(*a*) High-throughput macromolecular crystallography due to the developments outlined in Section 1.3.1, leading to the new field of 'structural genomics'.

(*b*) Crystallography of very large complexes. While it is now clear that an atomic structure of a complex of 58 proteins and three RNA molecules, the ribosome, is around the corner, crystallographers will widen their horizons and start dreaming of structures like the nuclear pore complex, which has a molecular weight of over 100 000 000 Da.

(*c*) A steady flow of membrane protein structures. Whereas Max Perutz could only list five structures in his book of 1992, there are now over 40 PDB entries for membrane proteins. Most of them are transmembrane proteins: bacteriorhodopsin, photoreaction centres, light-harvesting complexes, cytochrome bc_1 complexes, cytochrome *c* oxidases, photosystem I, porins, ion channels and bacterial toxins such as haemolysin and LukF. Others are monotopic membrane proteins such as squalene synthase and the cyclooxygenases. Clearly, membrane protein crystallography is gaining momentum at present and may open the door to atomic insight in neurotransmitter pharmacology in the next decade.

What if we dream beyond the obvious? One day, medicinal crystallography may contribute to:

(*a*) The design of submacromolecular agonists and antagonists of proteins and nucleic acids in a matter of a day by integrating rapid structure determinations, using only a few nanograms of protein, with the power of combinatorial and, in particular, computational chemistry.

(*b*) 'Structural toxicology' based on 'human structural genomics'. Once the hundreds of thousands of structures of human proteins and complexes with other proteins and nucleic acids have been determined, truly predictive toxicology may become possible. This will not only speed up the drug-development process, but may substantially reduce the suffering of animals in preclinical tests.

(*c*) The creation of completely new classes of drugs to treat addiction, organ regeneration, aging, memory enhancement *etc.*

One day, crystallography will have revealed the structure of hundreds of thousands of proteins and nucleic acids from human and pathogen, and their complexes with each other and with natural and designed low-molecular-weight ligands. This will form an extraordinarily precious database of knowledge for furthering the health of humans. Hence, in the course of the 21st century, crystallography is likely to become a major driving force for improving health care and disease prevention, and will find a well deserved place in future books describing progress in medicine, sometimes called 'The Greatest Benefit to Mankind' (Porter, 1999).

We wish to thank Heidi Singer for terrific support in preparing the manuscript, and Drs Alvin Kwiram, Michael Gelb, Seymour Klebanov, Wes Van Voorhis, Fred Buckner, Youngsoo Kim and Rein Zwierstra for valuable comments.

References

Achari, A., Somers, D. O., Champness, J. N., Bryant, P. K., Rosemond, J. & Stammers, D. K. (1997). *Crystal structure of the anti-bacterial sulfonamide drug target dihydropteroate synthase. Nature Struct. Biol.* **4**, 490–497.

Adman, E. T., Stenkamp, R. E., Sieker, L. C. & Jensen, L. H. (1978). *A crystallographic model for azurin at 3 Å resolution. J. Mol. Biol.* **123**, 35–47.

Aertgeerts, K., De Bondt, H. L., De Ranter, C. J. & Declerck, P. J. (1995). *Mechanisms contributing to the conformational and functional flexibility of plasminogen activator inhibitor-1. Nature Struct. Biol.* **2**, 891–897.

Ævarsson, A., Chuang, J. L., Wynn, R. M., Turley, S., Chuang, D. T. & Hol, W. G. J. (2000). *Crystal structure of human branched-chain α-ketoacid dehydrogenase and the molecular basis of multienzyme complex deficiency in maple syrup urine disease. Struct. Fold. Des.* **8**, 277–291.

Allaire, M., Chernaia, M. M., Malcolm, B. A. & James, M. N. (1994). *Picornaviral 3C cysteine proteinases have a fold similar to chymotrypsin-like serine proteinases. Nature (London)*, **369**, 72–76.

Allured, V. S., Collier, R. J., Carroll, S. F. & McKay, D. B. (1986). *Structure of exotoxin A of Pseudomonas aeruginosa at 2.0-Å resolution. Proc. Natl Acad. Sci. USA*, **83**, 1320–1324.

Almassy, R. J. & Dickerson, R. E. (1978). *Pseudomonas cytochrome c551 at 2.0 Å resolution: enlargement of the cytochrome c family. Proc. Natl Acad. Sci. USA*, **75**, 2674–2678.

Amos, L. A. & Lowe, J. (1999). *How Taxol stabilises microtubule structure. Chem. Biol.* **6**, R65–R69.

Arnold, E., Das, K., Ding, J., Yadav, P. N., Hsiou, Y., Boyer, P. L. & Hughes, S. H. (1996). *Targeting HIV reverse transcriptase for anti-AIDS drug design: structural and biological considerations for chemotherapeutic strategies. Drug Des. Discov*. **13**, 29–47.

Arnold, E. & Rossmann, M. G. (1988). *The use of molecular-replacement phases for the refinement of the human rhinovirus 14 structure. Acta Cryst.* A**44**, 270–283.

Arnold, E. & Rossmann, M. G. (1990). *Analysis of the structure of a common cold virus, human rhinovirus 14, refined at a resolution of 3.0 Å. J. Mol. Biol.* **211**, 763–801.

Arnold, G. F. & Arnold, E. (1999). *Using combinatorial libraries to develop vaccines. ASM News*, **65**, 603–610.

Arnold, G. F., Resnick, D. A., Li, Y., Zhang, A., Smith, A. D., Geisler, S. C., Jacobo-Molina, A., Lee, W., Webster, R. G. & Arnold, E. (1994). *Design and construction of rhinovirus chimeras incorporating immunogens from polio, influenza, and human immunodeficiency viruses. Virology*, **198**, 703–708.

Arnoux, P., Haser, R., Izadi, N., Lecroisey, A., Delepierre, M., Wandersman, C. & Czjzek, M. (1999). *The crystal structure of HasA, a hemophore secreted by Serratia marcescens. Nature Struct. Biol.* **6**, 516–520.

Athanasiadis, A., Vlassi, M., Kotsifaki, D., Tucker, P. A., Wilson, K. S. & Kokkinidis, M. (1994). *Crystal structure of PvuII endonuclease reveals extensive structural homologies to EcoRV. Nature Struct. Biol.* **1**, 469–475.

Baca, A. M., Sirawaraporn, R., Turley, S., Athappilly, F., Sirawaraporn, W. & Hol, W. G. J. (2000). *Crystal structure of Mycobacterium tuberculosis 6-hydroxymethyl-1,8-dihydropteroate synthase in complex with pterin monophosphate: new insight into the enzymatic mechanism and sulfa-drug action. J. Mol. Biol.* **302**, 1193–1212.

Baldwin, E. T., Bhat, T. N., Gulnik, S., Hosur, M. V., Sowder, R. C. I., Cachau, R. E., Collins, J., Silva, A. M. & Erickson, J. W. (1993). *Crystal structures of native and inhibited forms of human cathepsin D: implications for lysosomal targeting and drug design. Proc. Natl Acad. Sci. USA*, **90**, 6796–6800.

Baldwin, E. T., Weber, I. T., St Charles, R., Xuan, J. C., Appella, E., Yamada, M., Matsushima, K., Edwards, B. F., Clore, G. M. & Gronenborn, A. M. (1991). *Crystal structure of interleukin 8: symbiosis of NMR and crystallography. Proc. Natl Acad. Sci. USA*, **88**, 502–506.

Baldwin, J. J., Ponticello, G. S., Anderson, P. S., Christy, M. E., Murcko, M. A., Randall, W. C., Schwam, H., Sugrue, M. F., Springer, J. P., Gautheron, P., Grove, J., Mallorga, P., Viader, M. P., McKeever, B. M. & Navia, M. A. (1989). *Thienothiopyran-2-sulfonamides: novel topically active carbonic anhydrase inhibitors for the treatment of glaucoma. J. Med. Chem.* **32**, 2510–2513.

Ban, N., Nissen, P., Hansen, J., Capel, M., Moore, P. B. & Steitz, T. A. (1999). *Placement of protein and RNA structures into a 5 Å-resolution map of the 50S ribosomal subunit. Nature (London)*, **400**, 841–847.

Banbula, A., Potempa, J., Travis, J., Fernandez-Catalan, C., Mann, K., Huber, R., Bode, W. & Medrano, F. (1998). *Amino-acid sequence and three-dimensional structure of the Staphylococcus aureus metalloproteinase at 1.72 Å resolution. Structure*, **6**, 1185–1193.

Banner, D. W., D'Arcy, A., Chene, C., Winkler, F. K., Guha, A., Konigsberg, W. H., Nemreson, Y. & Kirchhofer, D. (1996). *The crystal structure of the complex of blood coagulation factor VIIa with soluble tissue factor. Nature*, **380**, 41–46.

Banner, D. W., D'Arcy, A., Janes, W., Gentz, R., Schoenfeld, H. J., Broger, C., Loetscher, H. & Lesslauer, W. (1993). *Crystal structure of the soluble human 55 kd TNF receptor–human TNF beta complex: implications for TNF receptor activation. Cell*, **7**, 431–445.

Baumann, U. (1994). *Crystal structure of the 50 kDa metallo protease from Serratia marcescens. J. Mol. Biol.* **242**, 244–251.

Beaman, T. W., Binder, D. A., Blanchard, J. S. & Roderick, S. L. (1997). *Three-dimensional structure of tetrahydrodipicolinate N-succinyltransferase. Biochemistry*, **36**, 489–494.

Beaman, T. W., Sugantino, M. & Roderick, S. L. (1998). *Structure of the hexapeptide xenobiotic acetyltransferase from Pseudomonas aeruginosa. Biochemistry*, **37**, 6689–6696.

Becker, J. W., Marcy, A. I., Rokosz, L. L., Axel, M. G., Burbaum, J. J., Fitzgerald, P. M., Cameron, P. M., Esser, C. K., Hagmann, W. K., Hermes, J. D. & Springer, J. P. (1995). *Stromelysin-1: three dimensional structure of the inhibited catalytic domain and of the C-truncated proenzyme. Protein Sci.* **4**, 1966–1976.

Bentley, G., Dodson, E., Dodson, G., Hodgkin, D. & Mercola, D. (1976). *Structure of insulin in 4-zinc insulin. Nature (London)*, **261**, 166–168.

Bernstein, B. E., Williams, D. M., Bressi, J. C., Kuhn, P., Gelb, M. H., Blackburn, G. M. & Hol, W. G. J. (1998). *A bisubstrate analog induces unexpected conformational changes in phosphoglycerate kinase from Trypanosoma brucei. J. Mol. Biol.* **279**, 1137–1148.

Bernstein, F. C., Koetzle, T. F., Williams, G. J., Meyer, E. F. Jr, Brice, M. D., Rodgers, J. R., Kennard, O., Shimanouchi, T. & Tasumi, M. (1977). *The Protein Data Bank. A computer-based archival file for macromolecular structures. Eur. J. Biochem.* **80**, 319–324.

Betz, M., Huxley, P., Davies, S. J., Mushtaq, Y., Pieper, M., Tschesche, H., Bode, W. & Gomis-Ruth, F. X. (1997). *1.8-Å crystal structure of the catalytic domain of human neutrophil collagenase (matrix metalloproteinase-8) complexed with a peptidomimetic hydroxamate primed-side inhibitor with a distinct selectivity profile. Eur. J. Biochem.* **247**, 356–363.

Bienkowska, J., Cruz, M., Atiemo, A., Handin, R. & Liddington, R. (1997). *The von Willebrand factor A3 domain does not contain a metal ion-dependent adhesion site motif. J. Biol. Chem.* **272**, 25162–25167.

Birrer, P. (1995). *Proteases and antiproteases in cystic fibrosis: pathogenetic considerations and therapeutic strategies. Respiration*, **62**, S25–S28.

Bjorkman, P. J. & Burmeister, W. P. (1994). *Structures of two classes of MHC molecules elucidated: crucial differences and similarities. Curr. Opin. Struct. Biol.* **4**, 852–856.

Bjorkman, P. J., Saper, M. A., Samraoui, B., Bennett, W. S., Strominger, J. L. & Wiley, D. C. (1987). *Structure of human class I histocompatibility antigen, HLA-A2. Nature (London)*, **329**, 506–512.

Blaber, M., DiSalvo, J. & Thomas, K. A. (1996). *X-ray crystal structure of human acidic fibroblast growth factor. Biochemistry*, **35**, 2086–2094.

Blake, C. C., Geisow, M. J., Oatley, S. J., Rerat, B. & Rerat, C. (1978). *Structure of prealbumin: secondary, tertiary and quaternary interactions determined by Fourier refinement at 1.8 Å. J. Mol. Biol.* **121**, 339–356.

