Calendar

If you know of any meetings other than those listed below, or of changes to this information, please let *Chemistry & Biology* know by fax (44 (0)171 580 8428) or e-mail (chembiol@cursci.co.uk).

Chemistry & Biology January 1998, 5:R19–R20

24–28 January, 1998
Angiogenesis and cancer, Hyatt Orlando, Orlando, FL.
Contact: American Association for Cancer Research, Public Ledger Building, Suite 826, 150 South Independence Mall West, Philadelphia, PA 19106-3483, USA.
Tel: +1 215 440 9300
Fax: +1 215 440 9313
e-mail: webmaster@aacr.org
http://www.aacr.org/confrnc.htm

3–5 February, 1998
Exploiting molecular diversity: combinatorial libraries for drug discovery, San Diego.
Contact: Cambridge Healthtech Inst., 1037 Chestnut St, Newton Upper Falls, MA 02164, USA.
Tel: +1 617 630 1300
Fax: +1 617 630 1325

4–6 February, 1998
ComTech 98: 2nd annual European conference on combinatorial technologies, Montreux, Switzerland.
Contact: Scitec SA, Av. De Provence 20, Lausanne 20, Switzerland, CH-1000.
Tel: +41 21 626 4630
Fax: +41 21 624 15 49
e-mail: symposia@worldcom.ch
http://www.scitec-robotics.com

6–7 February, 1998
Molecular recognition in drug design: docking and scoring, San Francisco.
Contact: Kristina Clarke, University of California San Francisco, Department of Pharmaceutical Chemistry, PO Box 0446, San Francisco, CA 94143-0446, USA.
Tel: +1 415 476 1913
Fax: +1 415 502 4690
e-mail: kristina@cgl.ucsf.edu
http://mdi.ucsf.edu

15–20 February, 1998
1998 Gordon research conference on the chemistry & biology of peptides, Ventura, CA.
http://www.caltech.edu/~biweb/peptides grc98.html

22–24 February, 1998
Miniturization technologies – practical applications in high throughput screening and combinatorial chemistry, Lake Tahoe, CA.
Contact: IBC USA Conferences, Inc., 225 Turnpike Road, Southborough, MA 01772-1749, USA.
Tel: +1 508 481-6400
Fax: +1 508 481-7911
e-mail: inq@ibcusa.com
http://www.ibcusa.com/conf/miniature/index.html

2–4 March, 1998
5th Annual exploiting molecular diversity: small molecule libraries for drug discovery, Coronado, CA.
Contact: Cambridge Healthtech Institute, 1037 Chestnut Street, Newton Upper Falls, MA, USA.
Tel: +1 617 630 1300
Fax: + 1 617 630 1325
e-mail: chi@healthtech.com
http://www.healthtech.com/conferences/

5–6 March, 1998
3rd Annual high throughput organic synthesis: developing small molecule libraries, Coronado, CA.
Contact: Cambridge Healthtech Institute, 1037 Chestnut Street, Newton Upper Falls, MA 02164, USA.
Tel: + 1 617-630 1300
Fax : + 1 617-630 1325
e-mail: chi@healthtech.com
http://www.healthtech.com/conferences/

21–24 March, 1998
ABRF '98. From genome to function – technical challenges of the post-genome era, San Diego, CA.
Contact: ABRF Meeting Office, 9650 Rockville Pike, Bethesda, MD 20814-3998, USA.
Tel: +1 301 530 7010
Fax: +1 301 530 7014
e-mail: abrf98@faseb.org
http://www.faseb.org/meetings/abrf/abrf98/abrfmp.htm

28 March–3 April, 1998
Keystone symposium on nuclear receptor gene family, Incline Village, Nevada.
Contact: Keystone Symposia, Drawer 1630, Silverthorne, CO 80498, USA.
Tel: 800 253 0685 or +1 970 262 1230
Fax: +1 970 262 1525,
e-mail: keystone@symposia.com

28 March–3 April, 1998
Angiogenesis and vascular remodelling, Steamboat Springs, Colorado.
Contact: Keystone Symposia, Drawer 1630, Silverthorne, CO 80498, USA.
Tel: 800 253-0685 or +1 970 262 1230
Fax: +1 970 262 1525
e-mail: keystone@symposia.com

