IN THE NEWS

Fishy goings-on in the laboratory

A robot with the mind of a fish; at first glance it looks like the plot of a bad B-movie. *The Guardian* (UK, 18 April) describes it as "an arrangement reminiscent of the genesis of the Daleks" and "the marriage of baby bloodsucker and Swiss engineering". *The Times* announces; "It cannot yet do the housework or repel alien invaders, but the first functioning cyborg … has arrived" (UK, 18 April). However, according to scientists in Chicago, it might be the key to developing sophisticated robotic devices that respond to nerve impulses.

A team led by Sandro Mussa-Ivaldi at Northwestern University have harnessed the mechanism that enables the lamprey eel to remain upright, linking it to "an off-the-shelf Swiss robot" (*The Guardian*, 18 April) to create a robotic creature that moves in response to light. Mussa-Ivaldi told the *Washington Post* (USA, 16 April) "Until the recent past, people were using biological systems to inspire technology. Now we have gone one step beyond, to tap into the nervous system itself". It is suspected that the robot might even have the capacity to learn, but keeping the brain tissue alive for long enough to find out remains a major challenge. "The brain remains alive for only a few days in its special solution before the machine expires, and another lamprey must die"(*The Times*, 18 April).

As the *Washington Post* points out, this is one of a number of recent examples of 'critter science'. They also report that scientists in Iowa are using moth antenna as odour detectors in a remote-controlled vehicle designed to sniff out land mines. Fans of the Dr Who TV series will no doubt be intrigued to learn that the Iowa team is headed by Tom Baker!

Heather Wood

ION CHANNELS

To open the gate, try every key

Have you ever tried to unlock a door and had to try every key on the ring before finding the correct one? The mutational analysis of ion channels is sometimes similar. If you want to identify the structural determinant of a given channel property — gating, ion selectivity, ligand binding — you must mutate a lot of residues before obtaining a channel with the desired characteristics. And not only that; each amino acid that you mutate could in theory be replaced by 19 others, making it possible that the one replacement you tried was ineffective but this position was actually important for channel function. Two recent papers published in *Neuron* describe a yeast-based genetic screen to identify mutant channels more rapidly and on a larger scale than conventional approaches. Its use has already led to a deeper insight into the gating mechanism of G-protein-activated, inwardly rectifying K^+ channels (GIRKs).

Yi *et al.* and Sadja *et al.* took advantage of a mutant yeast strain that lacks K^+ transporters and therefore fails to grow in low K^+ concentrations. But if a constitutively active K^+ channel is expressed, then yeast can grow again. The authors of both papers subjected the entire sequence of two different GIRK channels to random mutagenesis, transformed mutant yeast with the mutated sequences, and looked at the colonies that managed to proliferate in low K^+. As binding of $\beta\gamma$ G-protein subunits is required to open GIRK channels and the wild-type channel does not rescue the yeast phenotype, yeast growth in low K^+ implied the expression of GIRK channels that became independent of G-protein activation. Further characterization of these G-protein-independent channels led the authors to identify several residues in the second transmembrane domain that were crucial for channel gating and to propose a structural mechanism for the transition between the closed and open states.

Remarkably, the residues identified in each paper were different despite the similarity of the approach. It would therefore be interesting to compare directly the rearrangements proposed in each article and test whether they are compatible with each other. But clearly, although this strategy allows you to test many more keys at a time, a lot of them seem to be capable of opening the gate.

Juan Carlos López

References and links

ORIGINAL RESEARCH PAPERS Yi, B. A. *et al.* Yeast screen for constitutively active mutant G protein-activated potassium channels. *Neuron* **29**, 657–667 (2001) | Sadja, R. *et al.* Coupling Gβγ-dependent activation to channel opening via pore elements in inwardly rectifying potassium channels. *Neuron* **29**, 669–680 (2001)
FURTHER READING Mark, M. D. & Herlitze, S. G-protein mediated gating of inward-rectifier K^+ channels. *Eur. J. Biochem.* **267**, 5830–5836 (2000)

AXON GUIDANCE

The midline loses its appeal

Developmental studies in insects and vertebrates have begun to explain how commissural axons manage to traverse the midline only once. Proteins such as the netrins attract their growth cones to the midline. Then, as they cross, the growth cones upregulate Roundabout (Robo), whose interaction with its ligand Slit generates repulsion. However, there is also growing evidence that growth cones lose their attraction for netrin as they cross the midline, although they often continue to express the netrin receptor DCC. In *Science*, Stein and Tessier-Lavigne report that the interaction between Slit and Robo might provide the key to the silencing of this attraction.

The authors exposed spinal neurons from stage 22 *Xenopus* embryos to Slit2 and netrin-1 *in vitro*. They showed that the growth cones were attracted towards netrin-1, but the attraction was silenced in the presence of Slit2. Surprisingly, the growth cones were not repelled by Slit2, either on its own or in conjunction with netrin-1. This is interesting because it confirms that the silencing of attraction to netrin-1 is not simply a net response to competing attractive and repulsive forces. Stage 28 growth cones were repelled by Slit2 but were not attracted by netrin-1, perhaps reflecting changes in responsiveness during neuronal maturation.

Removal of the cytoplasmic domains of DCC or Robo prevented Slit2-mediated silencing of attraction to netrin-1. By constructing chimeric proteins, the authors showed that silencing could be achieved even when the Robo cytoplasmic domain was activated through a different ectodomain such as Met, which binds hepatocyte growth factor (also known as scatter factor) rather than Slit. Therefore, silencing seems to be mediated by activation of Robo rather than through a direct interaction between Slit2 and DCC. Indeed, immunoprecipitation experiments confirmed that Slit2 promotes the association of Robo with DCC.

Stein and Tessier-Lavigne propose that the binding of Slit to Robo induces a conformational change that enables the cytoplasmic domain of Robo to interact with that of DCC, thereby silencing the attraction between netrin-1 and its receptor. So, activation of Robo by Slit2 could both inhibit the attraction of growth cones to the midline and induce their repulsion away from it, providing a simple switch to prevent them from being presented with conflicting signals.

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References and links

ORIGINAL RESEARCH PAPER Stein, E. and Tessier-Lavigne, M. Hierarchical organization of guidance receptors: silencing of netrin attraction by Slit through a Robo/DCC receptor complex. *Science* **291**, 1928–1938 (2001)
FURTHER READING Guthrie, S. Axon guidance: starting and stopping with Slit. *Curr. Biol.* **9**, R432–R435 (1999)