Prof M Carr - Molecular basis of the control of eukaryotic gene expression.

Research in my group is focussed on determining the structures, functions, interactions and mechanisms of action of proteins and protein complexes involved in key biological processes of significant medical importance. A major component of this work has been the successful use of NMR-based methods to determine new protein structures and to investigate protein-drug, protein-protein and protein-DNA interactions. The ongoing research in my group aims to integrate the information obtained from molecular, cellular and structural biology-based approaches to provide a detailed understanding of the function of proteins involved in disease states, which is an essential prerequisite for a rational, knowledge-based approach to drug discovery and development. In addition, through close collaboration with pharmaceutical companies such as UCB-Celltech we aim to make a major contribution to the design and development of important new drugs, such as therapeutic antibodies targeted at secreted signalling proteins (cytokines, chemokines, etc.) or cell surface receptors.

Control of eukaryotic gene expression is dependent upon the assembly of a diverse range of protein-protein and protein-nucleic acid complexes, which are formed in a dynamic and highly regulated process. The main focus of current work in my group is the highly conserved, eukaryotic protein Pdcd4, which has recently emerged as a key regulator of both transcription and translation, mediated via specific protein-protein and perhaps protein-RNA interactions. Pdcd4 has also been identified as an important new type of tumour suppressor in mammalian cells and has very recently been shown to play an essential role in cellular responses to DNA damage. The overall aim of ongoing work is to determine the molecular basis of the cellular functions of Pdcd4, which should lead to a clearer picture of the functions associated with its role as a tumour suppressor. A major aspect of this work will be the determination of high resolution structures for functional domains of Pdcd4 and tight complexes formed with functional partners, such as eIF4A, eIF4G, c-Jun and p300. This will also be complemented by structure-guided mutagenesis studies aimed at associating interesting surface features of Pdcd4 (potential functional sites) with specific cellular functions, such as its role in DNA damage response. This research programme forms part of a successful and long-term collaboration with Prof. Karl-Heinz Klempnauer's group at the University of Münster in Germany.

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