29 March–2 April, 1998
215th American chemists society national meeting, Dallas, Texas.
Contact: American Chemical Society Meetings Department, 1155 Sixteenth Street, N.W. Washington, D.C. 20036, USA.
Tel: +1 202 872 4396
Fax: +1 202 872 6128
e-mail: natlmtgs@acs.org

5–9 April, 1998
Triennial meeting of the nucleic acids and molecular biology group of the RSC and Biochemical Society – NACON-IV, Sheffield, UK.
Contact: Drs J Grasby and M Blackburn, Department of Chemistry, University of Sheffield, Sheffield S3 7HF, UK.
Tel: +44 (0)114 222 9462,
Fax: +44 (0)114 273 8673
e-mail: j.a.grasby@sheffield.ac.uk or g.m.blackburn@sheffield.ac.uk

20–21 April, 1998
IBC's Seventh annual international conference: high-throughput screening, Wyndham Emerald Plaza Hotel, San Diego, CA.
Contact: IBC USA Conferences, Inc., 225 Turnpike Road, Southborough, MA 01772-1749, USA.
Tel: +1 508 481 6400
Fax: +1 508 481 7911
e-mail: 7911inq@ibcusa.com
http://www.ibcusa.com/conf/screening/index.html

8–10 May, 1998
5th Conference on metal ions in medicine and biology, Munich, Germany.
Contact: Dr V Negretti di Bratter, Hahn Meitner Institut Berlin, Glienicker Str. 100, Berlin, Germany, D-14109
Fax: + 49 030 8062 2781
e-mail: negretti@hrni.de
http://www.hmi.de/bereiche/N/NG/Events.html

13–17 May, 1998
18th Blankanese conference – orphan receptors and novel ligands, Hamburg–Blankanese, Germany.
Contact: Dr D Richter, Institut fur Zellbiochemie, UKE, Martinistr. 52, 20246 Hamburg, Germany.
Fax: +49 40 4717 4541
e-mail: richter@uke.uni-hamburg.de

16–20 May, 1998
American society for biochemistry & molecular biology annual meeting, Washington, DC.
http://www.faseb.org/meetings/asbmb/asbmb98/asbmbcfp.html

3–7 May, 1998
Proteins that bind RNA, Avalon, NJ.
Contact: Mrs Helen F Pirrello, Department of Molecular Biology and Biochemistry, Rutgers, The State University of New Jersey, Center for Advanced Biotechnology and Medicine, 679 Hoes Lane, Piscataway, NJ 08855-1179, USA.
Tel: +1 732 235 4962
Fax: +1 732 235 4880
e-mail: pirrello@mbcl.rutgers.edu,
http://cpmcnet.columbia.edu/www/protRNAmtg

14–18 June, 1998
Proteases and protease inhibitors in cancer, Nyborg Strand Conference Center, Fyn, Denmark.
Contact: American Association for Cancer Research, Public Ledger Building, Suite 826, 150 South Independence Mall West, Philadelphia, PA 19106-3483, USA.
Tel: +1 215 440 9300
Fax: +1 215 440 9313
e-mail: webmaster@aacr.org
http://www.aacr.org/confrnc.htm

14–19 June, 1998
Gordon research conference on bioorganic chemistry, Proctor Academy, Andover, New Hampshire, USA.
http://www.grc.uri.edu/98sched.htm

28 June–3 July, 1998
1998 Reaction mechanisms conference, Asilomar Conference Center, Carmel, CA.
Contact: Angel Kim, Department of Chemistry & Biochemistry UCLA , 405 Hilgard Avenue, Los Angeles, CA 90095-1569 USA.
Tel: +1 310 206 1036
Fax: +1 310 206 3722
http://www.chem.ucla.edu/conf/reaction.html

1–4 July, 1998
2nd European symposium on antimicrobial agents, Hradec Kralove, Czech Republic.
Contact: Antimicrobial Symposium Secretariat, Dept. of Inorganic and Organic Chemistry, Faculty of Pharmacy, Charles University, Heyrovskeho 1203, Hradec Kralove, 500 05 Czech Republic.
Tel: + 420 49 5210002
Fax: + 420 49 5067343
e-mail: palat@faf.cuni.cz
http://www.faf.cuni.cz/antimicr/

