Izraeli *et al.* analyse mice in which the early response gene, *SIL*, is knocked-out. These embryos have axial midline defects and randomized cardiac looping. Midline signalling by sonic hedgehog (Shh) is also blocked. The authors show that the normally asymmetric expression of *nodal*, *lefty-2* and transcription factor, *Pitx2*, is disrupted. *Shh* mutants, which have axial defects but normal heart looping, also show ectopic bilateral expression of these genes, but with later onset than in the *SIL* knockout. Thus, *SIL* could be involved in a pathway leading to early, Shh-independent suppression of these genes on the right.

Patel *et al.* show that nodal signalling in chick affects mesodermal expression of two transcription factors, *Pitx2*, which is activated on the left, and *SnR* (*snail*-related), which is inhibited on the left and hence expressed on the right. Antisense reduction of SnR causes abnormal heart looping. If SnR is severely inhibited, *Pitx2* is activated ectopically on the right, but reversion of heart looping is still seen in embryos where *Pitx2* expression is normal, so SnR could act downstream of *nodal* to suppress *Pitx2* on the right, but might also play a *Pitx2*-independent role in left–right development. Chick *lefty* is an obvious candidate for further studies.

1 Izraeli, S. *et al.* (1999) Regulation of midline development by antagonism of *lefty* and *nodal* signaling. *Nature* 399, 691–693

2 Bisgrove, B. *et al.* (1999) Nodal signalling and the roles of the transcription factors SnR and Pitx2 in vertebrate left-right asymmetry. *Development* 126, 3253–3262

3 Patel, K. *et al.* (1999) Mutation phenotypes in vertebrates suggest that establishment of the embryonic midline and of left-right asymmetry are linked. *Curr. Biol.* 9, 609–612

Alison Snape

alison.snape@kcl.ac.uk

Mice that can't get high

Humans have been experimenting with extracts of the plant *Cannabis sativa* for thousands of years, for medicinal and recreational purposes, and usually in blissful ignorance of the underlying pharmacology. In recent history, it has been shown that there are two mammalian receptors for cannabinoids that presumably respond normally to the endogenous ligand, anandamide. The CB1 receptor is expressed primarily in the brain, whereas the CB2 receptor is found in the immune system. The creation of CB1 knockout mice[1,2] has both clarified and complicated our understanding of the effects of cannabinoids. As expected, these mice lack all specific binding of cannabinoid agonists in the central nervous system and lose most, but not all, of the physiological responses to cannabinoids. Behaviourally, the knockout mice are less pain-sensitive in supraspinal pain responses and have reduced locomotor activity. They are extremely hypoactive in a test for exploratory activity, although no different from normal mice when challenged with balancing on a rotating beam. Paradoxically, the behavioural changes resemble the direct effects of cannabinoids, perhaps as a result of adaptive neuronal changes in the mutant mice. Significant alterations in neuropeptide levels were indeed found in some parts of the brain that normally express high CB1 levels. Some of the other phenotypes are also puzzling. The CB1 knockout mice exhibit a sixfold increase in mortality rate, dying suddenly for no obvious reason. When treated with a high dose of Δ^9-THC, the major psychoactive ingredient in marijuana, the knockout mice fail to show normal effects such as catalepsy, hypomobility and hypothermia, but instead assume a hunched posture, frequently lick their abdomens and suffer from strong diarrhoea. These responses are not seen in wild-type mice, but are also present in CB1–CB2 double knockout mice, so there must be effects of cannabinoids that are not mediated through the known receptor pathways.

1 Zimmer, A. *et al.* (1999) Increased mortality, hypoactivity and hypoalgesia in cannabinoid CB1 receptor knockout mice. *Proc. Natl. Acad. Sci. U. S. A.* 96, 5780–5785

2 Steiner, H. *et al.* (1999) Altered gene expression in striatal projection neurons in CB1 cannabinoid receptor knockout mice. *Proc. Natl. Acad. Sci. U. S. A.* 96, 5786–5790

Jonathan Hodgkin

jah@
mrc-lmb.cam.ac.uk

Novel floral patterns

Our understanding of plant developmental, biochemical and physiological pathways has been greatly enhanced over the last decade by work on the small crucifer *Arabidopsis thaliana*. In particular, the molecular genetic analysis of floral development has led to a detailed 'ABC' model of organ identity during flower determination. However, it is not clear how well these models in *Arabidopsis* (a higher eudicot) can be extended to other distantly related plant species. To address this issue, Kramer and Irish[1] examined the expression of two B class genes, *APETALA3* (*AP3*) and *PISTILLATA1* (*PI*) in flowers of several species of the lower eudicot subclass Ranunculidae. These species, include two from the family Papaveraceae (Iceland poppy and bloodroot), one from the family Fumariaceae (fringed bleeding heart) and two from the family Ranunculaceae (buttercup). Gene- and genome-duplication events both seem to have contributed to the diversification of the *AP3* and *PI* lineages within the Ranunculidae. Thus, expression patterns were examined for all gene family members in these lineages. In developing stamen primordia, the temporal and spatial expression patterns of RNA and protein were similar between the Ranunculidae and higher eudicot (*Arabidopsis* and *Antirrhinum*) *AP3* and *PI* orthologs. However, temporal and spatial patterns of *AP3* and *PI* expression in the Ranunculid species in petal primordia were very different from those found in *Arabidopsis* and *Antirrhinum*: *AP3* and *PI* were both expressed in young petal primoridia, but expression diminished during petal development, eventually becoming restricted to the extreme edges of the petal. In *Arabidopsis* and *Antirrhinum*, the continual expression of *AP3* and *PI* throughout petal development is essential for the development of normal petal form. As the authors suggest, these differences in gene-expression patterns indicate that the ABC model is not rigidly conserved across Angiosperms and probably reflects the independent derivation of petals from either stamens or sterile bracts. Alternatively, *PI* might play a similar role in higher and lower eudicots during the initiation of petal primordia, but could have been replaced by novel B group genes that would function to direct petal differentiation during the later stages. Clearly, the evolution of floral pattern is not quite as simple as A,B,C.

1 Kramer, E. M. and Irish, V.F. (1999) Evolution of genetic mechanisms controlling petal development. *Nature* 353, 31–37

Tom Brutnell

tom.brutnell@
plant-sciences.
oxford.ac.uk