In vivo screen for suppressors of long QT syndrome

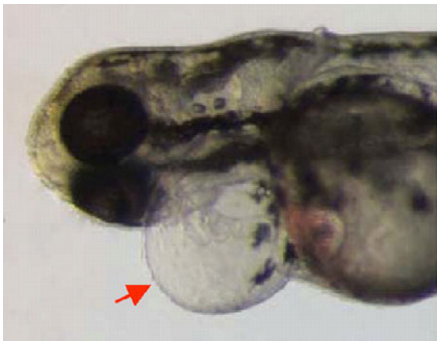

Figure reproduced from: **Arnaout, R., Ferrer, T., Huisken, J., Spitzer, K., Stainier, D. Y., Tristani-Firouzi, M. and Chi, N. C.** (2007). Zebrafish model for human long QT syndrome. *Proc. Natl. Acad. Sci. USA* **104**, 11316-11321.

Long QT syndrome (LQTS) involves delayed repolarisation of the heart, causing heart problems or sudden death. It can be congenital (usually due to mutations in genes encoding cardiac ion channels, such as *KCNH2*) or acquired, and is also a side effect of many drugs, but there are limited treatment options. Among model organisms, the zebrafish offers many advantages for analysing LQTS. Peal et al. carried out an in vivo functional screen using the zebrafish *breakdance* mutant, which displays many features of human LQTS owing to a mutation in *kcnh2*, and identified two drugs that correct the cardiac phenotype. These results and future in vivo screens will contribute to the development of novel targeted therapeutics for LQTS patients. *S.A.*

Peal, D. S., Mills, R. W., Lynch, S. N., Mosley, J. M., Lim, E., Ellinor, P. T., January, C. T., Peterson, R. T. and Milan, D. J. (2010). Novel chemical suppressors of long QT syndrome identified by an in vivo functional screen. *Circulation* [Epub ahead of print] doi:10.1161/CIRCULATIONAHA.110.003731.

Muscle senescence regulates systemic tissue ageing in flies

Age-related diseases are typically preceded by loss of muscle strength, but the mechanisms of age-related muscle weakness and their contribution to systemic ageing were unknown. Using *Drosophila* as a model, Demontis and Perrimon now demonstrate that impaired function of ageing muscles is associated with the progressive accumulation of protein aggregates. Specifically, they found that the transcription factor FOXO and its target, 4E-BP, were required for the removal of damaged proteins from muscle tissue (i.e. for maintenance of normal muscle proteostasis), and FOXO-deficient flies had abnormal muscle proteostasis. By contrast, muscle-specific overexpression of FOXO preserved muscle function, extended life span, and reduced feeding and insulin secretion, which in turn slowed the accumulation of protein aggregates in other tissues with age. These findings indicate that FOXO–4E-BP signalling in muscle regulates systemic tissue ageing, opening up new avenues for therapies that prevent age-related muscle degeneration and extend life span. *M.R.*

Demontis, F. and Perrimon, N. (2010). FOXO/4E-BP signaling in *Drosophila* muscles regulates organism-wide proteostasis during aging. *Cell* **143**, 813-825.

Invasive human epithelial neoplasia in 3D

It is becoming increasingly clear that tumour cells must be studied in the context of their 3D tissue microenvironment to obtain accurate information about their biology and identify relevant drug targets. Ridky et al. describe a new 3D in vitro model of invasive neoplasia that can be derived using the four stratified squamous epithelia that are associated with human cancer: epidermis, oropharynx, oesophagus and cervix. The authors transformed the epithelia by inducing tumour-associated signalling pathways and then cultured them with an intact basement membrane supported by cell-populated living stroma. This multi-tissue model recapitulated many features of in vivo tumour progression, including epithelial invasion of the basement membrane. Gene-expression profiling provided further support that the system faithfully models human epithelial cancer, and inhibitor studies indicate that it could be used to screen for new therapeutics, including those that target the tumour microenvironment. *S.A.*

Ridky, T. W., Chow, J. M., Wong, D. J. and Khavari, P. A. (2010). Invasive three-dimensional organotypic neoplasia from multiple normal human epithelia. *Nat. Med.* [Epub ahead of print] doi:10.1038/nm.2265.

EphB2: potential therapeutic target for Alzheimer's disease

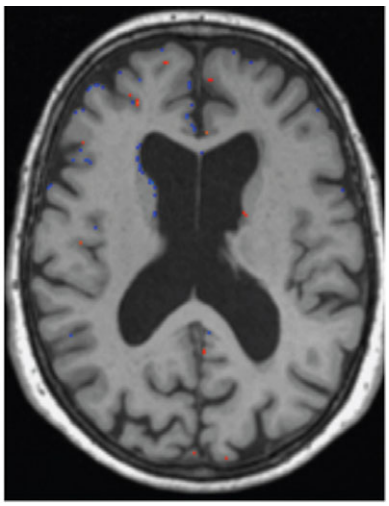

Figure reproduced from: **Smith, A. D., Smith, S. M., de Jager, C. A., Whitbread, P., Johnston, C., Agacinski, G., Oulhaj, A., Bradley, K. M., Jacoby, R. and Refsum, H.** (2010). Homocysteine-lowering by B vitamins slows the rate of accelerated brain atrophy in mild cognitive impairment: a randomized controlled trial. *PLoS One* **5**, e12244.

Cognitive dysfunction in Alzheimer's disease (AD) is associated with the accumulation of amyloid-β (Aβ) oligomers in the brain, which are thought to impair neurotransmission by interfering with the function of neuronal NMDA-type glutamate receptors. Although AD has been associated with low levels of EphB2 – a receptor tyrosine kinase that regulates NMDA receptors – whether EphB2 depletion contributes to cognitive dysfunction has been unclear. Using the human amyloid precursor (hAPP) transgenic mouse model of AD, Cissé and colleagues now show that Aβ oligomers cause depletion of EphB2 levels and, in turn, decrease synaptic strength and cognitive defects. Aβ oligomers were found to interact directly with EphB2 and trigger its degradation. Knockdown of EphB2 in nontransgenic mice caused neuronal deficits similar to those in the hAPP mice, whereas rescue of EphB2 levels in hAPP mice by using viral vectors corrected cognitive deficits. These results clarify the role of EphB2 in learning and memory, and suggest that it might be a therapeutic target for AD. *M.R.*

Cissé, M., Halabisky, B., Harris, J., Devidze, N., Dubal, D. B., Sun, B., Orr, A., Lotz, G., Kim, D. H., Hamto, P. et al. (2010). Reversing EphB2 depletion rescues cognitive functions in Alzheimer model. *Nature* [Epub ahead of print] doi:10.1038/nature09635.