12–17 July, 1998
Chemistry and biology of tetyrapyrroles – Gordon research conference, Newport, RI, USA.
Contact: Gordon Research Conferences, University of Rhode Island, P.O. Box 984, West Kingston, Rhode Island 02892-0984, USA.
Tel: + 1 401 783-4011
Fax + 1 401 783-7644
e-mail: grc@grcmail.grc.uri.edu
http://www.grc.uri.edu/progra~2/tetra.htm

9–14 August, 1998
XIX International carbohydrate symposium, San Diego, USA.
Contact: ICS 98 Symposium Secretariat, Department of Chemistry, 516 Physical Sciences 1, University of California, Irvine, CA 92697-2025, USA
Tel: +1 714 824 8976
Fax: +1 714 824 1372
e-mail: ics98@uci.edu
http://www.ics98.uci.edu

23–27 August, 1998
216th American chemists society national meeting, Boston, Massachusetts.
Contact: American Chemical Society Meetings Department, 1155 Sixteenth Street, N.W. Washington, D.C. 20036, USA.
Tel: +1 202 872 4396
Fax: +1 202 872 6128
e-mail: natlmtgs@acs.org

6–10 September, 1998
Thirteenth international round table: nucleosides, nucleotides and their biological applications, Montpellier, France.
Contact: Drs Gilles Gosselin and Bernard Rayner, Universite MontpellierII, Case courrier 008, Sciences et Techniques du Languedoc, Place Eugene Bataillon, 34095 Montpellier Cedex 5, France.
Tel: + 33 04 67 14 38 55
Fax: + 33 04 67 04 20 29
e-mail: irt@univ-montp2.fr

Elsewhere in biology

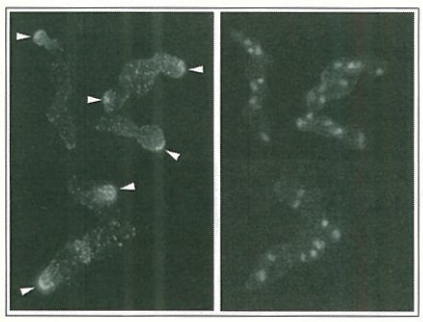
A selection of interesting papers published last month in *Chemistry & Biology*'s sister journals, *Current Biology*, *Folding & Design* and *Structure*, chosen and summarized by the staff of *Chemistry & Biology*.

Chemistry & Biology January 1998, 5:R21–R25

☐ **An IQGAP-related protein controls actin-ring formation and cytokinesis in yeast.**

J Andrew Epp and John Chant (1997). *Curr. Biol.* **7**, 921–929.

Proteins of the IQGAP family have been identified as candidate effectors for the Rho family of GTPases; however, little



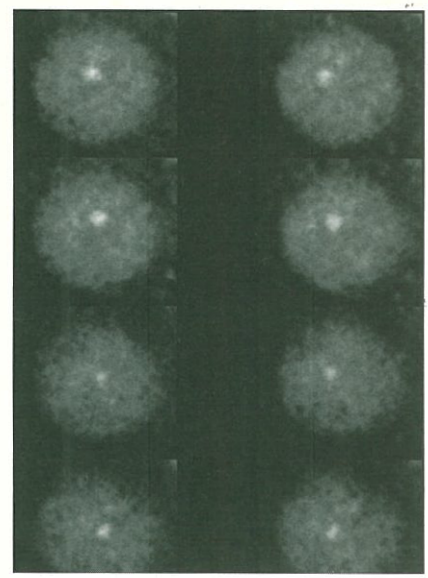
is known about their cellular functions. The domain structures of IQGAP family members make them excellent candidates as regulators of the cytoskeleton: their sequences include an actin-binding domain homologous to that found in calponin, IQ motifs for interaction with calmodulin, and a GTPase-binding domain. The genomic sequence of *Saccharomyces cerevisiae* revealed a single gene encoding an IQGAP family member (denoted IQGAP-related protein: Iqg1). Iqg1 and IQGAPs share similarity along their entire length, with an amino-terminal calponin-homology (CH) domain, IQ repeats, and a conserved carboxyl terminus. In contrast to IQGAPs, Iqg1 lacks an identifiable GAP motif, a WW domain, and IR repeats, although the functions of these domains in IQGAPs are not well defined. Deletion of the *IQG1* gene resulted in lethality. Cellular defects included a deficiency in cytokinesis, altered actin organization, aberrant nuclear segregation, and cell lysis. Consistent with a role in cytokinesis, Iqg1 co-localizes with an actin ring encircling the mother–bud neck late in the cell cycle — a putative cytokinetic ring. *IQG1* overexpression resulted in premature actin-ring formation, suggesting that Iqg1 activity temporally controls formation of this structure during the cell cycle. Yeast IQGAP-related protein, Iqg1, is an important regulator of cellular morphogenesis, inducing actin-ring formation in association with cytokinesis.

