A view of the inside

The current understanding of development has been shaped by studies in which gene promoters are fused to β-galactosidase (β-gal), or more recently, green fluorescent protein. However, because they depend on light microscopy, these techniques are limited in their ability to probe opaque tissues. Now on page 321, Louie et al. describe a way to use magnetic resonance imaging (MRI) to view domains of gene expression within the interior of a *Xenopus* embryo. With the goal of tracking gene expression in a living embryo dynamically over time, Louie et al. have developed a contrast agent (1-(2-(β-galactopyranosyloxy)propyl)-4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane)gadolinium(III) (EgadMe), that yields an MR image upon cleavage by β-gal. In the inactivated form, EgadMe's coordination with water is blocked, and thus the molecule is invisible by MRI. β-gal enzymatically cleaves a sugar off the contrast agent, thereby freeing a coordination site for water and converting it to an active, MRI-visible state.

Testing *Bt* refuge strategies

Crops expressing insecticidal proteins from *Bacillus thuringiensis* ("*Bt* crops") are becoming increasingly popular with farmers as a way of increasing crop yield and reducing insecticide use. However, some fear that widespread cultivation of *Bt* crops will accelerate the rate at which insects acquire resistance to the toxin. To prevent this, farmers have adopted planting strategies to provide *Bt*-susceptible insects with stands of nontransgenic plants as "refuges," which will perpetuate susceptible alleles in the insect population. On page 339, Shelton et al. describe results of a two-year field study in which they released insects with a known frequency of resistance into plots planted with various types of refuges, to investigate the impact of the refuges on the size of the insect population, as well as the frequency of resistance alleles.

Next month in *Nature Biotechnology*:

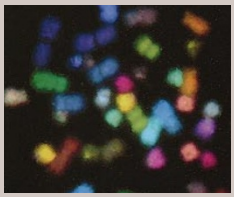
Identifying DNA targets of chromatin proteins

Recombination to remove selectable marker genes from transgenic plants

In vivo tracking of hematopoietic cells

Technical Reports

Actinomycete bacteria produce the majority of the microbial metabolites that have found use in medicine and agriculture. Until now, these bacteria have not been sufficiently characterized to allow efficient genetic manipulation. The genes necessary to produce a given metabolite tend to be carried within gene clusters many kilobases in length. On page 343 of this issue, Sosio et al. report that they have cloned 100 kb of actinomycete DNA into bacterial artificial chromosomes, where they are stably maintained in an integrated state.



On page 345, Henegariu et al. describe a method for labeling nucleotides with fluorescent dyes that will cut the cost of procedures that use these reagents by as much as 200-fold. They demonstrate that fluorescent nucleotides prepared by their technique can be incorporated by nick translation or PCR into DNA probes, which could then be successfully used in fluorescent in situ hybridization (FISH) analysis of metaphase chromosomes.

Review

The task of assigning function to the ever-increasing numbers of genes arising from the genome projects has prompted efforts to exploit structural information to infer biological activity. The conservation of protein folds suggests that proteins can be categorized into families on the basis of sequence similarity. Using this approach, unknown proteins with a fold similar to another protein of known activity can be assumed to have a similar function. Present estimates suggest around 5,000–15,000 new protein structures would provide enough information to model almost all possible proteins. In the review on p. 283, Skolnick et al. describe pilot structural genomics projects currently under way, theoretical approaches for predicting structure/function from sequence, and the biological implications of using structural information.

Metabolic engineering

The ultimate goal of the various genome sequencing projects is to gain sufficient understanding of the physiology of the organisms under study to enable exploitation of the genetic information to advance human health, agricultural production and industrial fermentation. A list of genes alone, however, is unlikely to provide sufficient information to manipulate the metabolism or pathophysiology of an organism in a predictable way. In this issue, Schuster et al. describe a method, called metabolic flux analysis, that is designed to convert a list of putative enzymes into a set of metabolic pathways. Their approach involves a rigorous definition of the constitutive activities of a given pathway as the sum of "elementary flux modes", each of which represents a minimal sequence of metabolic steps that can operate independently of each other. Applications should include more efficient identification of important drug targets and assigning and/or corroborating specific activities to orphan gene sequences (see p. 326).

Hemophilia bypassed

Hemophilia is caused by deficiencies or defects in blood coagulation Factor IX or Factor VIII. However, therapies based on simply replacing these defective or deficient plasma proteins with recombinant versions can lead to the development of inhibitory antibodies. In this case, alternate therapies are used in which the need for these factors is bypassed by providing recombinant Factor VIIa, another plasma activator of coagulation. Unfortunately the high cost and short half-life of Factor VIIa limits its clinical usefulness. To get around these problems, Ton-That et al. have developed an implant containing a chamber with immobilized Factor XIIa, which is an activator of Factor VII. The patient's plasma enters the chamber, and Factor VII is cleaved by Factor XIIa to an active form, Factor VIIa, which then diffuses back out into the bloodstream. This then triggers a biochemical cascade that culminates in the formation of the biochemical framework for blood coagulation (see p. 289).