WEB WATCH

Behavioural ethic-ette

On 19 March 2001, The Nuffield Council on Bioethics posted a public consultation document on its Web site to seek public opinion on the ethical, legal and social implications of research into the genetics of variation in human behaviour. Over 1,000 copies of this document have also been sent to interested individuals and UK organizations, including academics, voluntary organizations, religious groups and members of parliament.

The responses to this document will inform, and provide discussion material for, a panel of experts assembled by the Council to consider the implications and applications of this area of genetics research. Some of the issues they will discuss include: the ethics of undertaking research into the genetics of human behaviour on human participants; the implications of using this research to develop genetic tests for certain behavioural characteristics and their use by, for example, employers and insurance companies; and the way in which genetic information might influence our perception of those with particular behavioural traits.

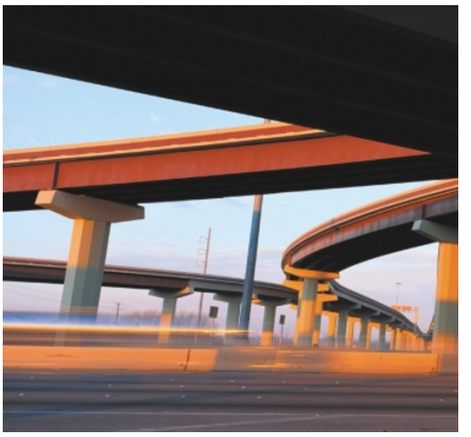
The consultation document begins with a brief introduction to behavioural genetics research — what it is and why it is studied — and then goes on to discuss some of the ethical and social issues that are raised by this research. Throughout the document, key questions are posed to provide a framework around which respondents can formulate their responses and opinions, some of which will be collated by the panel in their final policy document, which is due to be published in early 2002.

So what do you do to become involved? Visit the Nuffield Council's Web site, download the policy document and return your comments to the Council before 31 July 2001.

Jane Alfred

DEVELOPMENTAL BIOLOGY

A twisted tale of BMP antagonists…



A paper featured in last month's Highlights showed the way in which genetics could be used to resolve a longstanding puzzle in signal transduction. This month, genetics provides the puzzle — and (along with some biochemistry) the solution. This is because three papers in *Nature* explain the counterintuitive observation that an inhibitor of BMP (bone morphogenetic protein) signalling is required for a peak of BMP signalling activity that occurs during development in both invertebrates and vertebrates.

In *Drosophila*, the dorsoventral gradient of Decapentaplegic (Dpp) — a fly orthologue of vertebrate BMPs — is regulated by several secreted factors, among them Short gastrulation (Sog) and Twisted gastrulation (Tsg). Previous evidence had indicated that both Tsg and Sog act as antagonists of Dpp. However, their mutant phenotypes point to a paradox. A peak in Dpp activity is required to specify a dorsal embryonic structure called the amnioserosa. As Dpp loss-of-function mutants lack this structure, one would expect it to be expanded in the absence of a Dpp antagonist. But surprisingly, Sog and Tsg loss-of-function fly embryos lack the amnioserosa completely.

A solution to this puzzle now emerges in the form of an unusual model for a morphogen gradient, in which Tsg has a dual role. First, Tsg stabilizes the interaction between Sog and Dpp and, thanks to its own diffusability, helps to distribute them throughout the embryo, shaping the gradients of both molecules in doing so. Second, it facilitates Sog's cleavage by a protease called Tolloid (Tld). Near the source of Sog on the embryo's ventral side, Tsg and Tld cannot keep up with the fresh supply of Sog, so here most Dpp is bound in Sog complexes. However, more dorsally, away from the Sog source, Tsg is no longer swamped by high Sog levels and, with the help of Tld, it contributes to Sog cleavage and to the release of active Dpp. These twin functions of Tsg — transport and release of Dpp — are required for the dorsal peak of Dpp activity and for the formation of the amnioserosa.

So what happens in vertebrates? It turns out that vertebrate TSG binds directly to chordin (the vertebrate homologue of Sog) and to BMP4 (Dpp), and increases chordin's affinity for BMP4. Overexpression of *tsg* mRNA in zebrafish results in a block in BMP

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… and a new family member?

Unravelling the role of BMP antagonists in controlling and fine tuning embryogenesis is a hot topic in developmental biology at present (see accompanying Highlight). And who'd have predicted that getting to the bottom of a mouse with no trunk might add further to the twists in this field? For that's what Elizabeth Lacy and colleagues might have done by identifying a novel, BMP-antagonist-like, gene that when mutated abolishes trunk development in mouse embryos.

The recessively lethal amnionless (*amn*) mutation, generated by a transgene insertion, disrupts the middle region of the primitive streak that gives rise to trunk mesoderm. After many years of work on *amn*, Lacy and colleagues made their breakthrough when they found a BAC that rescued the *amn* phenotype. Their analysis showed that this BAC spanned the insertion site and contained three genes, but only one of them in its entirety. Lacy's team found deletions in this gene in *amn* mutants at the transgene integration site and confirmed its role by knocking it out to reproduce the *amn* mutant phenotype.

The *amn* gene encodes a novel type I transmembrane protein, the extracellular domain of which shows sequence similarity to the cysteine-rich (CR) domains of BMP inhibitors such as Sog, Tsg and chordin (see accompanying Highlight). These CR domains mediate the activity of BMP antagonists by binding BMPs and sequestering them away from their receptors. In a comparison of mouse *amn* to its fly and human homologues, the authors found it was this amino-terminal, CR-containing region that was most highly conserved.

Expression studies showed that *amn* is exclusively expressed in the extra-embryonic visceral endoderm (VE) tissue, but curiously throughout the VE and not just where it overlies the middle primitive streak. Furthermore, *amn* is expressed on the apical surface of the VE, which faces away from the embryonic epiblast (see picture). This raises the question of how Amn mediates its effects without directly interacting with this