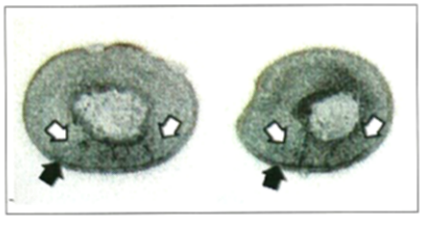
Elsewhere in biology

A selection of interesting papers published last month in *Chemistry & Biology*'s sister journals, *Current Biology*, *Folding & Design* and *Structure*, chosen and summarized by the staff of *Chemistry & Biology*.

Chemistry & Biology June 1998, **5**:153–156

A highly conserved RNA-binding protein for cytoplasmic mRNA localization in vertebrates.
James O Deshler, Martin I Highett, Tatiana Abramson, Bruce J Schnapp (1998). *Curr. Biol.* **8**, 489–496.

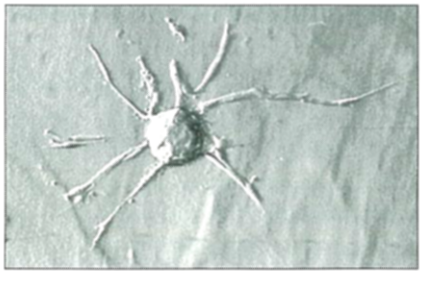
Cytoplasmic mRNA localization is a widespread mechanism for restricting the translation of specific mRNAs to distinct regions of eucaryotic cells. This process involves specific interactions between cellular factors and localization signals in the 3′ untranslated regions of the localized mRNA. Because only a few of these cellular factors have been identified, it is not known whether common factors are utilized for the localization of different mRNAs. The authors recently discovered Vera, a



protein that binds specifically to the *Vg1* localization element and is involved in the localization of *Vg1* mRNA in *Xenopus* oocytes. To characterize further the role of Vera in the localization of *Vg1* mRNA, the authors have purified the Vera protein and cloned its gene. Vera is homologous to chicken zip-code-binding protein (ZBP), which binds to a short RNA sequence required for localization of β-actin mRNA in chick embryo fibroblasts. The predicted amino-acid sequences of Vera and ZBP contain five RNA-binding domains and putative signals for nuclear localization and export. Like the binding of ZBP to β-actin mRNA, Vera specifically binds to a repeated sequence motif in the *Vg1* localization element that is required for *Vg1* mRNA localization in *Xenopus* oocytes. Vera, a highly conserved component of the mRNA localization machinery, participates in localizing different mRNAs in different cell types. Thus, Vera appears to be a general factor for mRNA localization, and additional factors may be required to specify diverse patterns of RNA localization.
8 April 1998, Research Paper, *Current Biology*

Angiopoietin-1 induces sprouting angiogenesis *in vitro*.
Thomas I Koblizek, Cornelia Weiss, George D Yancopoulos, Urban Deutsch, Werner Risau (1998). *Curr. Biol.* **8**, 529–532.

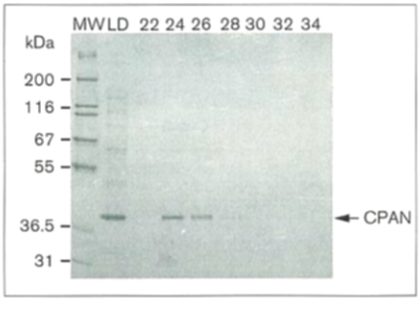
Sprouting of new capillaries from pre-existing blood vessels is a hallmark of angiogenesis during embryonic development and solid tumor growth. In addition to the vascular endothelial growth factor (VEGF) and its receptors, the Tie receptors and their newly identified ligands, the angiopoietins, have been implicated in the control of blood vessel formation. Although 'knockouts' of the gene encoding the Tie2 receptor, or its activating ligand angiopoietin-1 (Ang1), result in embryonic lethality in mice due to an



absence of remodeling and sprouting of blood vessels, biological activity *in vitro* has not yet been described for this receptor–ligand system. In an assay in which a monolayer of endothelial cells were cultured on microcarrier beads and embedded in three-dimensional fibrin gels, recombinant Ang1 induced the formation of capillary sprouts in a dose-dependent manner that was completely inhibited by soluble Tie2 receptor extracellular domains. Suboptimal concentrations of VEGF and Ang1 acted synergistically to induce sprout formation. Thus, the biological activity of Ang1 *in vitro* is consistent with the specific phenotype of mice deficient in Tie2 or Ang1. The data suggest that, like in other developmental systems, blood vessel formation requires a hierarchy of master-control genes in which VEGF and angiopoietins, along with their receptors, are amongst the most important regulators.
13 April 1998, Brief Communication, *Current Biology*

