosis and an acute decrease in core body temperature to near that of the surrounding air. The data directly demonstrate the requirement of an intact serotonin network for respiratory and temperature homeostasis, and introduce a powerful model to examine underlying mechanisms of SIDS and other disorders associated with serotonin abnormalities. *M.R.*

Ray, R. S., Corcoran, A. E., Brust, R. D., Kim, J. C., Richerson, G. B., Nattie, E. and Dymecki, S. M. (2011). Impaired respiratory and body temperature control upon acute serotonergic neuron inhibition. *Science* **333**, 637-642.