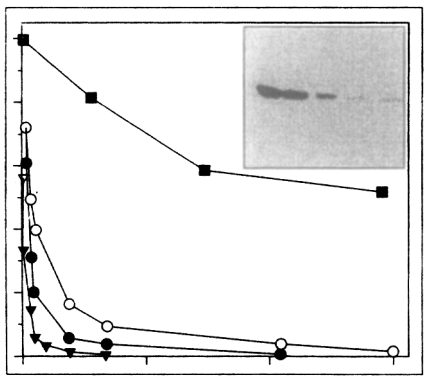
of PI 3-kinase. Ras and R-Ras thus stimulate PKB/Akt through a non-autocrine mechanism that involves PI 3-kinase. Transformation assays in fibroblasts suggest that PKB/Akt and Raf are part of distinct oncogenic signaling pathways. Both the Raf-MAP kinase and PI 3-kinase-PKB/Akt pathways are activated 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.



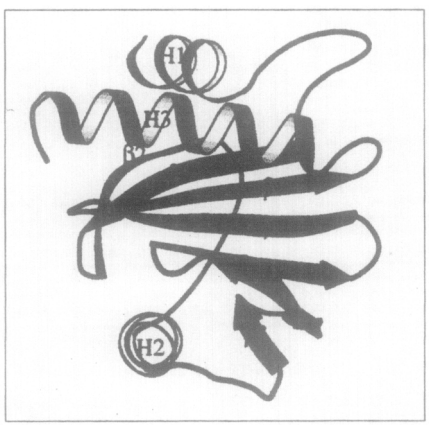
Identifying the region(s) of p21^{WAF1} that contain its inhibitor activity may inform the development of novel anti-proliferative drugs for use in tumours with a defective p53 pathway. The authors report the discovery of small synthetic peptides based on the sequence of p21^{WAF1} that bind to and inhibit 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.

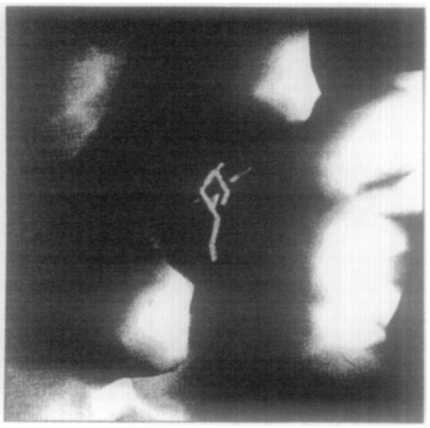
The profilins are a group of ubiquitous actin monomer binding proteins that are responsible for regulating the normal distribution of filamentous actin networks in eukaryotic cells. Profilins can induce allergic responses in almost 20% of all pollen allergic patients. The paper describes the X-ray crystal 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



exist. The structure of BPP provides a molecular basis for understanding allergen cross-reactivity, and the detailed chemical and physical description of the major reactive epitopes provides a database for the design of ligands that may reduce the allergic response.
15 January 1997, Research Article, *Structure*

☐ **A new function for a common fold: the crystal structure of quinolinic acid phosphoribosyltransferase.** Janina C Eads, Derya Ozturk, Tom B Wexler, Charles Grubmeyer and James C Sacchettini (1997). *Structure* **5**, 47–58.