Blankenfeldt, W., Nowicki, C., Montemartini-Kalisz, M., Kalisz, H. M. & Hecht, H. J. (1999). *Crystal structure of Trypanosoma cruzi tyrosine aminotransferase: substrate specificity is influenced by cofactor binding mode. Protein Sci.* **8**, 2406–2417.

Bochkarev, A., Barwell, J. A., Pfuetzner, R. A., Furey, W. Jr, Edwards, A. M. & Frappier, L. (1995). *Crystal structure of the DNA-binding domain of the Epstein–Barr virus origin-binding protein EBNA 1. Cell*, **83**, 39–46.

Bode, W., Mayr, I., Baumann, U., Huber, R., Stone, S. R. & Hofsteenge, J. (1989). *The refined 1.9 Å crystal structure of human alpha-thrombin: interaction with* D*-Phe-Pro-Arg chloromethylketone and significance of the Tyr-Pro-Pro-Trp insertion segment. EMBO J.* **8**, 3467–3475.

Bode, W., Reinemer, P., Huber, R., Kleine, T., Schnierer, S. & Tschesche, H. (1994). *The X-ray crystal structure of the catalytic domain of human neutrophil collagenase inhibited by a substrate analogue reveals the essentials for catalysis and specificity. EMBO J.* **13**, 1263–1269.

Bode, W., Wei, A. Z., Huber, R., Meyer, E., Travis, J. & Neumann, S. (1986). *X-ray crystal structure of the complex of human leukocyte elastase (PMN elastase) and the third domain of the turkey ovomucoid inhibitor. EMBO J.* **5**, 2453–2458.

Borkakoti, N., Winkler, F. K., Williams, D. H., D'Arcy, A., Broadhurst, M. J., Brown, P. A., Johnson, W. H. & Murray, E. J. (1994). *Structure of the catalytic domain of human fibroblast collagenase complexed with an inhibitor. Nature Struct. Biol.* **1**, 106–110.

Borst, P. (1999). *Multidrug resistance: a solvable problem? Ann. Oncol.* **10**, S162–S164.

Brandhuber, B. J., Boone, T., Kenney, W. C. & McKay, D. B. (1987). *Three-dimensional structure of interleukin-2. Science*, **238**, 1707–1709.

Brange, J. (1997). *The new era of biotech insulin analogues. Diabetologia*, **40**, S48–S53.

Breton, R., Housset, D., Mazza, C. & Fontecilla-Camps, J. C. (1996). *The structure of a complex of human 17-beta-hydroxysteroid dehydrogenase with estradiol and $NADP^+$ identifies two principal targets for the design of inhibitors. Structure*, **4**, 905–915.

Brown, J. H., Jardetzky, T. S., Gorga, J. C., Stern, L. J., Urban, R. G., Strominger, J. L. & Wiley, D. C. (1993). *Three-dimensional structure of the human class II histocompatibility antigen HLA-DR1. Nature (London)*, **364**, 33–39.

Browner, M. F., Smith, W. W. & Castelhano, A. L. (1995). *Matrilysin-inhibitor complexes: common themes among metalloproteases. Biochemistry*, **34**, 6602–6610.

Bruns, C. M., Hubatsch, I., Ridderstrom, M., Mannervik, B. & Tianer, J. A. (1999). *Human glutathione transferase A4-4 crystal structures and mutagenesis reveal the basis of high catalytic efficiency with toxic lipid peroxidation products. J. Mol. Biol.* **288**, 427–439.

Bruns, C. M., Nowalk, A. J., Arvai, A. S., McTigue, M. A., Vaughan, K. G., Mietzner, T. A. & McRee, D. E. (1997). *Structure of Hemophilus influenzae Fe(+3)-binding protein reveals convergent evolution within a superfamily. Nature Struct. Biol.* **4**, 919–924.

Brzozowski, A. M., Pike, A. C., Dauter, Z., Hubbard, R. E., Bonn, T., Engstrom, O., Ohman, L., Greene, G. L., Gustafsson, J. A. & Carlquist, M. (1997). *Molecular basis of agonism and antagonism in the oestrogen receptor. Nature (London)*, **389**, 753–758.

Bullock, T. L., Roberts, T. M. & Stewart, M. (1996). *2.5 Å resolution crystal structure of the motile major sperm protein (MSP) of Ascaris suum. J. Mol. Biol.* **263**, 284–296.

Burke, K. L., Dunn, G., Ferguson, M., Minor, P. D. & Almond, J. W. (1988). *Antigen chimaeras of poliovirus as potential new vaccines. Nature (London)*, **332**, 81–82.

Bussiere, D. E., Pratt, S. D., Katz, L., Severin, J. M., Holzman, T. & Park, C. H. (1998). *The structure of VanX reveals a novel amino-dipeptidase involved in mediating transposon-based vancomycin resistance. Mol. Cell*, **2**, 75–84.

Cameron, A. D., Sinning, I., L'Hermite, G., Olin, B., Board, P. G., Mannervik, B. & Jones, T. A. (1995). *Structural analysis of human alpha-class glutathione transferase A1-1 in the apo-form and in complexes with ethacrynic acid and its glutathione conjugate. Structure*, **3**, 717–727.

Carfi, A., Pares, S., Duee, E., Galleni, M., Duez, C., Frere, J. M. & Dideberg, O. (1995). *The 3-D structure of a zinc metallo-beta-lactamase from Bacillus cereus reveals a new type of protein fold. EMBO J.* **14**, 4914–4921.

Carrell, R. W. & Gooptu, B. (1998). *Conformational changes and diseases – serpins, prions and Alzheimer's. Curr. Opin. Struct. Biol.* **8**, 799–809.

Carrell, R. W., Stein, P. E., Fermi, G. & Wardell, M. R. (1994). *Biological implications of a 3 Å structure of dimeric antithrombin. Structure*, **2**, 257–270.

Carter, D. C. & Ho, J. X. (1994). *Structure of serum albumin. Adv. Protein Chem.* **45**, 153–203.

Cate, J. H., Yusupov, M. M., Zusupova, G. Z., Earnest, T. N. & Noller, H. F. (1999). *X-ray crystal structures of 70S ribosome functional complexes. Science*, **285**, 2095–2104.

Champness, J. N., Achari, A., Ballantine, S. P., Bryant, P. K., Delves, C. J. & Stammers, D. K. (1994). *The structure of Pneumocystis carinii dihydrofolate reductase to 1.9 Å resolution. Structure*, **2**, 915–924.

Chan, D. C., Fass, D., Berger, J. M. & Kim, P. S. (1997). *Core structure of gp41 from the HIV envelope glycoprotein. Cell*, **89**, 263–273.

Chang, G., Spencer, R. H., Lee, A. T., Barclay, M. T. & Rees, D. C. (1998). *Structure of the MscL homolog from Mycobacterium tuberculosis: a gated mechanosensitive ion channel. Science*, **282**, 2220–2226.

Chang, Y., Mochalkin, I., McCance, S. G., Cheng, B., Tulinsky, A. & Castellino, F. J. (1998). *Structure and ligand binding determinants of the recombinant kringle 5 domain of human plasminogen. Biochemistry*, **37**, 3258–3271.

Charifson, P. S. (1997). *Practical Application of Computer-Aided Drug Design*. New York: Marcel Dekker Inc.

Chitarra, V., Holm, I., Bentley, G. A., Petres, S. & Longacre, S. (1999). *The crystal structure of C-terminal merozoite surface protein 1 at 1.8 Å resolution, a highly protective malaria vaccine candidate. Mol. Cell*, **3**, 457–464.

Cho, Y., Gorina, S., Jeffrey, P. D. & Pavletich, N. P. (1994). *Crystal structure of a p53 tumor suppressor–DNA complex: understanding tumorigenic mutations. Science*, **265**, 346–355.

Choe, S., Bennett, M. J., Fujii, G., Curmi, P. M., Kantardjieff, K. A., Collier, R. J. & Eisenberg, D. (1992). *The crystal structure of diphtheria toxin. Nature*, **357**, 216–222.

Choi, H. J., Kang, S. W., Yang, C. H., Rhee, S. G. & Ryu, S. E. (1998). *Crystal structure of a novel human peroxidase enzyme at 2.0 Å resolution. Nature Struct. Biol.* **5**, 400–406.

Choudhury, D., Thompson, A., Stojanoff, V., Langermann, S., Pinkner, J., Hultgren, S. J. & Knight, S. D. (1999). *X-ray structure of the Fim-C-FimH chaperone–adhesin complex from uropathogenic Escherichia coli. Science*, **285**, 1061–1066.

Chudzik, D. M., Michels, P. A., de Walque, S. & Hol, W. G. J. (2000). *Structures of type 2 peroxisomal targeting signals in two trypanosomatid aldolases. J. Mol. Biol.* **300**, 697–707.

Cirilli, M., Zheng, R., Scapin, G. & Blanchard, J. S. (1993). *Structural symmetry: the three-dimensional structure of Haemophilus influenzae diaminopimelate epimerase. Biochemistry*, **37**, 16452–16458.

Ciszak, E. & Smith, G. D. (1994). *Crystallographic evidence for dual coordination around zinc in the T3R3 human insulin hexamer. Biochemistry*, **33**, 1512–1517.

Clackson, T., Yang, W., Rozamus, L. W., Hatada, M., Amara, J. F., Rollins, C. T., Stevenson, L. F., Magari, S. R., Wood, S. A., Courage, N. L., Lu, X., Cerasoli, F. J., Gilman, M. & Holt, D. A. (1998). *Redesigning an FKBP–ligand interface to generate chemical dimerizers with novel specificity. Proc. Natl Acad. Sci. USA*, **95**, 10437–10442.

Cleasby, A., Wonacott, A., Skarzynski, T., Hubbard, R. E., Davies, G. J., Proudfoot, A. E., Bernard, A. R., Payton, M. A. & Wells, T. N. (1996). *The X-ray crystal structure of phosphomannose isomerase from Candida albicans at 1.7 Å resolution. Nature Struct. Biol.* **3**, 470–479.

Clemons, W. M. J., May, J. L., Wimberly, B. T., McCutcheon, J. P., Capel, M. S. & Ramakrishnan, V. (1999). *Structure of a bacterial 30S ribosomal subunit at 5.5 Å resolution. Nature (London)*, **400**, 833–840.

Cobessi, D., Tete-Favier, F., Marchal, S., Azza, S., Branlant, G. & Aubry, A. (1999). *Apo and holo crystal structures of an NADP-dependent aldehyde dehydrogenase from Streptococcus mutans. J. Mol. Biol.* **290**, 161–173.

Colby, T. D., Vanderveen, K., Strickler, M. D., Markham, G. D. & Goldstein, B. M. (1999). *Crystal structure of human type II inosine monophosphate dehydrogenase: implications for ligand binding and drug design. Proc. Natl Acad. Sci. USA*, **96**, 3531–3536.

Cole, S. T., Brosch, R., Parkhill, J., Garnier, T., Churcher, C., Harris, D., Gordon, S. V., Eiglmeier, K., Gas, S., Barry, C. E. III, Tekaia, F., Badcock, K., Basham, D., Brown, D., Chillingworth, T., Connor, R., Davies, R., Devlin, K., Feltwell, T., Gentles, S., Hamlin, N., Holroyd, S., Hornby, T., Jagels, K., Krogh, A., McLean, J., Moule, S., Murphy, L., Oliver, K., Osborne, J., Quail, M. A., Rajandream, M. A., Rogers, J., Rutter, S., Seeger, K., Skelton, J., Squares, R., Squares, S., Sulston, J. E., Taylor, K., Whitehead, S. & Barrell, B. G. (1998). *Deciphering the biology of Mycobacterium tuberculosis from the complete genome sequence. Nature (London)*, **393**, 537–544.

Collins, F. S. (1992). *Cystic fibrosis: molecular biology and therapeutic implications. Science*, **256**, 774–779.

Concha, N. O., Rasmussen, B. A., Bush, K. & Herzberg, O. (1996). *Crystal structure of the wide-spectrum binuclear zinc beta-lactamase from Bacteroides fragilis. Structure*, **4**, 823–836.

Conlon, H. D., Baqai, J., Baker, K., Shen, Y. Q., Wong, B. L., Noiles, R. & Rausch, C. W. (1995). *2-step immobilized enzyme conversion of cephalosporin-c to 7-aminocephalosporanic acid. Biotechnol. Bioeng.* **46**, 510–513.