31 October 1997, Research Paper, *Current Biology*

☐ **Interphase chromosomes undergo constrained diffusional motion in living cells.**

WF Marshall, A Straight, JF Marko, J Swedlow, A Dernburg, A Belmont, AW Murray, DA Agard and JW Sedat (1997). *Curr. Biol.* **7**, 930–939.

Structural studies of fixed cells have revealed that interphase chromosomes are highly organized into specific arrangements in the nucleus, and have led to a picture of the nucleus as a static structure with immobile chromosomes held in fixed positions, an impression apparently confirmed by recent photobleaching studies. Functional studies of chromosome behavior, however, suggest that many essential processes, such as recombination, require interphase chromosomes to move around within the nucleus. To reconcile these contradictory views, the authors exploited methods for tagging specific chromosome sites in living cells of *Saccharomyces cerevisiae* with green fluorescent protein and in *Drosophila melanogaster* with fluorescently labeled topoisomerase II. Combining these techniques with submicrometer single-particle tracking, the motion of interphase chromatin was directly measured. The authors found that chromatin does indeed undergo significant diffusive motion within the nucleus, but this motion is constrained such that a given chromatin segment is free to move within only a limited subregion of the nucleus. Chromatin diffusion was found to be insensitive to metabolic inhibitors, suggesting that it results from classical Brownian motion



rather than from active motility. Nocodazole greatly reduced chromatin confinement, suggesting a role for the cytoskeleton in the maintenance of nuclear architecture. The constrained diffusion of chromatin is consistent with a highly defined nuclear architecture, but also allows enough motion for processes requiring chromosome motility to take place.

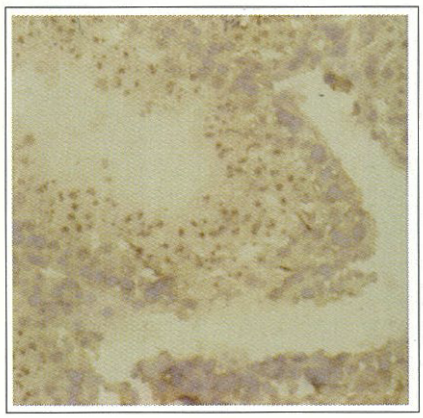
5 November 1997, Research Paper, *Current Biology*

☐ **Atm-dependent interactions of a mammalian Chk1 homolog with meiotic chromosomes.**

G Flaggs, AW Plug, KM Dunks, KE Mundt, JC Ford, MRE Quiggle, EM Taylor, CH Westphal, T Ashley, MF Hoekstra and AM Carr (1997). *Curr. Biol.* **7**, 977–986.

Checkpoint pathways prevent cell-cycle progression in the event of DNA lesions. Checkpoints are well defined in mitosis, where lesions can be the result of extrinsic damage, and they are critical in meiosis, where DNA breaks are a programmed step in meiotic recombination. In mitotic yeast cells, the Chk1 protein couples DNA repair to the

cell-cycle machinery. The Atm and Atr proteins are mitotic cell-cycle proteins that also associate with chromatin during meiotic prophase I. The genetic and regulatory interaction between Atm and mammalian Chk1 appears to be important for integrating DNA-damage repair with cell-cycle arrest. The authors have identified structural homologs of yeast Chk1 in human and mouse. $Chk1^{Hu/Mo}$ has protein kinase activity