CPAN, a human nuclease regulated by the caspase-sensitive inhibitor DFF45.
Robert Halenbeck, Heather MacDonald, Anne Roulston, Timothy T Chen, Leah Conroy, Lewis T Williams (1998). *Curr. Biol.* **8**, 537–540.

Induction of apoptosis by death receptors such as Fas or tumour necrosis factor (TNF) R1 leads to distinct changes in cell morphology, activation of the caspase protease cascade, and the degradation of nuclear chromatin by activated nucleases. Here, the authors describe the purification and cDNA cloning of a novel 40 kDa endonuclease from Jurkat cells that is activated by caspases. These protein, designated caspase-activated nuclease (CPAN), is sufficient to degrade naked DNA and to

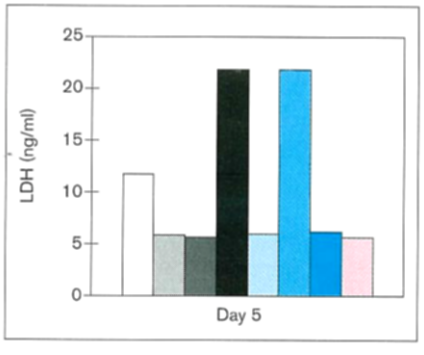


induce apoptotic morphology and DNA fragmentation in naive nuclei. CPAN is highly homologous to a recently

described mouse nuclease, CAD, and may represent the human homologue. The authors show that the activity of human CPAN is regulated by DFF45, a protein inhibitor necessary for CPAN expression and stabilization in an inactive state in living cells. Proteolytic cleavage of DFF45 by caspases *in vitro* leads to dissociation of DFF45 fragments from CPAN and activation of CPAN as an endonuclease.
13 April 1998, Brief Communication, *Current Biology*

- **Neuronal apoptosis induced by HIV-1 gp120 and the chemokine SDF-1 is mediated by the chemokine receptor CXCR4.**
  Joseph Hesselgesser, Dennis Taub, Padmavathi Baskar, Michael Greenberg, James Hoxie, Dennis L Kolson, Richard Horuk (1998). *Curr. Biol.* **8**, 595–598.

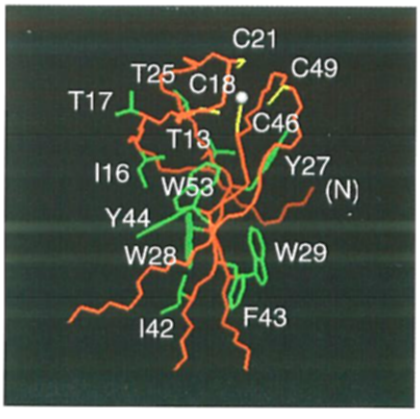
CXCR4, a seven transmembrane domain G-protein-coupled receptor for the Cys–X–Cys class of chemokines, is one of several chemokine receptors that can act as a co-receptor with CD4 for the human immunodeficiency virus (HIV-1) glycoprotein gp120. CXCR4 can mediate the entry of HIV-1 strains that specifically infect T cells, such as the IIIB strain. Recent reports indicate that gp120 can signal through CXCR4 and it has been suggested that signal transduction, mediated by the viral



envelope, might influence viral-associated cytopathicity or apoptosis. Neuronal apoptosis is a feature of HIV-1 infection in the brain, although the exact mechanism is unknown. Here, the authors address the possible role of CXCR4 in inducing apoptosis using cells of the hNT human neuronal cell line; these cells resemble immature post-mitotic cholinergic neurons and have a number of neuronal characteristics. The authors find that both IIIB gp120 and the Cys–X–Cys chemokine SDF-1α can directly induce apoptosis in hNT neurons in the absence of CD4 and in a dose-dependent manner.
27 April 1998, Brief Communication, *Current Biology*

- **High-resolution structure of an archaeal zinc ribbon defines a general architectural motif in eukaryotic RNA polymerases.**
  Bing Wang, David NM Jones, Brian P Kaine and Michael A Weiss (1998). Structure 6, 555–569.

