SL301

RE-PROGRAMMING AROMATIC *STREPTOMYCES* POLYKETIDE SYNTHASE GENES TO MAKE NOVEL ANTIBIOTICS

D. A. Hopwood, John Innes Centre, Norwich NR4 7UH, U.K.

The carbon chains of *Streptomyces* aromatic polyketide antibiotics are assembled, reduced (where appropriate), and cyclised by polyketide synthases (PKS) consisting of non-covalent associations of protein subunits encoded by clusters of closely linked genes. Over the past five years, in collaborations with the groups of D. H. Sherman (now at the University of Minnesota) and C. Khosla (now at Stanford University), we have attempted to elucidate the basis of PKS "programming" (that is, determination of the choice of starter unit and number of malonyl extender units, and the patterns of keto group reduction and carbon chain cyclisation) by a genetics-led approach. This involves the construction in a *Streptomyces* host of hybrid PKS gene clusters, containing mixtures of subunit genes from two or more different PKS gene sets, and analysis of the novel polyketides produced. The structures of these compounds allow deductions to be made about the various aspects of PKS programming. Fortunately, most (though not all) heterologous combinations of PKS subunits have turned out to be functional. So far, a specific subunit, resembling but distinct from the ketosynthase, has been implicated in the control of carbon chain length; the "minimal" PKS, consisting of the ketosynthase, chain length factor and acyl carrier protein, has been shown to control the regiochemistry of the critical first cyclisation; two other subunits have been implicated in the second cyclisation; and aspects of the specificity (or lack of it) of the PKS ketoreductase have been revealed.