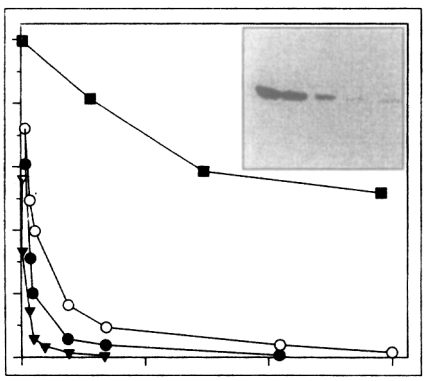
of PI 3-kinase. Ras and R-Ras thus stimulate PKB/Akt through a non-autocrine mechanism that involves PI 3-kinase. Transformation assays in fibroblasts suggest that PKB/Akt and Raf are part of distinct oncogenic signaling pathways. Both the Raf-MAP kinase and PI 3-kinase-PKB/Akt pathways are activated by Ras, but only the PI 3-kinase-PKB/Akt pathway is activated by R-Ras. PI 3-kinase, and downstream targets such as PKB/Akt, are likely to be essential mediators of transformation induced by R-Ras.
20 December 1996*, Research Paper, *Current Biology*

☐ **Cell-cycle arrest and inhibition of Cdk4 activity by small peptides based on the carboxy-terminal domain of p21^{WAF1}.** Kathryn L Ball, Sonia Lain, Robin Fåhraeus, Carl Smythe and David P Lane (1996). *Curr. Biol.* **7**, 71–80.

The damage-inducible cell-cycle checkpoint pathway regulated by p53 is commonly inactivated in human cancer. If the activity of key downstream effectors, such as the cyclin-dependent kinase (Cdk) inhibitor p21^{WAF1}, can be mimicked, it may be possible to restore growth suppression. The primary function of p21^{WAF1} appears to be the inhibition of G1 cyclin–Cdk complexes.



Identifying the region(s) of p21^{WAF1} that contain its inhibitor activity may inform the development of novel anti-proliferative drugs for use in tumours with a defective p53 pathway. The authors report the discovery of small synthetic peptides based on the sequence of p21^{WAF1} that bind to and inhibit cyclin D1–Cdk4. When introduced into cells, both a 20 amino acid and truncated 8 amino acid peptide blocked phosphorylation of the retinoblastoma protein (pRb) and induced a potent G1/S growth arrest. These data support the idea that the carboxyl terminus of p21^{WAF1} is important in the inhibition of Cdk4 activity *in vivo*. The fact that a small peptide is sufficient to mimic p21^{WAF1} function and produce a G1 cell-cycle arrest in tissue culture cell systems makes the cyclin D1–Cdk4 system a realistic and exciting target for the design of novel synthetic compounds that can act as anti-proliferative agents in human cells.
20 December 1996*, Research Paper, *Current Biology*

☐ **Detecting native-like properties in combinatorial libraries of *de novo* proteins.** Sushmita Roy, Kimberly J Helmer and Michael H Hecht (1996). *Folding & Design* **2**, 89–92.

Combinatorial methods based on binary patterning of polar and nonpolar residues have been used to generate large libraries of *de novo* α-helical proteins. Within such libraries, the ability to find structures that resemble natural proteins requires a rapid method to sort through large collections of proteins and detect those possessing 'native-like' features. This paper presents such a method and applies it to an initial collection of *de novo* proteins. The method identifies proteins with native-like properties from libraries of *de novo* sequences expressed *in vivo* and prepared using a novel 'rapid prep' freeze/thaw procedure; chromatographic purification was not required. The semi-crude samples were analyzed for native-like features by one-dimensional ^{1}H NMR spectroscopy. The authors found native-like features for several proteins among a collection of sequences designed by binary patterning. Native-like properties can thus be detected using a method that requires neither isotopic enrichment nor chromatographic purification. The method can be used to screen for native-like properties among large collections of *de novo* sequences. The authors conclude that although the binary code strategy does not explicitly design tertiary packing, it can nonetheless generate proteins that possess native-like properties, and that the availability of a rapid assay for detecting native-like properties will facilitate the design and isolation of novel proteins with desirable properties.
29 January 1997*, Research Paper, *Folding & Design*

☐ **The molecular basis for allergen cross-reactivity: crystal structure and IgE-epitope mapping of birch pollen profilin.** Alexander A Fedorov, Tanja Ball, Nicole M Mahoney, Rudolf Valenta and Steven C Almo (1997). *Structure* **5**, 33–45.

The profilins are a group of ubiquitous actin monomer binding proteins that are responsible for regulating the normal distribution of filamentous actin networks in eukaryotic cells. Profilins can induce allergic responses in almost 20% of all pollen allergic patients. The paper describes the X-ray crystal structure of birch pollen profilin (BPP) at 2.4 Å resolution. The major IgE-reactive epitopes were mapped and found to cluster on the amino-terminal and carboxy-terminal α helices, and on a segment of the protein containing two strands of the β sheet. The prevalent epitopic areas are located in regions with conserved sequence and secondary structure and overlap the binding sites for natural profilin ligands, indicating that the native ligand-free profilin acts as the original cross-sensitizing agent. Structural homology indicates that the basic features of the G actin–profilin interaction are conserved in all eukaryotic organisms, but suggests that mechanistic differences in the binding of proline-rich ligands may