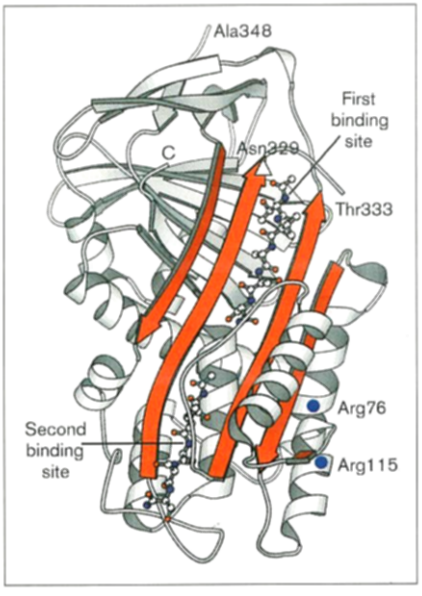
Transcriptional initiation and elongation provide control points in gene expression. Eukaryotic RNA polymerase II subunit 9 (RPB9) regulates start-site selection and elongational arrest. RPB9 contains Cys4 Zn^{2+}-binding motifs which are



conserved in archaea and homologous to those of the general transcription factors TFIIB and TFIIS. The structure of an RPB9 domain from the hyperthermophilic archaeon *Thermococcus celer* was determined at high resolution using NMR spectroscopy. The structure consists of an apical tetrahedral Zn^{2+}-binding site, central β sheet and disordered loop. The planar architecture of the RPB9 zinc ribbon — distinct from that of a conventional globular domain — can accommodate significant differences in the alignment of polar, non-polar and charged sidechains. Such divergence is associated with local and non-local changes in structure. The RPB9 structure is distinguished by a fourth β strand (extending the central β sheet) in a well ordered amino-terminal segment and also differs from TFIIS (but not TFIIB) in the orientation of its apical Zn^{2+}-binding site. Cys4 Zn^{2+}-binding sites with distinct patterns of polar, non-polar and charged residues are conserved among unrelated RNAP subunits and are predicted to form variant zinc ribbons.
15 May 1998, Research Paper, *Structure*

- **Interfering with the inhibitory mechanism of serpins: crystal structure of a complex formed between cleaved plasminogen activator inhibitor type 1 and a reactive-centre loop peptide.**
  Yafeng Xue, Petter Björquist, Tord Inghardt, Marcel Linschoten, Djordje Musil, Lennart Sjölin and Johanna Deinum (1998). *Structure* **6**, 627–636.

Plasminogen activator inhibitor type 1 (PAI-1) is an important endogenous regulator of the fibrinolytic system. Reduction of PAI-1 activity has been shown to enhance the dissolution of blood clots. Like other serpins, PAI-1 binds covalently to a target serine protease, thereby irreversibly inactivating the enzyme. During this process the exposed reactive-centre loop of PAI-1 is believed to undergo a conformational change, becoming inserted into β sheet A of the serpin. Incubation with peptides from the reactive-centre loop transform serpins into a substrate for their target protease. It has been hypothesised that these peptides bind to β sheet A, thereby hindering the conformational rearrangement leading to loop insertion and formation of the stable serpin–protease complex. The authors report here the 1.95 Å X-ray crystal structure of a complex of a glycosylated mutant of PAI-1, PAI-1-Ala335Glu, with two molecules of the inhibitory reactive-centre loop peptide N-Ac-TVASS-NH_2.



