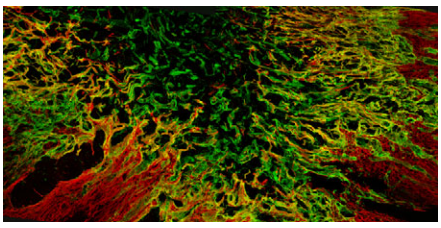
Identification of progenitors capable of kidney regeneration in zebrafish

Unlike adult mammals, which can repair but not regenerate new nephrons, fish generate nephrons de novo throughout life and after kidney injury. To explore mechanisms of kidney regeneration that could one day be applied to treat renal disease in humans, Diep et al. used the zebrafish as a model to identify and characterise progenitor cells responsible for nephron regeneration. Using transplantation experiments, they traced the source of new adult nephrons back to small aggregates of cells containing kidney progenitors. As previously found for mouse nephrons, individual zebrafish nephrons are derived from multiple nephron progenitors, which the authors suggest have self-renewing properties. Furthermore, gene-expression analyses indicated conservation between mammals and zebrafish with respect to the factors involved in renal development. These results provide hope that nephron progenitors with self-renewing potential might also be present in the human adult kidney and could be coaxed out of a dormant state to stimulate kidney regeneration following injury or disease. *S.A.*

Diep, C. Q., Ma, D., Deo, R. C., Holm, T. M., Naylor, R. W., Arora, N., Wingert, R. A., Bollig, F., Djordjevic, G., Lichman, B. et al. (2011). Identification of adult nephron progenitors capable of kidney regeneration in zebrafish. *Nature* **470**, 95-100.

Cancer drug promotes axon regeneration



Confocal image of a fibrotic scar, a major obstacle to axon regeneration, in a lesioned rat spinal cord. Image provided courtesy of F. Hellal and F. Bradke, Max Planck Institute of Neurobiology.

Two of the main processes that hinder spinal cord repair after injury are scar-tissue formation and lack of axon growth, and microtubule formation is a key component of both. Hellal et al. therefore investigated whether Taxol, a microtubule-stabilising drug that is widely used in cancer therapy to limit cell division, could reduce these effects following spinal cord injury (SCI). In rats, application of a low dose of Taxol at the site of SCI interfered with mechanisms important for scar formation, such as TGFβ signalling, transduction of which requires the microtubule network. In addition to decreasing scar formation, Taxol treatment reduced the amount of growth-inhibitory chondroitin sulfate proteoglycans at the lesion site, which together created an environment conducive to axon growth. Moreover, Taxol treatment induced axon regeneration, resulting in functional improvement. By targeting the cytoskeleton, at which growth inhibitory signals converge, rather than interfering with single inhibitory factors, Taxol could provide multi-targeted therapy for SCI, and has the advantage of being an approved drug. Future research will aim to discover whether regeneration is seen when the time between injury and treatment is increased. *J.H.*

Hellal, F., Hurtado, A., Ruschel, J., Flynn, K. C., Laskowski, C. J., Umlauf, M., Kapitein, L. C., Strikis, D., Lemmon, V., Bixby, J. et al. (2011). Microtubule stabilization reduces scarring and causes axon regeneration after spinal cord injury. *Science* [Epub ahead of print] DOI:10.1126/science.1201148.

Inhibiting RHO geranylgeranylation has an unexpected outcome on inflammation

Rheumatoid arthritis is a painful and debilitating inflammatory disorder with no known cure. It has been hypothesised that targeting the activity of RHO family proteins might be an effective therapeutic strategy, as these proteins are required for the function of macrophages, which contribute to immunopathology in arthritic joints. However, this notion is challenged in a recent paper by Khan et al. Unexpectedly, mice deficient for a key RHO-activating enzyme, geranylgeranyltransferase type I (GGTase-I), specifically in macrophages were found to develop spontaneous and severe joint inflammation resembling erosive rheumatoid arthritis. Macrophage-specific deficiency in GGTase-I was sufficient to induce pro-inflammatory signalling pathways and initiate the disease owing to sustained activation of RHO family proteins in macrophages. These data indicate that GGTase-I is not essential for the activity of RHO family proteins, and that inhibition of this enzyme can worsen, rather than prevent, the progression of rheumatoid arthritis. *M.R.*

Khan, O. M., Ibrahim, M. X., Jonsson, I. M., Karlsson, C., Liu, M., Sjogren, A. K., Olofsson, F. J., Brisslert, M., Andersson, S., Ohlsson, C. et al. (2011). Geranylgeranyltransferase type I (GGTase-I) deficiency hyperactivates macrophages and induces erosive arthritis in mice. *J. Clin. Invest.* **121**, 628-639.

Linking phospholipid homeostasis with cardiac lipotoxicity in flies

Obesity is a major contributor to hypertension and heart disease. Elevated blood lipids accumulate in peripheral tissues such as the heart, causing deleterious effects on tissue function, a condition known as lipotoxicity. Lim et al. used *Drosophila* to identify a novel pathway leading to obesity-induced cardiac lipotoxicity that is independent of excess caloric intake but involves dysregulated membrane phospholipid homeostasis. They report that the *easily shocked* (*eas*) mutant, which is defective in the synthesis of the abundant membrane phospholipid phosphatidylethanolamine (PE), exhibits elevated triglyceride levels in the heart, tachycardia (accelerated heart rate), cardiac constriction (akin to restrictive cardiomyopathy), and is prone to cardiac arrest and fibrillation under stress conditions. PE deficiency overactivates the *Drosophila* sterol regulatory element-binding protein (dSREBP) lipogenic pathway, which globally regulates lipid homeostasis. Suppressing the dSREBP pathway in *eas* hearts rescues the cardiac defects and normalises triglyceride levels. These results support the hypothesis that phospholipid homeostasis and cardiac lipotoxicity are molecularly linked, and further our understanding of obesity-related disease pathogenesis. *M.R.*

Lim, H. Y., Wang, W., Wessells, R. J., Ocorr, K. and Bodmer, R. (2011). Phospholipid homeostasis regulates lipid metabolism and cardiac function through SREBP signaling in *Drosophila*. *Genes. Dev.* **25**, 189-200.