Cooper, J. B., McIntyre, K., Badasso, M. O., Wood, S. P., Zhang, Y., Garbe, T. R. & Young, D. (1995). *X-ray structure analysis of the iron-dependent superoxide dismutase from Mycobacterium tuberculosis at 2.0 Å resolution reveals novel dimer–dimer interactions. J. Mol. Biol.* **246**, 531–544.

Correll, C. C., Batie, C. J., Ballou, D. P. & Ludwig, M. L. (1992). *Phthalate dioxygenase reductase: a modular structure for electron transfer from pyridine nucleotides to [2Fe–2S]. Science*, **258**, 1604–1610.

Crennell, S., Garman, E., Laver, G., Vimr, E. & Taylor, G. (1994). *Crystal structure of Vibrio cholerae neuraminidase reveals dual lectin-like domains in addition to the catalytic domain. Structure*, **2**, 535–544.

Curry, S., Mandelkow, H., Brick, P. & Franks, N. (1998). *Crystal structure of human serum albumin complexed with fatty acid reveals an asymmetric distribution of binding sites. Nature Struct. Biol.* **5**, 827–835.

Cushman, D. W. & Ondetti, M. A. (1991). *History of the design of captopril and related inhibitors of angiotensin converting enzyme. Hypertension*, **17**, 589–592.

Cutfield, S. M., Dodson, E. J., Anderson, B. F., Moody, P. C., Marshall, C. J., Sullivan, P. A. & Cutfield, J. F. (1995). *The crystal structure of a major secreted aspartic proteinase from Candida albicans in complexes with two inhibitors. Structure*, **3**, 1261–1271.

Das, K., Ding, J., Hsiou, Y., Clark, A. D. Jr, Moereels, H., Koymans, L., Andries, K., Pauwels, R., Janssen, P. A. J., Boyer, P. L., Clark, P., Smith, R. H. Jr, Kroeger Smith, M. B., Michejda, C. J., Hughes, S. H. & Arnold, E. (1996). *Crystal structures of 8-Cl and 9-Cl TIBO complexed with wild-type HIV-1 RT and 8-Cl TIBO complexed with the Tyr181Cys HIV-1 RT drug-resistant mutant. J. Mol. Biol.* **264**, 1085–1100.

Davies, J. F., Delcamp, T. J., Prendergast, N. J., Ashford, V. A., Freisheim, J. H. & Kraut, J. (1990). *Crystal structures of recombinant human dihydrofolate reductase complexed with folate and 5-deazafolate. Biochemistry*, **29**, 9467–9479.

De Bondt, H. L., Rosenblatt, J., Jancarik, J., Jones, H. D., Morgan, D. O. & Kim, S. H. (1993). *Crystal structure of cyclin-dependent kinase 2. Nature (London)*, **363**, 595–602.

Deller, M. C. & Jones, E. Y. (2000). *Cell surface receptors. Curr. Opin. Struct. Biol.* **10**, 213–219.

Derewenda, U., Derewenda, Z., Dodson, E. J., Dodson, G. G., Reynolds, C. D., Smith, G. D., Sparks, C. & Swenson, D. (1989). *Phenol stabilizes more helix in a new symmetrical zinc insulin hexamer. Nature (London)*, **338**, 594–596.

Dessen, A., Quemard, A., Blanchard, J. S., Jacobs, W. R. J. & Sacchettini, J. C. (1995). *Crystal structure and function of the isoniazid target of Mycobacterium tuberculosis. Science*, **267**, 1638–1641.

DeVos, A. M., Tong, L., Milburn, M. V., Matias, P. M., Jancarik, J., Noguchi, S., Nishimura, S., Miura, K., Ohtsuka, E. & Kim, S. H. (1988). *Three-dimensional structure of an oncogene protein: catalytic domain of human c-H-ras p21. Science*, **239**, 888–893.

DeVos, A. M., Ultsch, M. & Kossiakoff, A. A. (1992). *Human growth hormone and extracellular domain of its receptor: crystal structure of the complex. Science*, **255**, 306–312.

Dhanaraj, V., Ye, Q.-Z., Johnson, L. L., Hupe, D. J., Otwine, D. F., Dunbar, J. B. J., Rubin, J. R., Pavlovsky, A., Humblet, C. & Blundell, T. L. (1996). *X-ray structure of a hydroxamate inhibitor complex of stromelysin catalytic domain and its comparison with members of the zinc metalloproteinase superfamily. Structure*, **4**, 375–386.

Dickerson, R. E. & Geis, I. (1983). *Hemoglobin.* Menlo Park: Benjamin Cummings Publishing Co.

Ding, J., Das, K., Tantillo, C., Zhang, W., Clark, A. D. Jr, Jessen, S., Lu, X., Hsiou, Y., Jacobo-Molina, A., Andries, K., Pauwels, R., Moereels, H., Koymans, L., Janssen, P. A. J., Smith, R. H. Jr, Kroeger Koepke, M., Michejda, C. J., Hughes, S. H. & Arnold, E. (1995). *Structure of HIV-1 reverse transcriptase in a complex with the non-nucleoside inhibitor alpha-APA R 95845 at 2.8 Å resolution. Structure*, **3**, 365–379.

Ding, J., McGrath, W. J., Sweet, R. M. & Mangel, W. F. (1996). *Crystal structure of the human adenovirus proteinase with its 11 amino acid cofactor. EMBO J.* **15**, 1778–1783.

Duggleby, H. J., Tolley, S. P., Hill, C. P., Dodson, E. J., Dodson, G. & Moody, P. C. (1995). *Penicillin acylase has a single-amino-acid catalytic centre. Nature (London)*, **373**, 264–268.

Dyda, F., Hickman, A. B., Jenkins, T. M., Engelman, A., Craigie, R. & Davies, D. R. (1994). *Crystal structure of the catalytic domain of HIV-1 integrase: similarity to other polynucleotidyl transferases. Science*, **266**, 1981–1986.

Eads, J. C., Scapin, G., Xu, Y., Grubmeyer, C. & Sacchettini, J. C. (1994). *The crystal structure of human hypoxanthine-guanine phosphoribosyltransferase with bound GMP. Cell*, **78**, 325–334.

Ealick, S. E., Cook, W. J., Vijay-Kumar, S., Carson, M., Nagabhushan, T. L., Trotta, P. P. & Bugg, C. E. (1991). *Three-dimensional structure of recombinant human interferon-gamma. Science*, **252**, 698–702.

Ealick, S. E., Rule, S. A., Carter, D. C., Greenhough, T. J., Babu, Y. S., Cook, W. J., Habash, J., Helliwell, J. R., Stoeckler, J. D., Parks, R. E. J., Chen, S. F. & Bugg, C. E. (1990). *Three-dimensional structure of human*

erythrocytic purine nucleoside phosphorylase at 3.2-Å resolution. J. Biol. Chem. **265**, 1812–1820.

Eckert, D. M., Malashkevish, V. N., Hong, L. H., Carr, P. A. & Kim, P. S. (1999). *Inhibiting HIV-1 entry: discovery of* D*-peptide inhibitors that target the gp41 coiled-coil pocket. Cell*, **99**, 103–115.

Ekstrom, J. L., Mathews, I. I., Stanley, B. A., Pegg, A. E. & Ealick, S. E. (1999). *The crystal structure of human S-adenosylmethionine decarboxylase at 2.25 Å resolution reveals a novel fold. Struct. Fold. Des.* **7**, 583–595.

Emsley, J., Cruz, M., Handin, R. & Liddington, R. (1998). *Crystal structure of the von Willebrand factor A1 domain and implications for the binding of platelet glycoprotein Ib. J. Biol. Chem.* **273**, 10396–10401.

Emsley, P., Charles, I. G., Fairweather, N. F. & Isaacs, N. W. (1996). *Structure of Bordetella pertussis virulence factor P.69 pertactin. Nature (London)*, **381**, 90–92.

Erickson, J., Neidhart, D. J., VanDrie, J., Kempf, D. J., Wang, X. C., Norbeck, D. W., Plattner, J. J., Rittenhouse, J. W., Turon, M., Wideburg, N., Kohlbrenner, W. E., Simmer, R., Helfrich, R., Paul, D. A. & Knigge, M. (1990). *Design, activity, and 2.8 Å crystal structure of a C2 symmetric inhibitor complexed to HIV-1 protease. Science*, **249**, 527–533.

Erickson, J. W. & Burt, S. K. (1996). *Structural mechanisms of HIV drug resistance. Annu. Rev. Pharmacol. Toxicol.* **36**, 545–571.

Erlandsen, H., Fusetti, F., Martinez, A., Hough, E., Flatmark, T. & Stevens, R. C. (1997). *Crystal structure of the catalytic domain of human phenylalanine hydroxylase reveals the structural basis for phenylketonuria. Nature Struct. Biol.* **4**, 995–1000.

Esser, C. K., Bugianesi, R. L., Caldwell, C. G., Chapman, K. T., Durette, P. L., Girotra, N. N., Kopka, I. E., Lanza, T. J., Levorse, D. A., Maccoss, M., Owens, K. A., Ponpipom, M. M., Simeone, J. P., Harrison, R. K., Niedzwiecki, L., Becker, J. W., Marcy, A. I., Axel, M. G., Christen, A. J., McDonnell, J., Moore, V. L., Olsqewski, J. M., Saphos, C., Visco, D. M., Shen, F., Colletti, A., Kriter, P. A. & Hagmann, W. K. (1997). *Inhibition of stromelysin-1 (MMP-3) by P1′-biphenylylethyl carboxyalkyl dipeptides. J. Med. Chem.* **40**, 1026–1040.

Fan, C., Moews, P. C., Walsh, C. T. & Knox, J. R. (1994). *Vancomycin resistance: structure of* D*-alanine:*D*-alanine ligase at 2.3 Å resolution. Science*, **266**, 439–443.

Fan, E., Zhang, Z., Minke, W. E., Hou, Z., Verlinde, C. L. M. J. & Hol, W. G. J. (2000). *A 10^5 gain in affinity for pentavalent ligands of E. coli heat-labile enterotoxin by modular structure-based design. J. Am. Chem. Soc.* **122**, 2663–2664.

Ferrer, M., Kapoor, T. M., Strassmaier, T., Weissenhorn, W., Skehel, J. J., Oprian, D., Schreiber, S. L., Wiley, D. C. & Harrison, S. C. (1999). *Selection of gp41-mediated HIV-1 cell entry inhibitors from biased combinatorial libraries of non-natural binding elements. Nature Struct. Biol.* **6**, 953–960.

Fields, B. A., Malchiodi, E. L., Li, H., Ysern, X., Stauffacher, C. V., Schlievert, P. M., Karjalainen, K. & Mariuzza, R. A. (1996). *Crystal structure of a T-cell receptor beta-chain complexed with a superantigen. Nature (London)*, **384**, 188–192.

Filman, D. J., Wien, M. W., Cunningham, J. A., Bergelson, J. M. & Hogle, J. M. (1998). *Structure determination of echovirus 1. Acta Cryst.* D**54**, 1261–1272.

Finzel, B. C., Baldwin, E. T., Bryant, G. L. J., Hess, G. F., Wilks, J. W., Trepod, C. M., Mott, J. E., Marshall, V. P., Petzold, G. L., Poorman, R. A., O'Sullivan, T. J., Schostarez, H. J. & Mitchell, M. A. (1998). *Structural characterizations of nonpeptidic thiadiazole inhibitors of matrix metalloproteinases reveal the basis for stromelysin selectivity. Protein Sci.* **7**, 2118–2126.

Focia, P. J., Craig, S. P. III, Nieves-Alicea, R., Fletterick, R. J. & Eakin, A. E. (1998). *A 1.4 Å crystal structure for the hypoxanthine phosphoribosyltransferase of Trypanosoma cruzi. Biochemistry*, **37**, 15066–15075.

Foster, B. A., Coffey, H. A., Morin, M. J. & Rastinejad, F. (1999). *Pharmacological rescue of mutant p53 conformation and function. Science*, **286**, 2507–2510.

Fox, M. P., Otto, M. J. & McKinlay, M. A. (1986). *Prevention of rhinovirus and poliovirus uncoating by WIN 51711, a new antiviral drug. Antimicrob. Agents Chemother.* **30**, 110–116.

Frankenberg, N., Erskine, P. T., Cooper, J. B., Shoolingin-Jordan, P. M., Jahn, D. & Heinz, D. W. (1999). *High resolution crystal structure of a Mg^{2+}-dependent porphobilinogen synthase. J. Mol. Biol.* **289**, 591–602.

Fremont, D. H., Matsumura, M., Stura, E. A., Peterson, P. A. & Wilson, I. A. (1992). *Crystal structures of two viral peptides in complex with murine MHC class I H-2Kb. Science*, **257**, 919–927.