Both bound peptide molecules are located between β strands 3A and 5A of the serpin. The binding kinetics of the peptide inhibitor to immobilised PAI-1-Ala335Glu, as monitored by surface plasmon resonance, are consistent with there being two different binding sites. The localisation of the inhibitory peptide in the complex strongly supports the theory that molecules binding in the space between β strands 3A and 5A of a serpin are able to prevent insertion of the reactive-centre loop into β sheet A, thereby abolishing the ability of the serpin to irreversibly inactivate its target enzyme. The characterisation of the two binding sites for the peptide inhibitor provides a solid foundation for computer-aided design of novel, low molecular weight PAI-1 inhibitors.
15 May 1998, Research Paper, *Structure*

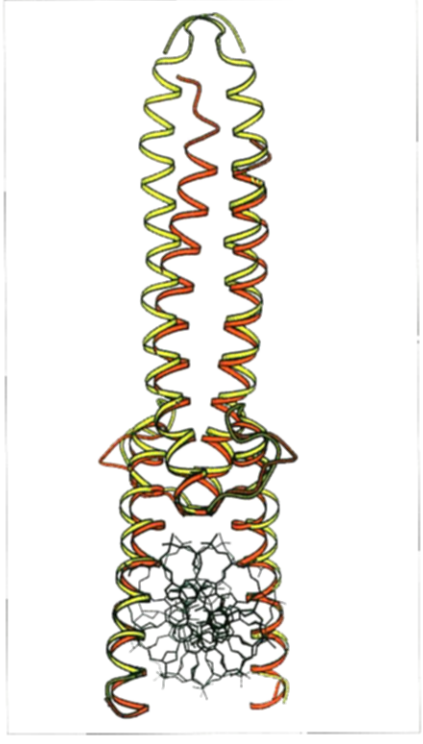
☐ **Solution structure of the heparin-binding domain of vascular endothelial growth factor.**
Wayne J Fairbrother, Mark A Champe, Hans W Christinger, Bruce A Keyt and Melissa A Starovasnik (1998). *Structure* **6**, 637–648.

Vascular endothelial growth factor (VEGF) is an endothelial cell-specific mitogen and is a potent angiogenic and vascular permeabilizing factor. VEGF is also an important mediator of pathological angiogenesis associated with cancer, rheumatoid arthritis and proliferative retinopathy. The binding of VEGF to its two known receptors, KDR and Flt-1, is modulated by cell-surface-associated heparin-like glycosaminoglycans and exogenous heparin or heparan sulfate. Heparin binding to $VEGF_{165}$, the most abundantly expressed isoform of VEGF, has been localized to the carboxy-terminal 55 residues; plasmin cleavage of $VEGF_{165}$ yields a homodimeric 110-residue amino-terminal receptor-binding domain ($VEGF_{110}$) and two

55-residue carboxy-terminal heparin-binding fragments. The endothelial cell mitogenic potency of $VEGF_{110}$ is decreased significantly relative to $VEGF_{165}$, indicating that the heparin-binding domains are critical for stimulating endothelial cell proliferation. The solution structure of the 55-residue heparin-binding domain of $VEGF_{165}$ has been solved using data from two-dimensional homonuclear and three-dimensional heteronuclear NMR spectroscopy. The heparin-binding domain of VEGF has no significant sequence or structural similarity to any known proteins and thus represents a novel heparin-binding domain. Most of the positively charged amino acid sidechains are localized on one side of the carboxy-terminal subdomain or on an adjacent disordered loop in the amino-terminal subdomain. The observed distribution of surface charges suggests that these residues constitute a heparin interaction site.
15 May 1998, Research Paper, *Structure*

☐ **Co-crystal structure of sterol regulatory element binding protein 1a at 2.3 Å resolution.**
A Párraga, L Bellsolell, AR Ferré-D'Amaré and Stephen K Burley (1998). *Structure* **6**, 661–672.

The sterol regulatory element binding proteins (SREBPs) are helix–loop–helix transcriptional activators that control expression of genes encoding proteins essential for cholesterol biosynthesis/uptake and fatty acid biosynthesis. Unlike helix–loop–helix proteins that recognize symmetric E-boxes (5′-CANNTG-3′), the SREBPs have a tyrosine instead of a conserved