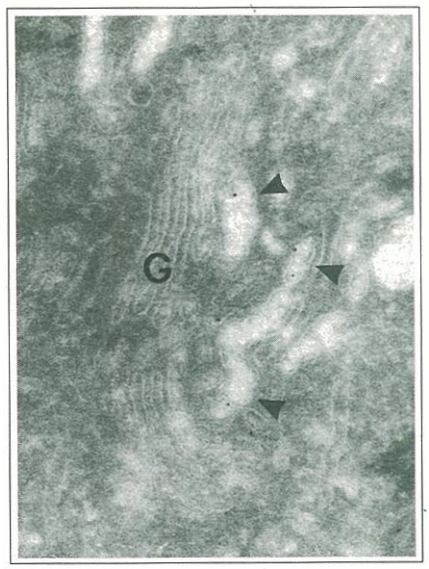
and is expressed in the testis. Chk1 accumulates in late zygotene and pachytene spermatocytes and is present along synapsed meiotic chromosomes. The association of Chk1 with meiotic chromosomes and levels of Chk1 protein depend upon a functional *Atm* gene product, but Chk1 is not dependent upon p53 for meiosis I functions. Mapping of *CHK1* to human chromosomes indicates that the gene is located at 11q22–23, a region marked by frequent deletions and loss of heterozygosity in human tumors. The Atm-dependent presence of Chk1 in mouse cells and along meiotic chromosomes, and the late pachynema co-localization of Atr and Chk1 on the unsynapsed axes of the paired X and Y chromosomes suggest that Chk1 acts as an integrator for Atm and Atr signals and may be involved in monitoring the processing of meiotic recombination. Furthermore, mapping of the *CHK1* gene to a region of frequent loss of heterozygosity in human tumors at 11q22–23 indicates that the *CHK1* gene is a candidate tumor suppressor gene.

12 November 1997, Research Paper, *Current Biology*

☐ Association of a phosphatidylinositol-specific 3-kinase with a human *trans*-Golgi network resident protein.

DM Hickinson, JM Lucocq, MC Towler, S Clough, J James, SR James, CP Downes and S Ponnambalam (1997). *Curr. Biol.* **7**, 987–990.

The eukaryotic *trans*-Golgi network (TGN) is a key site for the formation of transport vesicles destined for different intracellular compartments. A key marker for the mammalian TGN is TGN38/46. This integral membrane glycoprotein cycles between the TGN and the cell surface and is implicated in recruitment of cytosolic factors and regulation of at least one type of vesicle formation at the mammalian TGN.



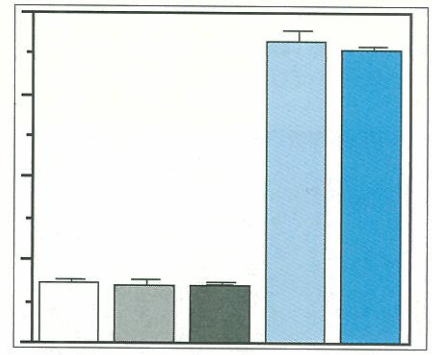
The authors have identified a phosphatidylinositol (PtdIns)-specific 3-kinase activity associated with the human orthologue (TGN46), which is sensitive to lipid kinase inhibitors. Treatment of HeLa cells with low levels of these inhibitors reveals subtle morphological changes in TGN46-positive compartments. These findings suggest a role for PtdIns 3-kinases and presumably for the product, PtdIns 3-phosphate, in the formation of secretory transport vesicles by mechanisms conserved in yeast and mammals.

29 September 1997, Brief Communication, *Current Biology*

☐ A novel receptor for Apo2L/TRAIL contains a truncated death domain.

SA Marsters, JP Sheridan, RM Pitti, A Huang, M Skubatch, D Baldwin, J Yuan, A Gurney, AD Goddard, P Godowski and A Ashkenazi (1997). *Curr. Biol.* **7**, 1003–1006.

Apo2 ligand (Apo2L, also called TRAIL for tumor necrosis factor (TNF)-related apoptosis-inducing ligand) belongs to the TNF family and activates apoptosis in tumor cells. Three closely related receptors bind Apo2L: DR4 and DR5, which contain cytoplasmic death domains and signal apoptosis, and DcR1, a decoy receptor that lacks a cytoplasmic tail and inhibits Apo2L function. By cross-hybridization with DcR1, the



authors have identified a fourth Apo2L receptor, which contains a cytoplasmic region with a truncated death domain. This protein was named decoy receptor 2 (DcR2). The DcR2 gene mapped to human chromosome 8p21, as did the genes encoding DR4, DR5 and DcR1. A single *DcR2* mRNA transcript showed a unique expression pattern in human tissues. Upon overexpression, DcR2 did not activate apoptosis or nuclear factor-κB but it substantially reduced cellular sensitivity to Apo2L-induced apoptosis. The results suggest that DcR2 functions as an inhibitory Apo2L receptor.