Freymann, D., Down, J., Carrington, M., Roditi, I., Turner, M. & Wiley, D. (1990). *2.9 Å resolution structure of the N-terminal domain of a variant surface glycoprotein from Trypanosoma brucei. J. Mol. Biol.* **216**, 141–160.

Fulop, V., Ridout, C. J., Greenwood, C. & Hajdu, J. (1995). *Crystal structure of the di-haem cytochrome c peroxidase from Pseudomonas aeruginosa. Structure*, **3**, 1225–1233.

Futterer, K., Wong, J., Grucza, R. A., Chan, A. C. & Waksman, G. (1998). *Structural basis for Syk tyrosine kinase ubiquity in signal transduction pathways revealed by the crystal structure of its regulatory SH2 domains bound to a dually phosphorylated ITAM peptide. J. Mol. Biol.* **281**, 523–537.

Gaboriaud, C., Serre, L., Guy-Crotte, O., Forest, E. & Fontecilla-Camps, J. C. (1996). *Crystal structure of human trypsin 1: unexpected phosphorylation of Tyr151. J. Mol. Biol.* **259**, 995–1010.

Gamblin, S. J., Cooper, B., Millar, J. R., Davies, G. J., Littlechild, J. A. & Watson, H. C. (1990). *The crystal structure of human muscle aldolase at 3.0 Å resolution. FEBS Lett.* **264**, 282–286.

Garboczi, D. N., Ghosh, P., Utz, U., Fan, Q. R., Biddison, W. E. & Wiley, D. C. (1996). *Structure of the complex between human T-cell receptor, viral peptide and HLA-A2. Nature (London)*, **384**, 134–141.

Garcia, K. C., Degano, M., Stanfield, R. L., Brunmark, A., Jackson, M. R., Petereson, P. A., Teyton, L. & Wilson, I. A. (1996). *An αβ T cell receptor structure at 2.5 Å and its orientation in the TCR–MHC complex. Science*, **274**, 209–219.

Gardner, M. J., Tettelin, H., Carucci, D. J., Cummings, L. M., Aravind, L., Koonin, E. V., Shallom, S., Mason, T., Yu, K., Fujii, C., Pederson, J., Shen, K., Jing, J., Aston, C., Lai, Z., Schwartz, D. C., Pertea, M., Salzburg, S., Zhou, L., Sutton, G. G., Clayton, R., White, O., Smith, H. O., Fraser, C. M., Adams, M. D., Venter, J. C. & Hoffman, S. L. (1998). *Chromosome 2 sequence of the human malaria parasite Plasmodium falciparum. Science*, **282**, 1126–1132.

Gatti, D. L., Palfey, B. A., Lah, M. S., Entsch, B., Massey, V., Ballou, D. P. & Ludwig, M. L. (1994). *The mobile flavin of 4-OH benzoate hydroxylase. Science*, **266**, 110–114.

Ghosh, D., Pletnev, V. Z., Zhy, D. W., Wawrzak, Z., Duax, W. L., Pangborn, W., Labrie, F. & Lin, S. W. (1995). *Structure of human estrogenic 17-beta-hydroxysteroid dehydrogenase at 2.20-Å resolution. Structure*, **3**, 503–513.

Giulian, D., Corpuz, M., Richmond, B., Wendt, E. & Hall, E. R. (1996). *Activated microglia are the principal glial source of thromboxane in the central nervous system. Neurochem. Int.* **29**, 65–76.

Gohlke, U., Gomis-Ruth, F. X., Crabbe, T., Murphy, G., Docherty, A. J. & Bode, W. (1996). *The C-terminal (haemopexin-like) domain structure of human gelatinase A (MMP2): structural implications for its function. FEBS Lett.* **378**, 126–120.

Gomis-Ruth, F. X., Gohlke, U., Betz, M., Knauper, V., Murphy, G., Lopez-Otin, C. & Bode, W. (1996). *The helping hand of collagenase-3 (MMP-13): 2.7 Å crystal structure of its C-terminal haemopexin-like domain. J. Mol. Biol.* **264**, 556–566.

Gomis-Ruth, F. X., Maskos, K., Betz, M., Bergner, A., Huber, R., Suzuki, K., Yoshida, N., Nagase, H., Brew, K., Bourenkov, G. P., Bartunik, H. & Bode, W. (1997). *Mechanism of inhibition of the human matrix metalloproteinase stromelysin-1 by TIMP-1. Nature (London)*, **389**, 77–81.

Gong, W., O'Gara, M., Blumenthal, R. M. & Cheng, X. (1997). *Structure of pvu II DNA-(cytosine N4) methyltransferase, an example of domain permutation and protein fold assignment. Nucleic Acids Res.* **25**, 2702–2715.

Goodwill, K. E., Sabatier, C., Marks, C., Raag, R., Fitzpatrick, P. F. & Stevens, R. C. (1997). *Crystal structure of tyrosine hydroxylase at 2.3 Å and its implications for inherited neurodegenerative diseases. Nature Struct. Biol.* **4**, 578–585.

Gordon, D. B., Marshall, S. A. & Mayo, S. L. (1999). *Energy functions for protein design. Curr. Opin. Struct. Biol.* **9**, 509–513.

Gorina, S. & Pavletich, N. P. (1996). *Structure of the p53 tumor suppressor bound to the ankyrin and SH3 domains of 53BP2. Science*, **274**, 1001–1005.

Gouet, P., Jouve, H. M. & Dideberg, O. (1995). *Crystal structure of Proteus mirabilis PT catalase with and without bound NADPH. J. Mol. Biol.* **249**, 933–954.

Gourley, D. G., Shrive, A. K., Polikarpov, I., Krell, T., Coggins, J. R., Hawkins, A. R., Isaacs, N. W. & Sawyer, L. (1999). *The two types of 3-dehydrogenase have distinct structures but catalyze the same overall reaction. Nature Struct. Biol.* **6**, 521–525.

Grant, R. A., Hiemath, C. N., Filman, D. J., Syed, R., Andries, K. & Hogle, J. M. (1994). *Structures of poliovirus complexes with anti-viral drugs: implications for viral stability and drug design. Curr. Biol.* **4**, 784–797.

Graves, B. J., Hatada, M. H., Hendrickson, W. A., Miller, J. K., Madison, V. S. & Satow, Y. (1990). *Structure of interleukin 1 alpha at 2.7-Å resolution. Biochemistry*, **29**, 2679–2684.

Grimes, J., Basak, A. K., Roy, P. & Stuart, D. (1995). *The crystal structure of bluetongue virus VP7. Nature (London)*, **373**, 167–170.

Hampele, I. C., D'Arcy, A., Dale, G. E., Kostrewa, D., Nielsen, J., Oefner, C., Page, M. G., Schonfeld, H. J., Stuber, D. & Then, R. L. (1997). *Structure and function of the dihydropteroate synthase from Staphylococcus aureus. J. Mol. Biol.* **268**, 21–30.

Han, S., Eltis, L. D., Timmis, K. N., Muchmore, S. W. & Bolin, J. T. (1995). *Crystal structure of the biphenyl-cleaving extradiol dioxygenase from a PCB-degrading pseudomonad. Science*, **270**, 976–980.

Hansen, J. L., Long, A. M. & Schultz, S. C. (1997). *Structure of the RNA-dependent RNA polymerase of poliovirus. Structure*, **5**, 1109–1122.

Harrington, D. J., Adachi, K. & Royer, W. E. Jr (1997). *The high resolution crystal structure of deoxyhemoglobin S. J. Mol. Biol.* **272**, 398–407.

Harris, S. F. & Botchan, M. R. (1999). *Crystal structure of the human papillomavirus type 18 E2 activation domain. Science*, **284**, 1673–1677.

He, X. M. & Carter, D. C. (1992). *Atomic structure and chemistry of human serum albumin. Nature (London)*, **358**, 209–215.

Hegde, R. S. & Androphy, E. J. (1998). *Crystal structure of the E2 DNA-binding domain from human papillomavirus type 16: implications for its DNA binding-site selection mechanism. J. Mol. Biol.* **284**, 1479–1489.

Hennig, M., Dale, G. E., D'Arcy, A., Danel, F., Fischer, S., Gray, C. P., Jolidon, S., Muller, F., Page, M. G., Pattison, P. & Oefner, C. (1999). *The structure and function of the 6-hydroxymethyl-7,8-dihydropterin pyrophosphokinase from Haemophilus influenzae. J. Mol. Biol.* **287**, 211–219.

Hennig, M., D'Arcy, A., Hampele, I. C., Page, M. G., Oefner, C. & Dale, G. E. (1998). *Crystal structure and reaction mechanism of 7,8-dihydroneopterin aldolase from Staphylococcus aureus. Nature Struct. Biol.* **5**, 357–362.

Herzberg, O. & Moult, J. (1987). *Bacterial resistance to beta-lactam antibiotics: crystal structure of beta-lactamase from Staphylococcus aureus PC1 at 2.5 Å resolution. Science*, **236**, 694–701.

Hill, C. P., Worthylake, D., Bancroft, D. P., Christensen, A. M. & Sundquist, W. I. (1996). *Crystal structures of the trimeric human immunodeficiency virus type 1 matrix protein: implications for membrane association and assembly. Proc. Natl Acad. Sci. USA*, **93**, 3099–3104.

Hodel, A. E., Gershon, P. D., Shi, X. & Quiocho, F. A. (1996). *The 1.85 Å structure of vaccinia protein VP39: a bifunctional enzyme that participates in the modification of both mRNA ends. Cell*, **85**, 247–256.

Hodgkin, D. C. (1971). *Insulin molecules: the extent of our knowledge. Pure Appl. Chem.* **26**, 375–384.

Hofmann, B., Schomburg, D. & Hecht, H. J. (1993). *Crystal structure of a thiol proteinase from Staphylococcus aureus V-8 in the E-64 inhibitor complex. Acta Cryst.* A**49**, C-102.

Hogle, J. M., Chow, M. & Filman, D. J. (1985). *Three-dimensional structure of poliovirus at 2.9 Å resolution. Science*, **229**, 1358–1365.

Hol, W. G. J. (1986). *Protein crystallography and computer graphics – toward rational drug design. Angew. Chem. Int. Ed. Engl.* **25**, 767–778.

Hoog, S. S., Smith, W. W., Qiu, X., Janson, C. A., Hellmig, B., McQueney, M. S., O'Donnell, K., O'Shannessy, D., DiLella, A. G., Debouck, C. & Abdel-Meguid, S. S. (1997). *Active site cavity of herpesvirus proteases revealed by the crystal structure of herpes simplex virus protease/inhibitor complex. Biochemistry*, **36**, 14023–14029.

Hough, E., Hansen, L. K., Birknes, B., Jynge, K., Hansen, S., Hordvik, A., Little, C., Dodson, E. & Derewenda, Z. (1989). *High-resolution (1.5 Å) crystal structure of phospholipase C from Bacillus cereus. Nature (London)*, **338**, 357–360.

Hsiou, Y., Das, K., Ding, J., Clark, A. D. Jr, Kleim, J. P., Rosner, M., Winkler, I., Riess, G., Hughes, S. H. & Arnold, E. (1998). *Structures of Tyr188Leu mutant and wild-type HIV-1 reverse transcriptase complexed with the non-nucleoside inhibitor HBY 097: inhibitor flexibility is a useful design feature for reducing drug resistance. J. Mol. Biol.* **284**, 313–323.

Hu, S. H., Peek, J. A., Rattigan, E., Taylor, R. K. & Martin, J. L. (1997). *Structure of TcpG, the DsbA protein folding catalyst from Vibrio cholerae. J. Mol. Biol.* **268**, 137–146.

Huang, H., Chopra, R., Verdine, G. L. & Harrison, S. C. (1998). *Structure of a covalently trapped catalytic complex of HIV-1 reverse transcriptase: implications for drug resistance. Science*, **282**, 1669–1675.

Huang, K., Strynadka, N. C., Bernard, V. D., Peanasky, R. J. & James, M. N. (1994). *The molecular structure of the complex of Ascaris chymotrypsin/elastase inhibitor with porcine elastase. Structure*, **2**, 679–689.

Huang, S., Xue, Y., Sauer-Eriksson, E., Chirica, L., Lindskog, S. & Jonsson, B. H. (1998). *Crystal structure of carbonic anhydrase from Neisseria gonorrhoeae and its complex with the inhibitor acetazolamide. J. Mol. Biol.* **283**, 301–310.

Hubbard, S. R. (1997). *Crystal structure of the activated insulin receptor tyrosine kinase in complex with peptide substrate and ATP analog. EMBO J.* **16**, 5572–5581.

