

Although many of these examples of topological control rely on a metal ion to control the geometry of reactants, it is possible to do this using other intermolecular interactions. Stoddart *et al.*<sup>9</sup> have recently made use of stacking interactions between electron-rich and electron-poor aromatic systems in a high-yield, metal-free, one-pot synthesis of catenanes (see also ref. 10).

The ability of intermolecular interactions, particularly those involving metal ions, to control the self-assembly of molecular aggregates is an area of intense current interest. The use of such interactions allows very specific control over the conformation and stoichiometry of the products. The methodologies emerging from these studies represent an amalgam of 'organic' and 'inorganic' techniques and expertise, and offer powerful

new approaches to the synthesis of compounds that are of interest for their glorious shapes as well as their potential to exhibit novel and specific interactions with biological molecules. □

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## TRANSGENIC MICE

# Gene expression and hair-loss

Paul E. Bowden

THE regulation of gene expression and the biological consequences of gene manipulation can be studied by the stable incorporation of 'foreign' genes either into somatic cells, or into the germ line of recipient organisms. Transgenic mice result from the successful integration of foreign genes into the germ line; in this way, the introduced genes are subject to the complete developmental programme of the organism. The transgenic approach has recently been used to study the expression and regulation of keratin genes, which encode the structural proteins of hair and skin. In a new report, Powell and Rogers<sup>1</sup> describe the dramatic consequences of expressing a single component of sheep hair (a type II intermediate filament (IF) keratin protein) at high concentrations in transgenic mice. Although expression of this keratin IF gene is tissue specific, its overexpression leads to an imbalance of the normal ordered array of hair structural proteins. The result is a weakened structure, and breaking of the hair shaft (wool fibre) leads to premature loss of hair (see figure). This does not seem to be simply a consequence of expressing a sheep keratin IF gene in a mouse, as mice having a lower level of transgene expression (50 copies or less) suffer no hair-loss. Furthermore, the amino acid sequences of the keratins of sheep wool and mouse hair are very similar<sup>2</sup>.

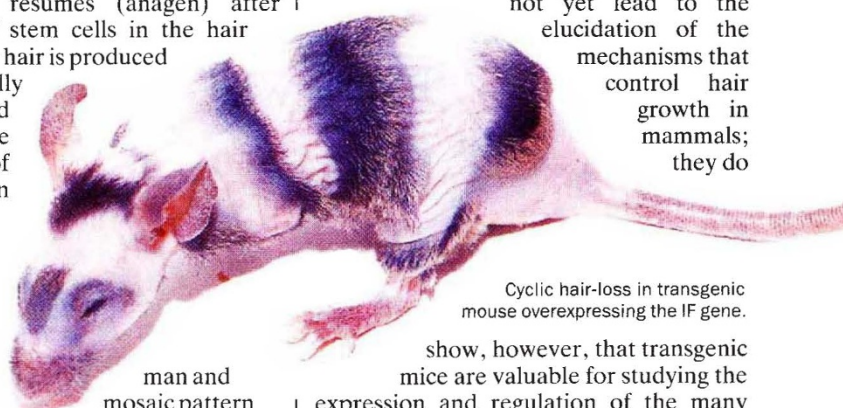
Hair from all mammals possesses a common structural plan and undergoes a cyclic programme of growth and differentiation. The hair follicle is first formed during embryonic development by down-growth and specialization of the epidermal basal cells, which also differentiate to

form the outer layers of the skin<sup>3</sup>. A complex multicellular structure is formed, which after a period of hair-specific differentiation and growth, produces a hair that protrudes beyond the surface of the skin. The follicle then attains a dormant state (telogen) during which the fully formed hair is retained in the follicle. Hair growth then resumes (anagen) after stimulation of stem cells in the hair bulb and a new hair is produced which eventually displaces the old one. Because the activity of hair follicles in the mouse is synchronized, waves of new hair growth occur in regular cycles<sup>4</sup>, whereas in sheep, a mosaic pattern of active hair follicles interspersed with dormant follicles is seen. Thus, the normal hair cycle, characterized by periods of active growth followed by dormancy, produces a continuous refurbishment of the coat (pelage) without significant loss of hair in any specific area of the skin.

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The hair fibre is composed of a cylindrical cortex with a central core (medulla) surrounded by a cuticle. The hair cortical cells contain a regular and distinctive arrangement of filaments (keratin IF proteins) embedded in a matrix of cysteine-rich and glycine-tyrosine-rich filament-associated proteins<sup>5</sup>. Between eight and ten hair-specific keratin IF proteins have been described<sup>6,7</sup> in addition to the keratin IF proteins expressed in other epithelia<sup>8,9</sup>. But the synthesis of filament-associated proteins seems to be a late event in hair differentiation and follows the synthesis of keratin IF proteins<sup>10,11</sup>. So precise regulation of the sequential expression of at least 20 genes is required to construct the filament-matrix array of the hair cortical cell.

Powell and Rogers<sup>1</sup> demonstrate that in transgenic mice with many copies (roughly 250) of the sheep wool keratin IF gene, the overproduction of keratin filaments leads to a reduced synthesis of the sulphur-rich and glycine-tyrosine-rich filament-associated proteins. This disrupts the normal ratio of filament to filament-associated protein, which has profound effects on hair structure and strength. The hairs produced are wavy and tend to break just below the skin surface. Similar findings have been described in several disorders of human hair<sup>12</sup>. This leads to the premature loss of hair that the authors observed in their transgenic mice. The new experiments do



Cyclic hair-loss in transgenic mouse overexpressing the IF gene.

not yet lead to the elucidation of the mechanisms that control hair growth in mammals; they do show, however, that transgenic mice are valuable for studying the expression and regulation of the many structural genes involved in this complex system, and that the biological consequences of manipulating the genome can be difficult to predict. □

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