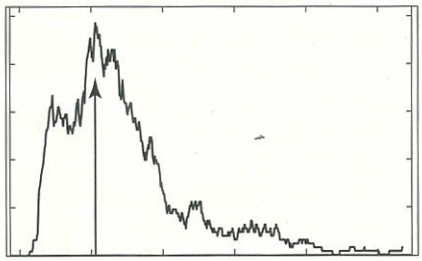
6 October 1997, Brief Communication, *Current Biology*

☐ Favorable domain size in proteins.

Dong Xu and Ruth Nussinov (1997). *Fold. Des.* **3**, 11–17.

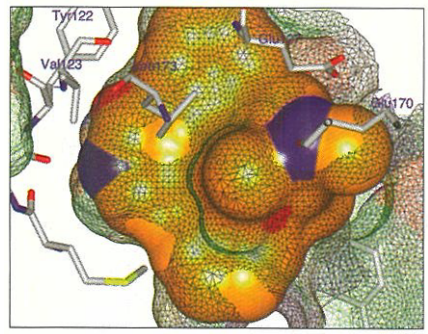
It has been observed that single-domain proteins and domains in multidomain

proteins favor a chain length in the range 100–150 amino acids. To understand the origin of the favored size, the authors constructed an empirical function for the free energy of unfolding versus the chain length. The parameters in the function are derived by fitting to the energy of hydration, entropy and enthalpy of unfolding of nine proteins. This energy function cannot be used to calculate the energetics accurately for individual proteins because the energetics also depend on other factors but the energy function statistically characterizes the general relationship between the free energy of unfolding and the size of the protein. The predicted optimal number of residues, which corresponds to the maximum free energy of unfolding, is 100, in agreement with a statistical analysis of protein domains derived from



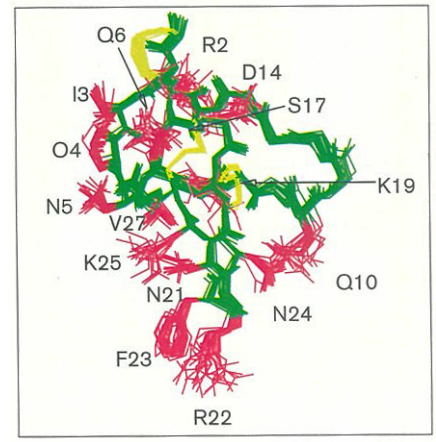
their experimental structures. This study shows that the energetic balance is the dominant factor governing protein size and forces a large protein to break into several domains during folding.
27 November 1997, Research Paper, *Folding and Design*

☐ **Solution structure and proposed binding mechanism of a novel potassium channel toxin κ-conotoxin PVIIA.**
Martin J Scanlon, David Naranjo, Linda Thomas, Paul F Alewood, Richard J Lewis and David J Craik (1997). *Structure* **5**, 1585–1597.
κ-PVIIA is a 27 residue polypeptide isolated from the venom of *Conus purpurascens* and is the first member of a new class of conotoxins that block potassium channels. In comparison to other ion channels of eukaryotic cell membranes, voltage-sensitive potassium channels are relatively simple and methodology has been developed for mapping their interactions with small-peptide toxins. PVIIA, therefore, is a valuable new probe of potassium channel structure. This study of the solution structure and mode of channel binding of PVIIA forms the basis for mapping the interacting residues at the conotoxin–ion channel interface. The three-dimensional structure of PVIIA resembles the triple-stranded β sheet/cystine-knot motif formed by a number of toxic and inhibitory peptides. Subtle structural differences are observed between PVIIA and other conotoxins with similar structural frameworks, however. Electrophysiological binding data suggest that PVIIA blocks channel currents by binding in a voltage-sensitive manner to the external vestibule and occluding the pore. Comparison of the electrostatic surface of PVIIA with that of the well-



characterised potassium channel blocker charybdotoxin suggests a likely binding orientation for PVIIA. On the basis of a comparison of the structures of PVIIA and charybdotoxin, the authors suggest that Lys19 of PVIIA is the residue which is responsible for physically occluding the pore of the potassium channel.
15 December 1997, Research Paper, *Structure*