Hubbard, S. R., Wei, L., Ellis, L. & Hendrickson, W. A. (1994). *Crystal structure of the tyrosine kinase domain of the human insulin receptor. Nature (London)*, **372**, 746–754.

Huizinga, E. G., Martijn van der Plas, R., Kroon, J., Sixma, J. J. & Gros, P. (1997). *Crystal structure of the A3 domain of human von Willebrand factor: implications for collagen binding. Structure*, **5**, 1147–1156.

Hulsmeyer, M., Hecht, H. J., Niefind, K., Hofer, B., Eltis, L. D., Timmis, K. N. & Schomburg, D. (1998). *Crystal structure of cis-biphenyl-2,3-dihydrodiol-2,3-dehydrogenase from a PCB degrader at 2.0 Å resolution. Protein Sci.* **7**, 1286–1293.

Hurley, T. D., Bosron, W. F., Hamilton, J. A. & Amzel, L. M. (1991). *Structure of human beta 1 beta 1 alcohol dehydrogenase: catalytic effects of non-active-site substitutions. Proc. Natl Acad. Sci. USA*, **88**, 8149–8153.

Isupov, M. N., Antson, A. A., Dodson, E. J., Dodson, G. G., Dementieva, I. S., Zakomirdina, L. N., Wilson, K. S., Dauter, Z., Lebedev, A. A. & Harutyunyan, E. H. (1998). *Crystal structure of tryptophanase. J. Mol. Biol.* **276**, 603–623.

Itzstein, M. von, Wu, W. Y., Kok, G. B., Pegg, M. S., Dyason, J. C., Jin, B., Van Phan, T., Smythe, M. L., White, H. F., Oliver, S. W., Colman, P. M., Varghese, J. N., Ryan, D. M., Woods, J. M., Bethell, R. C., Hotham, V. J., Cameron, J. M. & Penn, C. R. (1993). *Rational design of potent sialidase-based inhibitors of influenza virus replication. Nature (London)*, **363**, 418–423.

Jackson, R. C. (1997). *Contributions of protein structure-based drug design to cancer chemotherapy. Semin. Oncol.* **24**, 164–172.

Jacobo-Molina, A., Ding, J., Nanni, R. G., Clark, A. D. Jr, Lu, X., Tantillo, C., Williams, R. L., Kamer, G., Ferris, A. L., Clark, P., Hizi, A., Hughes, S. H. & Arnold, E. (1993). *Crystal structure of human immunodeficiency virus type 1 reverse transcriptase complexed with double-stranded DNA at 3.0 Å resolution shows bent DNA. Proc. Natl Acad. Sci. USA*, **90**, 6320–6324.

Jain, S., Drendel, W. B., Chen, Z. W., Mathews, F. S., Sly, W. S. & Grubb, J. H. (1996). *Structure of human beta-glucuronidase reveals candidate lysosomal targeting and active-site motifs. Nature Struct. Biol.* **3**, 375–381.

Jia, Z., Vandonselaar, M., Quail, J. W. & Delbaere, L. T. (1993). *Active-centre torsion-angle strain revealed in 1.6 Å-resolution structure of histidine-containing phosphocarrier protein. Nature (London)*, **361**, 94–97.

Kallarakal, A. T., Mitra, B., Kozarich, J. W., Gerlt, J. A., Clifton, J. G., Petsko, G. A. & Kenyon, G. L. (1995). *Mechanism of the reaction catalyzed by mandelate racemase: structure and mechanistic properties of the K166R mutant. Biochemistry*, **34**, 2788–2797.

Kallen, J., Spitzfaden, C., Zurini, M. G. M., Wider, G., Widmer, H., Wuethrich, K. & Walkinshaw, M. D. (1991). *Structure of human cyclophilin and its binding site for cyclosporin A determined by X-ray crystallography and NMR spectroscopy. Nature (London)*, **353**, 276–279.

Kannan, K. K., Notstrand, B., Fridborg, K., Lovgren, S., Ohlsson, A. & Petef, M. (1975). *Crystal structure of human erythrocyte carbonic anhydrase B. Three-dimensional structure at a nominal 2.2-Å resolution. Proc. Natl Acad. Sci. USA*, **72**, 51–55.

Karpusas, M., Nolte, M., Benton, C. B., Meier, W., Lipscomb, W. N. & Goelz, S. (1997). *The crystal structure of human interferon beta at 2.2-Å resolution. Proc. Natl Acad. Sci. USA*, **94**, 11813–11818.

Ke, H., Zydowsky, L. D., Liu, J. & Walsh, C. T. (1991). *Crystal structure of recombinant human T-cell cyclophilin A at 2.5-Å resolution. Proc. Natl Acad. Sci. USA*, **88**, 9483–9487.

Kim, H., Certa, U., Döbelli, H., Jakob, P. & Hol, W. G. J. (1998). *Crystal structure of fructose-1,6-bisphosphate aldolase from the human malaria parasite Plasmodium falciparum. Biochemistry*, **37**, 4388–4396.

Kim, H., Feil, I. K., Verlinde, C. L. M. J., Petra, P. H. & Hol, W. G. J. (1995). *Crystal structure of glycosomal glyceraldehyde-3-phosphate dehydrogenase from Leishmania mexicana: implication for structure-based drug design and a new position for the inorganic phosphate binding site. Biochemistry*, **34**, 14975–14986.

Kim, K. K., Song, H. K., Shin, D. H., Hwang, K. Y. & Suh, S. W. (1997). *The crystal structure of a triacylglycerol lipase from Pseudomonas cepacia reveals a highly open conformation in the absence of a bound inhibitor. Structure*, **5**, 173–185.

Kim, Y., Yoon, K.-H., Khang, Y., Turley, S. & Hol, W. G. J. (2000). *The 2.0 Å crystal structure of cephalosporin acylase. Struct. Fold. Des.* **8**, 1059–1068.

Kissinger, C. R., Parge, H. E., Knighton, D. R., Lewis, C. T., Pelletier, L. A., Tempczyk, A., Kalish, V. J., Tucker, K. D., Showalter, R. E., Moomaw, E. W., Gastinel, L. N., Habuka, N., Chen, X., Maldonado, F., Barker, J. E., Bacquet, R. & Villafranca, J. E. (1995). *Crystal structures of human calcineurin and the human FKBP12-FK506-calcineurin complex. Nature (London)*, **378**, 641–644.

Kitadokoro, K., Hagishita, S., Sato, T., Ohtan, M. & Miki, K. (1998). *Crystal structure of human secretory phospholipase A2-IIA complex with the potent indolizine inhibitor 120–1032. J. Biochem.* **123**, 619–623.

Kitov, P. I., Sadowska, J. M., Mulvey, G., Armstrong, G. D., Ling, H., Pannu, N. S., Read, R. J. & Bundle, D. R. (2000). *Shiga-like toxins are neutralized by tailored multivalent carbohydrate ligands. Nature (London)*, **403**, 669–672.

Knighton, D. R., Kan, C. C., Howland, E., Janson, C. A., Hostomska, Z., Welsh, K. M. & Matthews, D. A. (1994). *Structure of and kinetic channelling in bifunctional dihydrofolate reductase-thymidylate synthase. Nature Struct. Biol.* **1**, 186–194.

Ko, T.-P., Safo, M. K., Musayev, F. N., Di Salvo, M. L., Wang, C., Wu, S.-H. & Abraham, D. J. (2000). *Structure of human erythrocyte catalase. Acta Cryst.* D**56**, 241–245.

Kohara, M., Abe, S., Komatsu, T., Tago, K., Arita, M. & Nomoto, A. (1988). *A recombinant virus between the Sabin 1 and Sabin 3 vaccine strains of poliovirus as a possible candidate for a new type 3 poliovirus live vaccine strain. J. Virol.* **62**, 2828–2835.

Kohlstaedt, L. A., Wang, J., Friedman, J. M., Rice, P. A. & Steitz, T. A. (1992). *Crystal structure at 3.5 Å resolution of HIV-1 reverse transcriptase complexed with an inhibitor. Science*, **256**, 1783–1790.

Kohno, M., Funatsu, J., Mikami, B., Kugimiya, W., Matsuo, T. & Morita, Y. (1996). *The crystal structure of lipase II from Rhizopus niveus at 2.2 Å resolution. J. Biochem.* **120**, 505–510.

Kopka, M. L., Yoon, C., Goodsell, D., Pjura, P. & Dickerson, R. E. (1985). *The molecular origin of DNA-drug specificity in netropsin and distamycin. Proc. Natl Acad. Sci. USA*, **82**, 1376–1380.

Krengel, U., Petsko, G. A., Goody, R. S., Kabsch, W. & Wittinghofer, A. (1990). *Refined crystal structure of the triphosphate conformation of H-ras p21 at 1.35-Å resolution: implications for the mechanism of GTP hydrolysis. EMBO J.* **9**, 2351–2359.

Kuntz, I. D. (1992). *Structure-based strategies for drug design and discovery. Science*, **257**, 1078–1082.

Kurihara, H., Mitsui, Y., Ohgi, K., Irie, M., Mizuno, H. & Nakamura, K. T. (1992). *Crystal and molecular structure of RNase Rh, a new class of microbial ribonuclease from Rhizopus niveus. FEBS Lett.* **306**, 189–192.

Kuzin, A. P., Nukaga, M., Nukaga, Y., Hujer, A. M., Bonomo, R. A. & Knox, J. R. (1999). *Structure of the SHV-1 beta-lactamase. Biochemistry*, **38**, 5720–5727.

Kwong, P. D., Wyatt, R., Robinson, J., Sweet, R. W., Sodroski, J. & Hendrickson, W. A. (1998). *Structure of an HIV gp120 envelope glycoprotein incomplex with the CD4 receptor and a neutralizing human antibody. Nature (London)*, **393**, 648–659.

Laba, D., Bauer, M., Huber, R., Fischer, S., Rudolph, R., Kohnert, U. & Bode, W. (1996). *The 2.3 Å crystal structure of the catalytic domain of recombinant two-chain human tissue-type plasminogen activator. J. Mol. Biol.* **258**, 117–135.

Lacy, D. B. & Stevens, R. C. (1998). *Unraveling the structure and modes of action of bacterial toxins. Curr. Opin. Struct. Biol.* **8**, 778–784.

Lacy, D. B., Tepp, W., Cohen, A. C., DasGupta, B. R. & Stevens, R. C. (1998). *Crystal structure of botulinum neurotoxin type A and implications for toxicity. Nature Struct. Biol.* **5**, 898–902.

Lantwin, C. B., Schlichting, I., Kabsch, W., Pai, E. F. & Krauth-Siegel, R. L. (1994). *The structure of Trypanosoma cruzi trypanothione reductase in the oxidized and NADPH reduced state. Proteins*, **18**, 161–173.

Le, H. V., Yao, N. & Weber, P. C. (1998). *Emerging targets in the treatment of hepatitis C infection. Emerg. Ther. Targets*, **2**, 125–136.

Lebron, J. A., Bennett, M. J., Vaughn, D. E., Chirino, A. J., Snow, P. M., Mintier, G. A., Feder, J. N. & Bjorkman, P. J. (1998). *Crystal structure of the hemochromatosis protein HFE and characterization of its interaction with transferrin receptor. Cell*, **93**, 111–123.

Lee, C. H., Saksela, K., Mirza, U. A., Chait, B. T. & Kuriyan, J. (1996). *Crystal structure of the conserved core of HIV-1 Nef complexed with a Src family SH3 domain. Cell*, **85**, 931–942.

Leonard, S. A., Gittis, A. G., Petrella, E. D., Pollard, T. D. & Lattman, E. E. (1997). *Crystal structure of the actin-binding protein actophorin from Acanthamoeba. Nature Struct. Biol.* **4**, 369–373.

Levine, M. M. & Noriega, F. (1995). *A review of the current status of enteric vaccines. Papua New Guinea Med. J.* **38**, 325–331.

Li, H., Dunn, J. J., Luft, B. J. & Lawson, C. L. (1997). *Crystal structure of Lyme disease antigen outer surface protein A complexed with an Fab. Proc. Natl Acad. Sci. USA*, **94**, 3584–3589.

Li, R., Sirawaraporn, P., Chitnumsub, P., Sirawaraporn, W. & Hol, W. G. J. (2000). *Three-dimensional structure of M. tuberculosis dihydrofolate reductase reveals opportunities for the design of novel tuberculosis drugs. J. Mol. Biol.* **295**, 307–323.

