s8a.m10.o3 **Molecular recognition in the action of protein kinases: the basis for affinity and specificity.** M. Noble[1], S. Arold[1], N. Brown[1], I. Campbell[2], J. Endicott[1], J. Gruber[1], L. Johnson[1], J. Ladbury[3], J. Tucker[1] and T. Ulmer[2]. *1) Laboratory of Molecular Biophysics, South Parks Road, Oxford U.K. 2) Department of Biochemistry, South Parks Road, Oxford, U.K. 3) Department of Biochemistry, University College, London, U.K.*
Keywords: kinases, recognition, regulation.

Protein kinases constitute approximately 5% of the genome of eukaryotic organisms, so that organisms such as man have between five and ten thousand such enzymes . Despite some functional redundancy, these kinases has each to have a specific method of activation, and a unique set of cellular substrates. I shall present results of work on two systems where this specificity is achieved by having a bipartite recognition system.

Cyclin dependent kinases (CDKs) regulate proteins which define the cell's phase in the cell cycle. Different pairings of CDK and cyclin molecules phosphorylate distinct subsets of cellular targets. Selection of these targets is key to ensuring the appropriate ordering of cellular events. Recognition involves two characteristic sequence motifs in CDK substrates: PxK immediately downstream of the phosphorylated serine/threonine residue, and RxLFG remote from the site of phosphorylation. We have studied the recognition of substrates by CDKs[1] through peptide binding studies with representative peptides. The src family of tyrosine kinases are governed by intrasteric regulation and regulation by phosphorylation. The repressed conformation of this family is characterised by phosphorylation on a tyrosine of the C-terminal tail, which binds with the kinase's own Src Homology 2 (SH2) domain. The active form of the kinase is characterised by dephosphorylation of the C-terminal tail, and phosphorylation on the kinase's activation segment. Dephosphorylation frees the SH2 and SH3 domains to target the kinase to the appropriate sub-cellular location. It is not known whether de-phosphorylation precedes relief of the intramolecular interaction. We have studied this through structural and thermodynamic characterisation of the interaction of a fyn SH2-SH3 pair, with a cognate binding region of the physiological activator Focal Adhesion Kinase (FAK)[2].

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[2] D. Illic, C. Damsky and T. Yamamoto: "Focal Adhesion kinase: at the crossroads of signal transduction". (1997) J.Cell Sci. 110, 401-407.

s8a.m10.o4 **Structure of Human TRAIL and its complex with a receptor.** M.-S. Kim. *Department of Life Science, and Division of Molecular and Life Science, Pohang University of Science and Technology, Pohang, Kyungbuk, 790-784, Korea (Tel) 82-562-279-2289, (Fax) 82-562-279-2199.*
Keywords: protein protein interactions.

TRAIL is a cytokine that induces apoptosis in a wide variety of tumor cells but not in normal cells. It contains an extraordinary elongated loop due to a unique insertion of 12-16 amino acids compared with other members of tumor necrosis factor (TNF) family. Biological implication of the frame insertion has not been clarified. We have determined the crystal structure of TRAIL in a complex with the extracellular domain of death receptor DR5 at 2.2 Å resolution. The structure reveals extensive contacts between the elongated loop and DR5 in an interaction mode that would not be allowed without the frame insertion. The observation, along with previous deletion analyses, identifies the critical role of the frame insertion as a molecular strategy conferring specificity for the recognition of cognate receptors. The structure also suggests that a built-in flexibility of the TNF receptor family members is likely to play a general and important role in binding and recognition of TNF family members.