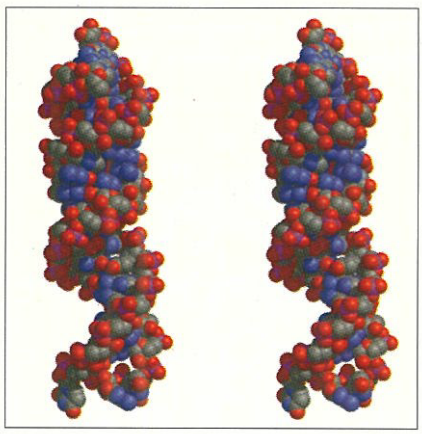
☐ **Staurosporine-induced conformational changes of cAMP-dependent protein kinase catalytic subunit explain inhibitory potential.**
Lars Prade, Richard A Engh, Andreas Girod, Volker Kinzel, Robert Huber and Dirk Bossemeyers (1997). *Structure* **5**, 1627–1637.
Staurosporine inhibits most protein kinases at low concentrations. As most tyrosine kinases are either proto oncoproteins or are involved in oncogenic signaling, the development of protein kinase inhibitors is a goal of cancer research. Staurosporine and many of its derivatives are being tested as anticancer drugs. To understand the mode of inhibition of staurosporine to protein kinases, the molecule was co-crystallized with the catalytic subunit of cAMP-dependent protein kinase. The crystal



structure of the protein kinase catalytic subunit with staurosporine bound to the adenosine pocket shows considerable induced-fit rearrangement of the enzyme and a unique open conformation. The inhibitor mimics several aspects of adenosine binding and induces conformational changes of neighboring enzyme residues. The results explain the high inhibitory potency of staurosporine, and also illustrate the flexibility of the protein kinase active site. The structure is not only useful for the design of improved anticancer therapeutics and signaling drugs, but also provides a deeper understanding of the conformational flexibility of the protein kinase.
15 December 1997, Research Paper, *Structure*

☐ **The loop E–loop D region of *Escherichia coli* 5S rRNA: the solution structure reveals an unusual loop that may be important for binding ribosomal proteins.**
Anne Dallas and Peter B Moore (1997). *Structure* **5**, 1639–1653.
5S ribosomal RNA is the smallest rRNA. Its Watson–Crick helices were

identified more than 20 years ago, but the conformations of its loops have long defied analysis. One of the three arms of 5S rRNA, residues 69–106 in *Escherichia coli*, contains a 14-residue internal loop called loop E. The sequence of loop E is conserved within kingdoms, and is

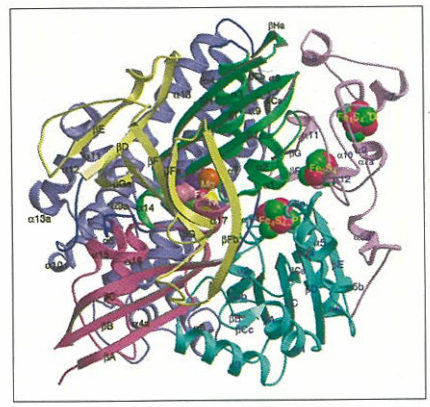


terminated by a pyrimidine-rich loop called loop D. Loop E is the binding site for the ribosomal protein L25 in the *E. coli* ribosome. The solution structure of a 42 nucleotide derivative of *E. coli* 5S rRNA that includes loops D and E has been determined by nuclear magnetic resonance spectroscopy. This structure rationalizes all the biochemical and chemical protection data available for the loop E–loop D arm of intact 5S rRNA. While the molecule is double helical over its entire length, the geometry of its internal loop is highly irregular, and its irregularities may explain why the loop E–loop D arm of 5S rRNA interacts specifically with ribosomal protein L25 in *E. coli*.
15 December 1997, Research Paper, *Structure*

☐ **Unusual ligand structure in Ni–Fe active center and an additional Mg site in hydrogenase revealed by high resolution X-ray structure analysis.**

Yoshiki Higuchi, Tatsuhiko Yagi and Noritake Yasuoka (1997). *Structure* **5**, 1671–1680.