Li de la Sierra, I., Pernot, L., Prange, T., Saludjian, P., Schiltz, M., Fourme, R. & Padron, G. (1997). *Molecular structure of the lipoamide dehydrogenase domain of a surface antigen from Neisseria meningitidis. J. Mol. Biol.* **269**, 129–141.

Libson, A. M., Gittis, A. G., Collier, I. E., Marmer, B. L., Goldberg, G. I. & Lattman, E. E. (1995). *Crystal structure of the haemopexin-like C-terminal domain of gelatinase A. Nature Struct. Biol.* **2**, 938–942.

Liljas, A., Kannan, K. K., Bergsten, P. C., Waara, I., Fridborg, K., Strandberg, B., Carlbom, U., Jarup, L., Lovgren, S. & Petef, M. (1972). *Crystal structure of human carbonic anhydrase C. Nat. New Biol.* **235**, 131–137.

Lin, J. H., Ostovic, D. & Vacca, J. P. (1998). *The integration of medicinal chemistry, drug metabolism, and pharmaceutical research and development in drug discovery and development. The story of Crixivan, an HIV protease inhibitor. Pharm. Biotechnol.* **99**, 233–255.

Ling, H., Boodhoo, A., Hazes, B., Cummings, M. D., Armstrong, G. D., Brunton, J. L. & Read, R. J. (1998). *Structure of the shiga-like toxin I B-pentamer complexed with an analogue of its receptor Gb3. Biochemistry*, **37**, 1777–1788.

Liu, S., Fedorov, A. A., Pollard, T. D., Lattman, E. E., Almo, S. C. & Magnus, K. A. (1998). *Crystal packing induces a conformational change in profilin-I from Acanthamoeba castellanii. J. Struct. Biol.* **123**, 22–29.

Liu, Y., Gong, W., Huang, C. C., Herr, W. & Cheng, X. (1999). *Crystal structure of the conserved core of the herpes simplex virus transcriptional regulatory protein VP16. Genes Dev.* **13**, 1692–1703.

Livnah, O., Johnson, D. L., Stura, E. A., Farrell, F. X., Barbone, F. P., You, Y., Liu, K. D., Goldsmith, M. A., He, W., Krause, C. D., Petska, S., Jolliffe, L. K. & Wilson, I. A. (1998). *An antagonist peptide-EPO receptor complex suggests that receptor dimerization is not sufficient for activation. Nature Struct. Biol.* **5**, 993–1004.

Livnah, O., Stura, E. A., Johnson, D. L., Middleton, S. A., Mulcahy, L. S., Wrighton, N. C., Dower, W. J., Jolliffe, L. K. & Wilson, I. A. (1996). *Functional mimicry of a protein hormone by a peptide agonist: the EPO receptor complex at 2.8 Å. Science*, **273**, 464–471.

Lobkovsky, E., Moews, P. C., Liu, H., Zhao, H., Frere, J. M. & Knox, J. R. (1993). *Evolution of an enzyme activity: crystallographic structure at 2-Å resolution of cephalosporinase from the ampC gene of Enterobacter cloacae P99 and comparison with a class A penicillinase. Proc. Natl Acad. Sci. USA*, **90**, 11257–11261.

Loebermann, H., Tokuoka, R., Deisenhofer, J. & Huber, R. (1984). *Human alpha 1-proteinase inhibitor. Crystal structure analysis of two crystal modifications, molecular model and preliminary analysis of the implications for function. J. Mol. Biol.* **177**, 531–557.

Loll, P. J. & Lattman, E. E. (1989). *The crystal structure of the ternary complex of staphylococcal nuclease, Ca^{2+}, and the inhibitor pdTp, refined at 1.65 Å. Proteins*, **5**, 183–201.

Love, R. A., Parge, H. E., Wickersham, J. A., Hostomsky, Z., Habuka, N., Moomaw, E. W., Adachi, T. & Hostomska, Z. (1996). *The crystal structure of hepatitis C virus NS3 proteinase reveals a trypsin-like fold and a structural zinc binding site. Cell*, **87**, 331–342.

Lovejoy, B., Cleasby, A., Hassell, A. M., Longley, K., Luther, M. A. W. D., McGeehan, G., McElroy, A. B., Drewry, D., Lambert, M. H. & Jordan, S. R. (1994). *Structure of the catalytic domain of fibroblast collagenase complexed with an inhibitor. Science*, **263**, 375–377.

Lovejoy, B., Hassell, A. M., Luther, M. A., Weigl, D. & Jordan, S. R. (1994). *Crystal structures of recombinant 19-kDa human fibroblast collagenase complexed to itself. Biochemistry*, **33**, 8207–8217.

Lukatela, G., Krauss, N., Theis, K., Selmer, T., Gieselmann, V., von Figura, K. & Saenger, W. (1998). *Crystal structure of human arylsulfatase A: the aldehyde function and the metal ion at the active site suggest a novel mechanism for sulfate ester hydrolysis. Biochemistry*, **37**, 3654–3664.

McGrath, M. E., Eakin, A. E., Engel, J. C., McKerrow, J. H., Craik, C. S. & Fletterick, R. J. (1995). *The crystal structure of cruzain: a therapeutic target for Chagas' disease. J. Mol. Biol.* **247**, 251–259.

McGrath, M. E., Palmer, J. T., Bromme, D. & Somoza, J. R. (1998). *Crystal structure of human cathepsin S. Protein Sci.* **7**, 1294–1302.

McLaughlin, P. J., Gooch, J. T., Mannherz, H. G. & Weeds, A. G. (1993). *Structure of gelsolin segment 1-actin complex and the mechanism of filament severing. Nature (London)*, **364**, 685–692.

McTigue, M. A., Wickersham, J. A., Pinko, C., Showalter, R. E., Parast, C. V., Tempczyk-Russell, A., Gehring, M. R., Mroczkowski, B., Kan, C. C., Villafranca, J. E. & Appelt, K. (1999). *Crystal structure of the kinase domain of human vascular endothelial growth factor receptor 2: a key enzyme in angiogenesis. Struct. Fold. Des.* **7**, 319–330.

McTigue, M. A., Williams, D. R. & Tainer, J. A. (1995). *Crystal structure of a schistosomal drug and vaccine target: glutathione S-transferase from Schistosoma japonica and its complex with the leading antischistosomal drug praziquantel. J. Mol. Biol.* **246**, 21–27.

Maldonado, E., Soriano-Garcia, M., Moreno, A., Cabrera, N., Garza-Ramos, G., de Gomez-Puyou, M., Gomez-Puyou, A. & Perez-Montfort, R. (1998). *Differences in the intersubunit contacts in triosephosphate isomerase from two closely related pathogenic trypanosomes. J. Mol. Biol.* **283**, 193–203.

Malik, P. & Perham, R. N. (1997). *Simultaneous display of different peptides on the surface of filamentous bacteriophage. Nucleic Acids Res.* **25**, 915–916.

Mande, S. C., Mainfroid, V., Kalk, K. H., Goraj, K., Marital, J. A. & Hol, W. G. J. (1994). *Crystal structure of recombinant human triosephosphate isomerase at 2.8 Å resolution. Protein Sci.* **3**, 810–821.

Mande, S. C., Mehra, F., Bloom, B. R. & Hol, W. G. J. (1996). *Structure of the heat shock protein chaperonin-10 of Mycobacterium leprae. Science*, **271**, 203–207.

Martin, A., Wychowski, C., Couderc, T., Crainic, R., Hogle, J. & Girard, M. (1988). *Engineering a poliovirus type 2 antigenic site on a type 1 capsid results in a chimaeric virus which is neurovirulent for mice. EMBO J.* **7**, 2839–2847.

Mather, T., Oganesseyan, V., Hof, P., Huber, R., Foundling, S., Esmon, S. & Bode, W. (1996). *The 2.8 Å crystal structure of Gla-domainless activated protein C. EMBO J.* **15**, 6822–6831.

Mathews, I. I., Vanderhoff-Hanaver, P., Castellino, F. J. & Tulinsky, A. (1996). *Crystal structures of the recombinant kringle 1 domain of human plasminogen in complexes with the ligands epsilon-aminocaproic acid and trans-4-(aminomethyl)cyclohexane-1-carboxylic acid. Biochemistry*, **35**, 2567–2576.

Matthews, D. A., Alden, R. A., Bolin, J. T., Freer, S. T., Hamlin, R., Xuong, N., Kraut, J., Poe, M., Williams, M. & Hoogsteen, K. (1977). *Dihydrofolate reductase: X-ray structure of the binary complex with methotrexate. Science*, **197**, 452–455.

Matthews, D. A., Smith, W. W., Ferre, R. A., Condon, B., Budahazi, G., Sisson, W., Villafranca, J. E., Janson, C. A., McElroy, H. E., Gribskov, C. L. & Worland, S. (1994). *Structure of human rhinovirus 3C protease reveals a trypsin-like polypeptide fold, RNA-binding site, and means for cleaving precursor polyprotein. Cell*, **77**, 761–771.

Meng, W., Sawasdikosol, S., Burakoff, S. J. & Eck, M. J. (1999). *Structure of the amino-terminal domain of Cbl complexed to its binding site on ZAP-70 kinase. Nature (London)*, **398**, 84–90.

Merritt, E. A., Sarfaty, S., van den Akker, F., L'hoir, C., Martial, J. A. & Hol, W. G. J. (1994). *Crystal structure of cholera toxin B-pentamer bound to receptor G_{M1} pentasaccharide. Protein Sci.* **3**, 166–175.

Merritt, E. A., Sarfaty, S., Feil, I. K. & Hol, W. G. J. (1997). *Structural foundation for the design of receptor antagonists targeting E. coli heat-labile enterotoxin. Structure*, **5**, 1485–1499.

Metcalf, P. & Fusek, M. (1993). *Two crystal structures for cathepsin D: the lysosomal targeting signal and active site. EMBO J.* **12**, 1293–1302.

Mikami, B., Adachi, M., Kage, T., Sarikaya, E., Nanmori, T., Shinke, R. & Utsumi, S. (1999). *Structure of raw starch-digesting Bacillus cereus beta-amylase complexed with maltose. Biochemistry*, **38**, 7050–7061.

Mikol, V., Ma, D. & Carlow, C. K. (1998). *Crystal structure of the cyclophilin-like domain from the parasitic nematode Brugia malayi. Protein Sci.* **7**, 1310–1316.

Milburn, M. V., Hassell, A. M., Lambert, M. H., Jordan, S. R., Proudfoot, A. E. I., Graber, P. & Wells, T. N. C. (1993). *A novel dimer configuration revealed by the crystal structure at 2.4-Å resolution of human interleukin-5. Nature (London)*, **363**, 172–176.

Miller, M. D., Tanner, J., Alpaugh, M., Benedik, M. J. & Krause, K. L. (1994). *2.1 Å structure of Serratia endonuclease suggests a mechanism for binding to double-stranded DNA. Nature Struct. Biol.* **1**, 461–468.

Minke, W. E., Hong, F., Verlinde, C. L. M. J., Hol, W. G. J. & Fan, E. (1999). *Using a galactose library for exploration of a novel hydrophobic pocket in the receptor binding site of the E. coli heat-labile enterotoxin. J. Biol. Chem.* **274**, 33469–33473.

Miyatake, H., Hata, Y., Fujii, T., Hamada, K., Morihara, K. & Katsube, Y. (1995). *Crystal structure of the unliganded alkaline protease from Pseudomonas aeruginosa IFO3080 and its conformational changes on ligand binding. J. Biochem. (Tokyo)*, **118**, 474–479.

Moser, J., Gerstel, B., Meyer, J. E., Chakraborty, T., Wehland, J. & Heinz, D. W. (1997). *Crystal structure of the phosphatidylinositol-specific phospholipase C from the human pathogen Listeria monocytogenes. J. Mol. Biol.* **273**, 269–282.

Mottonen, J., Strand, A., Symersky, J., Sweet, R. M., Danley, D. E., Gioghegan, K. F., Gerard, R. D. & Goldsmith, E. J. (1992). *Structural basis of latency in plasminogen activator inhibitor-1. Nature (London)*, **355**, 270–273.

Muchmore, S. W., Sattler, M., Liang, H., Meadows, R. P., Harlan, J. E., Yoon, H. S., Nettesheim, D., Chang, B. S., Thompson, C. B., Wong, S. L., Ng, S. L. & Fesik, S. W. (1996). *X-ray and NMR structure of human Bcl-xL, an inhibitor of programmed cell death. Nature (London)*, **381**, 335–341.

Mulichak, A. M., Tulinsky, A. & Ravichandran, K. G. (1991). *Crystal and molecular structure of human plasminogen kringle 4 refined at 1.9-Å resolution. Biochemistry*, **30**, 10576–10588.