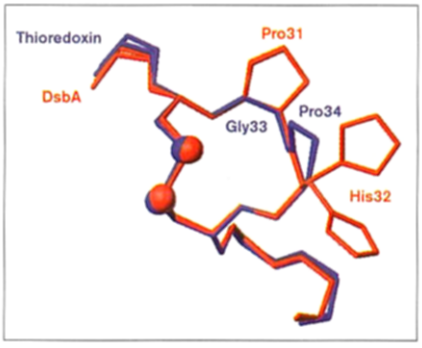


arginine in their basic regions. This difference allows recognition of an asymmetric sterol regulatory element (StRE, 5′-ATCACCCCAC-3′). The co-crystal structure of the DNA-binding portion of SREBP-1a bound to an StRE

reveals a quasi-symmetric homodimer with an asymmetric DNA–protein interface. One monomer binds the E-box half site of the StRE (5′-ATCAC-3′) using sidechain–base contacts typical of other helix–loop–helix proteins. The non-E-box half site (5′-GTGGG-3′) is recognized through entirely different protein–DNA contacts. Although the SREBPs are structurally similar to the E-box-binding helix–loop–helix proteins, the Arg→Tyr substitution yields dramatically different DNA-binding properties that explain how they recognize StREs and regulate expression of genes important for membrane biosynthesis.
15 March 1998, Research Paper, *Structure*

☐ **A single dipeptide sequence modulates the redox properties of a whole enzyme family.**
Martina Huber-Wunderlich, Rudi Glockshuber-Wunderlich, Rudi Glockshuber (1998). *Fold. Des.* **3**, 161–171.

Disulfide exchange reactions are catalyzed by thiol/disulfide oxidoreductases. These enzymes possess a thioredoxin fold and contain a catalytic disulfide with the sequence Cys–X–X–Cys at the amino terminus of an α helix. Despite these similarities, the various members differ strongly in their redox potentials (-122 mV to -270 mV). Using the strong oxidant DsbA from *Escherichia coli* as a model system, the authors investigated whether the redox properties of these enzymes can be modulated rationally by exchange of the X–X dipeptide. The X–X dipeptide of DsbA (Cys30–Pro31–His32–Cys33) was exchanged by the dipeptides of eukaryotic protein disulfide isomerase (PDI; Gly–His), glutaredoxin (Pro–Tyr), and thioredoxin (Gly–Pro) from *E. coli*. All variants were less oxidizing than wild-type DsbA and their redox potentials were in the order of the related natural enzymes (DsbA > PDI > glutaredoxin > thioredoxin). The equilibrium constant between glutathione and the thioredoxin-like variant increased 1200-fold compared with wild-type DsbA. The variants also showed a strong increase in the pK_a of the nucleophilic cysteine (Cys30). As for glutaredoxin and thioredoxin, the catalytic disulfide stabilized the corresponding variants while



destabilizing wild-type DsbA and the PDI-like variant. The X–X dipeptide in the active site of thiol/disulfide oxidoreductases appears to be the main determinant of the redox properties of these enzymes. This empirical finding should be very useful for the design of new thiol/disulfide oxidoreductases with altered redox potentials and for studying the function of these enzymes *in vivo*.
30 March 1998, Research Paper, *Folding & Design*

☐ **Models of protein interactions: how to choose one.**
Rose Du, Alexander Yu Grosberg, Toyoichi Tanaka (1998). *Fold. Des.* **3**, 203–211.

There have been many attempts to approximate realistic protein interaction energies by coarse graining (i.e. considering interactions between amino acids rather than those between atoms). In particular, many 20-letter models have been derived (corresponding to the 20 naturally occurring amino acids). Because such models remain computationally infeasible, many two-letter models have been proposed as further simplifications. The choice of which model to use remains arbitrary, however. In this work, the authors formulate the framework within which the quality of approximate interaction potentials with respect to folding can be defined explicitly. Using a recently proposed criterion for comparing interaction matrices, the authors compare various 20 × 20 interaction matrices and obtain the two-letter model that most closely approximates each 20 × 20 matrix. The authors find that there are considerable differences among the 20 × 20 matrices. In particular, some matrices are much more similar to the hydrophobic model than others. Furthermore, the authors find that although the best two-letter approximation of a 20-letter model is a significantly better approximation than a random two-letter model, it is still a poor approximation of realistic protein interactions. The determination of the best two-letter approximations of various 20-letter models of protein interaction energies reveals the degree to which hydrophobic interactions dominate in each of the models and hence in proteins.
14 April 1998, Research Paper, *Folding & Design*