The hydrogenase of *Desulfovibrio* sp. catalyzes the reversible oxidoreduction of molecular hydrogen, in conjunction with a specific electron acceptor, cytochrome c_3. The Ni–Fe active center of *Desulfovibrio* hydrogenase has an unusual ligand structure with non-protein ligands. An atomic model at high resolution is required to make concrete assignment of the ligands which coordinate the Ni–Fe center. These in turn will provide insight into the mechanism of electron transfer during the reaction catalysed by hydrogenase. The X-ray structure of the hydrogenase from *Desulfovibrio vulgaris* Miyazaki has been solved. The overall folding pattern and the spatial arrangement of the metal centers are very similar to those found in *Desulfovibrio gigas* hydrogenase. This crystal structure enabled the authors to assign the non-protein ligands to the Fe atom in the Ni–Fe site and revealed the presence of a Mg center, located



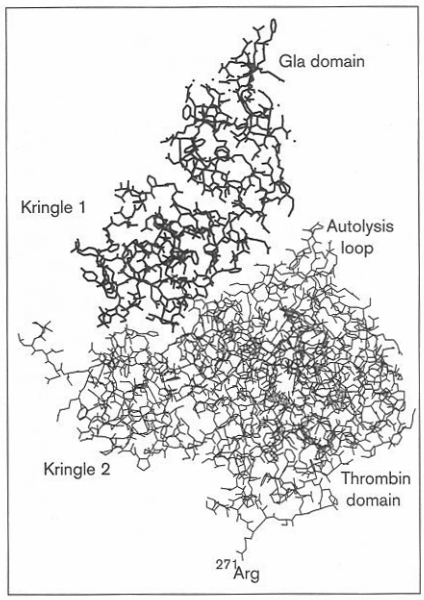
approximately 13 Å from the Ni–Fe active center. From the nature of the electron-density map, stereochemical geometry and atomic parameters of the refined structure, the most probable candidates for the four ligands, coordinating the Ni–Fe center, have been proposed to be diatomic S=O, C≡O and C≡N molecules and one sulfur atom. These ligands may have a role as an electron sink during the electron transfer reaction between the hydrogenase and its biological counterparts, and they could stabilize the redox state of Fe(II), which may not change during the catalytic cycle and is independent of the redox transition of the Ni. The hydrogen-bonding system between the Ni–Fe and the Mg centers suggests the possible involvement of the Mg center in the reaction cycles of hydrogen metabolism.
15 December 1997, Research Paper, *Structure*

☐ **New insights into the regulation of the blood clotting cascade derived from the X-ray crystal structure of bovine meizothrombin des F1 in complex with PPACK.**

Philip D Martin, G Malkowski, Jeffrey Box, Charles T Emson and Brian FP Edwards (1997). *Structure* **5**, 1681–1693.

The conversion of prothrombin to thrombin by factor Xa is the penultimate step in the blood clotting cascade. *In vivo*, where the conversion occurs primarily on activated platelets in association with factor Va and Ca^{2+} ions, meizothrombin is the major intermediate of the two step reaction. Meizothrombin rapidly loses the fragment 1 domain (F1) by autolysis to become meizothrombin des F1 (mzTBN-F1). The physiological properties of mzTBN-F1 differ dramatically from those of thrombin due to the presence of prothrombin fragment 2 (F2), which remains covalently attached to the activated thrombin domain in mzTBN-F1. The crystal structure of mzTBN-F1 has been determined by molecular replacement, using only the thrombin domain. The protease active site was inhibited with D-Phe–Pro–Arg-chloromethylketone (PPACK) to reduce autolysis. The mobile linker chain connecting the so-called kringle and thrombin domains and the first two *N*-acetylglucsoamine residues attached to the latter were seen in the electron-density maps. The F2 kringle domain in mzTBN-F1 is bound to the electropositive heparin-binding site on thrombin in an orientation that is systematically shifted and has significantly more interdomain contacts compared to a noncovalent complex of free F2 and free thrombin. F2 in mzTBN–F1 forms novel hydrogen bonds to the carbohydrate chain of thrombin and perhaps stabilizes a unique, rigid conformation of the γ-autolysis loop through non-local

effects. The F2 linker chain, which does not interfere with the active site or fibrinogen-recognition site, is arranged so that the two sites cleaved by factor



Xa are separated by 36 Å. The two mzTBN-F1 molecules in the asymmetric unit share a tight 'dimer' contact in which the active site of one molecule is partially blocked by the F2 kringle domain of its partner. This interaction suggests a new model for prothrombin organization.

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