Mulichak, A. M., Wilson, J. E., Padmanabhan, K. & Garavito, R. M. (1998). *The structure of mammalian hexokinase-1. Nature Struct. Biol.* **5**, 555–560.

Muller, Y. A., Ultsch, M. H. & DeVos, A. M. (1996). *The crystal structure of the extracellular domain of human tissue factor refined to 1.7-Å resolution. J. Mol. Biol.* **256**, 144–159.

Muller, Y. A., Ultsch, M. H., Kelley, R. F. & DeVos, A. M. (1994). *Structure of the extracellular domain of human tissue factor: location of the factor VIIa binding site. Biochemistry*, **33**, 10864–10870.

Murray, C. J. & Salomon, J. A. (1998). *Modeling the impact of global tuberculosis control strategies. Proc. Natl Acad. Sci. USA*, **95**, 13881–13886.

Murray, I. A., Cann, P. A., Day, P. J., Derrick, J. P., Sutcliffe, M. J., Shaw, W. V. & Leslie, A. G. (1995). *Steroid recognition by chloramphenicol acetyltransferase: engineering and structural analysis of a high affinity fusidic acid binding site. J. Mol. Biol.* **254**, 993–1005.

Murray, M. G., Kuhn, R. J., Arita, M., Kawamura, N., Nomoto, A. & Wimmer, E. (1988). *Poliovirus type 1/type 3 antigenic hybrid virus constructed in vitro elicits type 1 and type3 neutralizing antibodies in rabbits and monkeys. Proc. Natl Acad. Sci. USA*, **85**, 3203–3207.

Murthy, H. M., Clum, S. & Padmanabhan, R. (1999). *Dengue virus NS3 serine protease. Crystal structure and insights into interaction of the active site with substrates by molecular modeling and structural analysis of mutational effects. J. Biol. Chem.* **274**, 5573–5580.

Musil, D., Zucic, D., Turk, D., Engh, R. A., Mayr, I., Huber, R., Popovic, T., Turk, V., Towatari, T., Katunuma, N. & Bode, W. (1991). *The refined 2.15 Å X-ray crystal structure of human liver cathepsin B: the structural basis for its specificity. EMBO J.* **10**, 2321–2330.

Nagar, B., Jones, R. G., Diefenbach, R. J., Isenman, D. E. & Rini, J. M. (1998). *X-ray crystal structure of C3d: a C3 fragment and ligand for complement receptor 2. Science*, **280**, 1277–1281.

Nam, H. J., Haser, W. G., Roberts, T. M. & Frederick, C. A. (1996). *Intramolecular interactions of the regulatory domains of the*

Bcr-Abl kinase reveal a novel control mechanism. Structure, **4**, 1105–1114.

Narayana, N., Matthews, D. A., Howell, E. E. & Nguyen-huu, X. (1995). *A plasmid-encoded dihydrofolate reductase from trimethoprim-resistant bacteria has a novel D2-symmetric active site. Nature Struct. Biol.* **2**, 1018–1025.

National Institute of Allergy and Infectious Diseases (1998). *The Jordan Report: Accelerated Development of Vaccines.* NIAID, Bethesda, MD.

Navia, M. A., Fitzgerald, P. M., McKeever, B. M., Leu, C. T., Heimbach, J. C., Herber, W. K., Sigal, I. S., Darke, P. L. & Springer, J. P. (1989). *Three-dimensional structure of aspartyl protease from human immunodeficiency virus HIV-1. Nature (London)*, **337**, 615–620.

Navia, M. A., McKeever, B. M., Springer, J. P., Lin, T. Y., Williams, H. R., Fluder, E. M., Dorn, C. P. & Hoogsteen, K. (1989). *Structure of human neutrophil elastase in complex with a peptide chloromethyl ketone inhibitor at 1.84-Å resolution. Proc. Natl Acad. Sci. USA*, **86**, 7–11.

Naylor, C. E., Eaton, J. T., Howells, A., Justin, N., Moss, D. S., Titball, R. W. & Basak, A. K. (1998). *Structure of the key toxin in gas gangrene. Nature Struct. Biol.* **5**, 738–746.

Nurizzo, D., Silvestrini, M. C., Mathieu, M., Cutruzzola, F., Bourgeois, D., Fulop, V., Hajdu, J., Brunori, M., Tegoni, M. & Cambillau, C. (1997). *N-terminal arm exchange is observed in the 2.15 Å crystal structure of oxidized nitrite reductase from Pseudomonas aeruginosa. Structure*, **5**, 1157–1171.

Oefner, C., D'Arcy, A. & Winkler, F. K. (1988). *Crystal structure of human dihydrofolate reductase complexed with folate. Eur. J. Biochem.* **174**, 377–385.

Oinonen, C., Tikkanen, R., Rouvinen, J. & Peltonen, L. (1995). *Three-dimensional structure of human lysosomal aspartylglucosaminidase. Nature Struct. Biol.* **2**, 1102–1108.

Ozaki, H., Sato, T., Kubota, H., Hata, Y., Katsube, Y. & Shimonishi, Y. (1991). *Molecular structure of the toxin domain of heat-stable enterotoxin produced by a pathogenic strain of Escherichia coli. A putative binding site for a binding protein on rat intestinal epithelial cell membranes. J. Biol. Chem.* **266**, 5934–5941.

Padmanabhan, K., Padmanabhan, K. P., Tulinsky, A., Park, C. H., Bode, W., Huber, R., Blankenship, D. T., Cardin, A. D. & Kisiel, W. (1993). *Structure of human des(1–45) factor Xa at 2.2-Å resolution. J. Mol. Biol.* **232**, 947–966.

Pai, E. F., Kabsch, W., Krengel, U., Holmes, K. C., John, J. & Wittinghofer, A. (1989). *Structure of the guanine-nucleotide-binding domain of the Ha-ras oncogene product p21 in the triphosphate conformation. Nature (London)*, **341**, 209–214.

Papageorgiou, A. C., Acharya, K. R., Shapiro, R., Passalacqua, E. F., Brehm, R. D. & Tranter, H. S. (1995). *Crystal structure of the superantigen enterotoxin C2 from Staphylococcus aureus reveals a zinc-binding site. Structure*, **3**, 769–779.

Papageorgiou, A. C., Tranter, H. S. & Acharya, K. R. (1998). *Crystal structure of microbial superantigen staphylococcal enterotoxin B at 1.5 Å resolution: implications for superantigen recognition by MHC class II molecules and T-cell receptors. J. Mol. Biol.* **277**, 61–79.

Pares, S., Mouz, N., Petillot, Y., Hakenbeck, R. & Dideberg, O. (1996). *X-ray structure of Streptococcus pneumoniae PBP2x, a primary penicillin target enzyme. Nature Struct. Biol.* **3**, 284–289.

Parge, H. E., Forest, K. T., Hickey, M. J., Christensen, D. A., Getzoff, E. D. & Tainer, J. A. (1995). *Structure of the fibre-forming protein pilin at 2.6 Å resolution. Nature (London)*, **378**, 32–38.

Parge, H. E., Hallewell, R. A. & Tainer, J. A. (1992). *Atomic structures of wild-type and thermostable mutant recombinant human Cu,Zn superoxide dismutase. Proc. Natl Acad. Sci. USA*, **89**, 6109–6113.

Patskovsky, Y. V., Patskovska, L. N. & Listowsky, I. (1999). *Functions of His107 in the catalytic mechanism of human glutathione s-transferase hGSTM1a-1a. Biochemistry*, **38**, 1193–1202.

Pauptit, R. A., Karlsson, R., Picot, D., Jenkins, J. A., Niklaus-Reimer, A. S. & Jansonius, J. N. (1988). *Crystal structure of neutral protease from Bacillus cereus refined at 3.0 Å resolution and comparison with the homologous but more thermostable enzyme thermolysin. J. Mol. Biol.* **199**, 525–537.

Pearl, L., O'Hara, B., Drew, R. & Wilson, S. (1994). *Crystal structure of AmiC: the controller of transcription antitermination in the amidase operon of Pseudomonas aeruginosa. EMBO J.* **13**, 5810–5817.

Pedelacq, J. D., Maveyraud, L., Prevost, G., Bab-Moussa, L., Gonzalez, A., Coucelle, E., Shepard, W., Monteil, H., Samama, J. P. & Mourey, L. (1999). *The structure of a Staphylococcus aureus leucocidin component (LukF-PV) reveals the fold of the water-soluble species of a family of transmembrane pore-forming toxins. Struct. Fold. Des.* **7**, 277–287.

Pedersen, L. C., Benning, M. M. & Holden, H. M. (1995). *Structural investigation of the antibiotic and ATP-binding sites in kanamycin nucleotidyltransferase. Biochemistry*, **34**, 13305–13311.

Perrakis, A., Tews, I., Dauter, Z., Oppenheim, A. B., Chet, I., Wilson, K. S. & Vorgias, C. E. (1994). *Crystal structure of a bacterial chitinase at 2.3 Å resolution. Structure*, **2**, 1169–1180.

Perutz, M. (1992). *Protein Structure. New Approaches to Disease and Therapy.* New York: W. H. Freeman & Co.

Petosa, C., Collier, R. J., Klimpel, K. R., Leppla, S. H. & Liddington, R. C. (1997). *Crystal structure of the anthrax toxin protective antigen. Nature (London)*, **385**, 833–838.

Pfuegl, G., Kallen, J., Schirmer, T., Jansonius, J. N., Zurini, M. G. M. & Walkinshaw, M. D. (1993). *X-ray structure of a decameric cyclophilin–cyclosporin crystal complex. Nature (London)*, **361**, 91–94.

Phillips, C., Dohnalek, J., Gover, S., Barrett, M. P. & Adams, M. J. (1998). *A 2.8 Å resolution structure of 6-phosphogluconate dehydrogenase from the protozoan parasite Trypanosoma brucei: comparison with the sheep enzyme accounts for differences in activity with coenzyme and substrate analogues. J. Mol. Biol.* **282**, 667–681.

Phillips, C. L., Ullman, B., Brennan, R. G. & Hill, C. P. (1999). *Crystal structures of adenine phosphoribosyltransferase from Leishmania donovani. EMBO J.* **18**, 3533–3545.

Pineo, G. F. & Hull, R. D. (1999). *Thrombin inhibitors as anticoagulant agents. Curr. Opin. Hematol.* **6**, 298–303.

Poljak, R. J., Amzel, L. M., Avey, H. P., Chen, B. L., Phizackerley, R. P. & Saul, F. (1973). *Three-dimensional structure of the Fab′ fragment of a human immunoglobulin at 2.8-Å resolution. Proc. Natl Acad. Sci. USA*, **70**, 3305–3310.

Porter, R. (1999). *The Greatest Benefit to Mankind: a Medical History of Humanity.* New York: W. W. Norton and Co., Inc.

Prasad, G. S., Earhart, C. A., Murray, D. L., Novick, R. P., Schlievert, P. M. & Ohlendorf, D. H. (1993). *Structure of toxic shock syndrome toxin 1. Biochemistry*, **32**, 13761–13766.

Pratt, K. P., Cote, H. C., Chung, D. W., Stenkamp, R. E. & Davie, E. W. (1997). *The primary fibrin polymerization pocket: three-dimensional structure of a 30-kDa C-terminal gamma chain fragment complexed with the peptide Gly-Pro-Arg-Pro. Proc. Natl Acad. Sci. USA*, **94**, 7176–7181.

Pratt, K. P., Shen, B. W., Takeshima, K., Davie, E. W., Fujikawa, K. & Stoddard, B. L. (1999). *Structure of the C2 domain of human factor VIII at 1.5 Å resolution. Nature (London)*, **402**, 439–442.

Priestle, J. P., Schar, H. P. & Grutter, M. G. (1988). *Crystal structure of the cytokine interleukin-1 beta. EMBO J.* **7**, 339–343.

Qiu, X., Culp, J. S., DiLella, A. G., Hellmig, B., Hoog, S. S., Janson, C. A., Smith, W. W. & Abdel-Meguid, S. S. (1996). *Unique fold and active site in cytomegalovirus protease. Nature (London)*, **383**, 275–279.

Qiu, X., Janson, C. A., Culp, J. S., Richardson, S. B., Debouck, C., Smith, W. W. & Abdel-Meguid, S. S. (1997). *Crystal structure of varicella-zoster virus protease. Proc. Natl Acad. Sci. USA*, **94**, 2874–2879.

Qiu, X., Verlinde, C. L. M. J., Zhang, S., Schmitt, M. P., Holmes, R. K. & Hol, W. G. J. (1995). *Three-dimensional structure of the diphtheria toxin repressor in complex with divalent cation co-repressors. Structure*, **3**, 87–100.

