## Building stronger bones

**Osteoporosis is a common disorder characterized by reduced bone density and increased risk of fractures. A new study by Eric Orwoll and colleagues identifies the gene 12/15-lipoxygenase (*Alox15*) as a negative regulator of bone mineral density (BMD) in mice and suggests a new therapeutic strategy for treating osteoporosis in humans (*Science* 303, 229–232; 2004). Orwoll and colleagues exploited natural variation between inbred mouse strains to identify a primary locus on chromosome 11 influencing peak BMD. After narrowing the genetic interval to 31 Mb, the authors identified *Alox15* as the only candidate gene in the region differentially expressed between the two strains. In particular, elevated *Alox15* levels were correlated with reduced BMD. Conversely, mice lacking 12/15-lipoxygenase showed a marked increase in bone strength. Pharmacological inhibition of this enzyme in two rodent models of osteoporosis likewise resulted in improved BMD. The authors propose that 12/15-lipoxygenase regulates BMD by generating endogenous ligands for PPARγ, a lipid-activated transcription factor that functions in pluripotent marrow stromal cells to negatively regulate osteoblast formation. The therapeutic value of these findings now awaits the establishment of a similar link between 12/15-lipoxygenase activity and the regulation of BMD in humans.** *KV*

## Transgenes in transit

It is generally understood that DNA from organisms we consume is degraded in the digestive process. A similar fate is assumed for transgenes, obviating concerns about the consumption of genetically modified foods. A study appearing in this month's *Nature Biotechnology* (22; 204–209) suggests that this assumption may not be justified. Human subjects were fed soy burgers and soy shakes containing genetically modified soybeans (expressing the transgene 5-enol-pyruvyl shikimate-3-phosphate synthase (*epsps*), which confers resistance to the herbicide glyphosate). After passage of the food through the entire gastrointestinal tract, the transgene was not detected using PCR. But when the authors investigated the digesta of individuals whose terminal ileum had been resected (ileostomy), they recovered the transgene in all cases. Thus, the authors conclude that ingested transgenes can persist at least as far as the upper gut in humans. PCR analysis of cultured microbes from the digesta through the ileostome identified the *epsps* product, suggesting that it had crossed kingdom barriers from a genetically modified plant source to the microflora. Whether it is expressed was not addressed by the authors, leaving open the question of the significance of the phenomenon. *DG*

## Gene-diet interaction in atherosclerosis?

James Dwyer and colleagues (*N. Engl. J. Med.* **350**, 29; 2004) report an association between markers of atherosclerosis and promoter variants of the gene *ALOX5* encoding 5-lipoxygenase, an enzyme that generates inflammatory leukotrienes from arachidonic acid. The associated mean increase in thickness of the carotid artery wall was comparable to that due to diabetes, the greatest risk factor for cardiovascular disease. This apparent atherogenic effect of genotype was worsened by consumption of arachidonic acid and n-6 polyunsaturated fatty acids and was ameliorated by consumption of marine n-3 fatty acids. The authors based their conclusions on 28 individuals, the 6% of their study population who did not carry the most common *ALOX5* allele. This 'wild-type' allele, W, with five Sp1 transcription factor binding sites, had the highest transcriptional activity in previously published promoter fusion assays. It is therefore surprising that the increase in mean artery wall thickness was found in the group 'homozygous' with respect to alleles other than W. It is even more remarkable that the thickening and the increase in the inflammatory marker C-reactive protein, were effects for which the variant alleles were apparently recessive to the 'wild-type'. *MA*

## A prion-like memory?

The dogma in memory research has been, roughly put, that training 'strengthens' synapses that are stably maintained and marked for access during recall of memories. Two papers from Eric Kandel and colleagues (*Cell* **115**, 879–891 and 893–904; 2003) propose an intriguing mechanism by which a synapse can maintain a memory over time. The papers build on the literature that places CPEB at the hub of regulating translation regulation. The authors show that the neuronal form of CPEB, Aplesia CPEB, might act as a mark of synapses by being upregulated by synaptic activity and required for maintenance of long-term facilitation and regulation of mRNA translation out at the synapse. Taking note of the amino acid composition of CPEB, the authors thought that the high levels of glutamine and asparagine at the N terminus resembled the domains of prion proteins. The exciting part of the work shows that the N-terminal domain does, in fact, have the properties of prions, being able to aggregate and convert Aplesia CPEB into a similar prion-like state that is stable and heritable in yeast. Thus, the protein can act as a switch to change the state of other CPEB proteins. The authors propose that the altered state might provide a lasting mark at the synapse that confers a long-term change in the protein's function as a translational regulator, as the prion-like state stimulates translation at a higher rate. *MS*

## Dissecting HIV RNA export

**The HIV-encoded Rev protein is required for the accumulation of viral RNAs in the cytoplasm. Nuria Sánchez-Velar and colleagues have now identified a distinct role for human Rev-interacting protein (hRIP) in Rev-dependent RNA trafficking (*Genes Dev.* advance online publication, 30 December 2003; doi:10.1101/gad.1149704). hRIP is a cellular protein originally found to interact with Rev in two-hybrid assays. Sánchez-Velar *et al.* show that knockdown of hRIP, either by introduction of a dominant-negative form or through RNAi, results in aberrant accumulation of Rev-directed RNAs at the nuclear periphery. They further show that this arrest is specific to Rev-associated transcripts and is not simply due to a global block in the transport of RNAs containing nuclear export sequences. The authors suggest that hRIP could facilitate the disassembly or transport of Rev-associated RNAs from the export complex at the nuclear periphery. The apparent specificity of hRIP in HIV RNA transport raises its profile as a potential drug target, although the authors caution that there may yet be a subset of cellular RNAs that also require hRIP to be released into the cytoplasm.** *AP*

*Research Notes written by Myles Axton, David Gresham, Alan Packer, Michael Stebbins, and Kyle Vogan*