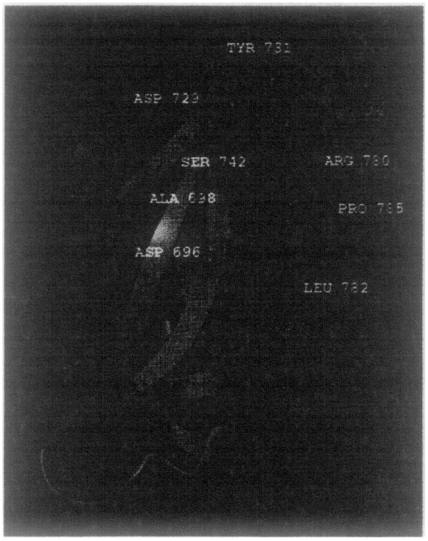
Quinolinic acid (QA) is a neurotoxin that has been shown to be present at high levels in the central nervous system of patients with certain diseases, such as AIDS and meningitis. Quinolinic acid phosphoribosyltransferase (QAPRTase) provides the only route for QA metabolism and is an essential step in *de novo* NAD biosynthesis. QAPRTase catalyzes the synthesis of nicotinic acid mononucleotide (NAMN) from QA and 5-phosphoribosyl-1-pyrophosphate (PRPP). The crystal structure of QAPRTase from *Salmonella typhimurium* was determined with bound QA (2.8 Å resolution) and with bound NAMN (3.0 Å resolution). The enzyme shows a completely novel fold for a PRTase enzyme, comprising a two-domain structure: a mixed α/β amino-terminal domain and an α/β barrel-like domain. The active site is located at the carboxy-terminal ends of the β strands of the α/β barrel, and is bordered by the amino-terminal domain of the second subunit of the dimer. The active site is largely composed of a number of conserved charged residues that appear to be important for substrate binding and catalysis. The structure shows a phosphate-binding site that appears to be conserved among many α/β-barrel enzymes including indole-3-glycerol phosphate synthase and flavocytochrome *b2*. The new fold demonstrates that the PRTase enzymes have evolved their similar chemistry from at least two completely different protein architectures.



15 January 1997, Research Article, *Structure*

☐ **The crystal structure of phenylalanyl-tRNA synthetase from *Thermus thermophilus* complexed with cognate $tRNA^{Phe}$.** Yehuda Goldgur, Lidia Mosyak, Ludmila Reshetnikova, Valentina Ankilova, Olga Lavrik, Svetlana Khodyreva and Mark Safro (1997). *Structure* **5**, 59–68.

In translating the genetic code each aminoacyl-tRNA synthetase (aaRS) must recognize its cognate tRNA and attach the corresponding amino acid to the acceptor end of tRNA, discriminating all the others. The $(\alpha\beta)_2$ phenylalanyl-tRNA synthetase (PheRS) is one of the most complex enzymes in the aaRS family and is characterized by anomalous charging properties. The crystal structure of *Thermus thermophilus* PheRS complexed with cognate tRNA has been solved (3.28 Å resolution), and shows that one $tRNA^{Phe}$ molecule binds across all four PheRS subunits. The interactions of PheRS with tRNA stabilize the flexible amino-terminal part of the α subunit. Anticodon recognition upon tRNA binding is performed by the B8 domain, which is similar in structure to the RNA-binding domain (RBD) of the small spliceosomal protein U1A. The *Th. thermophilus* PheRS approaches the anticodon loop from the minor groove side. The interactions of $tRNA^{Phe}$ with PheRS, particularly with the coiled-coil domain of the subunit, result in conformational changes when compared with uncomplexed yeast $tRNA^{Phe}$. The $tRNA^{Phe}$ is a newly recognized type of RNA molecule specifically interacting with the RBD fold. In addition, a new type of anticodon-binding domain emerges in the aaRS family. The uniqueness of PheRS in charging 2′OH of tRNA is dictated by the size of its adenine-binding pocket and by the local conformation of the tRNA's CCA end. With the availability of this three-dimensional structure of the complex between multisubunit PheRS and $tRNA^{Phe}$, a fuller picture of the specific tRNA–aaRS interactions is beginning to emerge.



15 January 1997, Research Article, *Structure*

☐ **The novel acidophilic structure of the killer toxin from halotolerant yeast demonstrates remarkable folding similarity with a fungal killer toxin.** Tatsuki Kashiwagi, Naoki Kunishima, Chise Suzuki, Fumihiko Tsuchiya, Sayuki Nikkuni, Yoji Arata and Kosuke Morikawa (1997). *Structure* **5**, 81–94.

Several strains of yeasts and fungi produce proteinaceous substances, termed killer toxins, which kill sensitive strains. The SMK toxin, secreted by the halotolerant yeast *Pichia farinosa* KK1 strain, uniquely exhibits its maximum killer activity under conditions of acidic pH and high salt concentration. The toxin is composed of two distinct subunits, α and β, which tightly interact with each other under acidic conditions, but are easily dissociated under neutral conditions and lose the killer activity. Two crystal structures of the SMK