Rabijns, A., De Bondt, H. L. & De Ranter, C. (1997). *Three-dimensional structure of staphylokinase, a plasminogen activator with therapeutic potential. Nature Struct. Biol.* **4**, 357–360.

Radhakrishnan, R., Walter, L. J., Hruza, A., Reichert, P., Trotta, P. P., Nagabhushan, T. L. & Walter, M. R. (1996). *Zinc mediated dimer of human interferon-alpha 2b revealed by X-ray crystallography. Structure*, **4**, 1453–1463.

Raghunathan, S., Chandross, R. J., Kretsinger, R. H., Allison, T. J., Penington, C. J. & Rule, G. S. (1994). *Crystal structure of human class mu glutathione transferase GSTM2–2. Effects of lattice packing on conformational heterogeneity. J. Mol. Biol.* **238**, 815–832.

Rano, T. A., Timkey, T., Peterson, E. P., Rotonda, J., Nicholson, D. W., Becker, J. W., Chapman, K. T. & Thornberry, N. A. (1997). *A combinatorial approach for determining protease specificities: application to interleukin-1 beta converting enzyme (ICE). Chem. Biol.* **4**, 149–155.

Rao, Z., Handford, P., Mayhew, M., Knott, V., Brownlee, G. G. & Stuart, D. (1995). *The structure of a Ca(2+)-binding epidermal growth factor-like domain: its role in protein–protein interactions. Cell*, **82**, 131–141.

Read, J. A., Wilkinson, K. W., Tranter, R., Sessions, R. B. & Brady, R. L. (1999). *Chloroquine binds in the cofactor binding site of Plasmodium falciparum lactate dehydrogenase. J. Biol. Chem.* **274**, 10213–10218.

Redinbo, M. R., Stewart, L., Kuhn, P., Champoux, J. J. & Hol, W. G. J. (1998). *Crystal structures of human topoisomerase I in covalent and noncovalent complexes with DNA. Science*, **279**, 1504–1513.

Reichmann, L., Clark, M., Waldmann, H. & Winter, G. (1988). *Reshaping human antibodies for therapy. Nature (London)*, **332**, 323–327.

Reinemer, P., Dirr, H. W., Ladenstein, R., Huber, R., Lo Bello, M., Federici, G. & Parker, M. W. (1992). *Three-dimensional structure of class pi glutathione S-transferase from human placenta in complex with S-hexylglutathione at 2.8 Å resolution. J. Mol. Biol.* **227**, 214–226.

Reinemer, P., Grams, F., Huber, R., Kleine, T., Schnierer, S., Piper, M., Tschesche, H. & Bode, W. (1994). *Structural implications for the role of the N terminus in the 'superactivation' of collagenases. A crystallographic study. FEBS Lett.* **338**, 227–233.

Ren, J., Esnouf, R., Garman, E., Somers, D., Ross, C., Kirby, I., Keeling, J., Darby, G., Jones, Y., Stuart, D. & Stammers, D. (1995). *High resolution structures of HIV-1 RT from four RT-inhibitor complexes. Nature Struct. Biol.* **2**, 293–302.

Ren, J., Esnouf, R. M., Hopkins, A. L., Jones, E. Y., Kirby, I., Keeling, J., Ross, C. K., Larder, B. A., Stuart, D. I. & Stammers, D. K. (1998). *3′-Azido-3′-deoxythymidine drug resistance mutations in HIV-1 reverse transcriptase can induce long range conformational changes. Proc. Natl Acad. Sci. USA*, **95**, 9518–9523.

Renwick, S. B., Snell, K. & Baumann, U. (1998). *The crystal structure of human cytosolic serine hydroxymethyltransferase: a target for cancer chemotherapy. Structure*, **15**, 1105–1116.

Resnick, D. A., Smith, A. D., Geisler, S. C., Zhang, A., Arnold, E. & Arnold, G. F. (1995). *Chimeras from a human rhinovirus 14–human immunodeficiency virus type 1 (HIV-1) V3 loop seroprevalence library induce neutralizing responses against HIV-1. J. Virol.* **69**, 2406–2411.

Rey, F. A., Heinz, F. X., Mandl, C., Kunz, C. & Harrison, S. C. (1995). *The envelope glycoprotein from tick-borne encephalitis virus at 2 Å resolution. Nature (London)*, **375**, 291–298.

Rigden, D. J., Phillips, S. E., Michels, P. A. & Fothergill-Gilmore, L. A. (1999). *The structure of pyruvate kinase from Leishmania mexicana reveals details of the allosteric transition and unusual effector specificity. J. Mol. Biol.* **291**, 615–635.

Ripka, W. C. (1997). *Design of antithrombotic agents directed at factor Xa*. In *Structure-Based Drug Design*, edited by P. Veerapandian, pp. 265–294. New York: Marcel Dekker.

Roberts, M. M., White, J. L., Grutter, M. G. & Burnett, R. M. (1986). *Three-dimensional structure of the adenovirus major coat protein hexon. Science*, **232**, 1148–1151.

Rodgers, D. W., Bamblin, S. J., Harris, B. A., Ray, S., Culp, J. S., Hellmig, B., Woolf, D. J., Debouck, C. & Harrison, S. C. (1995). *The structure of unliganded reverse transcriptase from the human immunodeficiency virus type 1. Proc. Natl Acad. Sci. USA*, **92**, 1222–1226.

Roe, S. M., Barlow, T., Brown, T., Oram, M., Keeley, A., Tsaneva, I. R. & Pearl, L. H. (1998). *Crystal structure of an octameric RuvA–Holliday junction complex. Mol. Cell*, **2**, 361–372.

Rolan, P. E., Parker, J. E., Gray, S. J., Weatherley, B. C., Ingram, J., Leavens, W., Wootton, R. & Posner, J. (1993). *The pharmacokinetics, tolerability and pharmacodynamics of tucaresol (589C80; 4[2-formyl-3-hydroxyphenoxymethyl] benzoic acid), a potential anti-sickling agent, following oral administration to healthy subjects. Br. J. Clin. Pharmacol.* **35**, 419–425.

Rossjohn, J., Feil, S. C., McKinstry, W. J., Tweten, R. K. & Parker, M. W. (1997). *Structure of a cholesterol-binding, thiol-activated cytolysin and a model of its membrane form. Cell*, **89**, 685–692.

Rossjohn, J., Feil, S. C., Wilce, M. C. J., Sexton, J. L., Spithill, T. W. & Parker, M. W. (1997). *Crystallization, structural determination and analysis of a novel parasite vaccine candidate: Fasciola hepatica glutathione S-transferase. J. Mol. Biol.* **273**, 857–872.

Rossjohn, J., McKinstry, W. J., Oakley, A. J., Verger, D., Flanagan, J., Chelvanayagam, G., Tan, K. L., Board, P. G. & Parker, M. W. (1998). *Human theta class glutathione transferase: the crystal structure reveals a sulfate-binding pocket within a buried active site. Structure*, **6**, 309–322.

Rossjohn, J., Polekhina, G., Feil, S. C., Allocati, N., Masulli, M., De Illio, C. & Parker, M. W. (1998). *A mixed disulfide bond in bacterial glutathione transferase: functional and evolutionary implications. Structure*, **6**, 721–734.

Rossmann, M. G., Arnold, E., Erickson, J. W., Frankenberger, E. A., Griffith, J. P., Hecht, H. J., Johnson, J. E., Kamer, G., Luo, M., Mosser, A. G., Rueckert, R. R., Sherry, B. & Vriend, G. (1985). *Structure of a human common cold virus and functional relationship to other picornaviruses. Nature (London)*, **317**, 145–153.

Roussel, A., Anderson, B. F., Baker, H. M., Fraser, J. D. & Baker, E. N. (1997). *Crystal structure of the streptococcal superantigen SPE-C: dimerization and zinc binding suggest a novel mode of interaction with MHC class II molecules. Nature Struct. Biol.* **4**, 635–643.

Rudenko, G., Bonten, E., d'Azzo, A. & Hol, W. G. J. (1995). *Three-dimensional structure of the human 'protective protein': structure of the precursor form suggests a complex activation mechanism. Structure*, **3**, 1249–1259.

Rudenko, G., Bonten, E., Hol, W. G. J. & d'Azzo, A. (1998). *The atomic model of the human protective protein/cathepsin A suggests a structural basis for galactosialidosis. Proc. Natl Acad. Sci. USA*, **95**, 621–625.

Russo, A. A., Tong, L., Lee, J. O., Jeffrey, P. D. & Pavletich, N. P. (1998). *Structural basis for inhibition of the cyclin-dependent kinase Cdk6 by the tumour suppressor p16INK4a. Nature (London)*, **395**, 237–243.

Rydel, T. J., Ravichandran, K. G., Tulinsky, A., Bode, W., Huber, R., Roitsch, C. & Fenton, J. W. I. (1990). *The structure of a complex of recombinant hirudin and human alpha-thrombin. Science*, **249**, 277–280.

Rydel, T. J., Yin, M., Padmanabhan, K. P., Blankenship, D. T., Cardin, A. D., Correa, P. E., Fenton, J. W. I. & Tulinsky, A. (1994). *Crystallographic structure of human gamma-thrombin. J. Biol. Chem.* **269**, 22000–22006.

Sarafianos, S. G., Das, K., Ding, J., Boyer, P. L., Hughes, S. H. & Arnold, E. (1999). *Touching the heart of HIV-1 drug resistance: the fingers close down on the dNTP at the polymerase active site. Chem. Biol.* **6**, R137–R146.

Sauer, F. G., Futterer, K., Pinkner, J. S., Dodson, K. W., Hultgren, S. J. & Waksman, G. (1999). *Structural basis of chaperone function and pilus biogenesis. Science*, **285**, 1058–1061.

Savva, R., McAuley-Hecht, K., Brown, T. & Pearl, L. (1995). *The structural basis of specific base-excision repair by uracil-DNA glycosylase. Nature (London)*, **373**, 487–493.

Scheffzek, K., Ahmadian, M. R., Kabsch, W., Wiesmuller, L., Lautwein, A., Schmitz, F. & Wittinghofer, A. (1997). *The Ras–RasGAP complex: structural basis for GTPase activation and its loss in oncogenic Ras mutants. Science*, **277**, 333–338.

Schiffer, C. A., Clifton, I. J., Davisson, V. J., Santi, D. V. & Stroud, R. M. (1995). *Crystal structure of human thymidylate synthase: a structural mechanism for guiding substrates into the active site. Biochemistry*, **34**, 16279–16287.

Schlagenhauf, E., Etges, R. & Metcalf, P. (1998). *The crystal structure of the Leishmania major surface proteinase leishmanolysin (gp63). Structure*, **6**, 1035–1046.

Schonbrunn, E., Sack, S., Eschenberg, S., Perrakis, A., Krekel, F., Amrhein, N. & Mandelkow, E. (1996). *Crystal structure of UDP-N-acetylglucosamine enolpyruvyltransferase, the target of the antibiotic fosfomycin. Structure*, **4**, 1065–1075.

Schreuder, H., Tardif, C., Trump-Kallmeyer, S., Soffientini, A., Sarubbi, E., Akeson, A., Bowlin, T., Yanofsky, S. & Barrett, R. W. (1997). *A new cytokine-receptor binding mode revealed by the crystal structure of the IL-1 receptor with an antagonist. Nature (London)*, **386**, 194–200.

Schreuder, H. A., de Boer, B., Dijkema, R., Mulders, J., Theunissen, H. J. M., Grootenhuis, P. D. J. & Hol, W. G. J. (1994). *The intact and cleaved human antithrombin III complex as a model for serpin-proteinase interactions. Nature Struct. Biol.* **1**, 48–54.

Schumacher, M. A., Carter, D., Ross, D. S., Ullman, B. & Brennan, R. G. (1996). *Crystal structures of Toxoplasma gondii HGXPRTase reveal the catalytic role of a long flexible loop. Nature Struct. Biol.* **3**, 881–887.

Schumacher, M. A., Carter, D., Scott, D. M., Roos, D. S., Ullman, B. & Brennan, R. G. (1998). *Crystal structures of Toxoplasma gondii uracil phosphoribosyltransferase reveal the atomic basis of pyrimidine discrimination and prodrug binding. EMBO J.* **17**, 3219–3232.

Schwabe, J. W. E., Chapman, L., Finch, J. T. & Rhodes, D. (1993). *The crystal structure of the estrogen receptor DNA-binding domain bound to DNA: how receptors discriminate between their response elements. Cell*, **75**, 567–578.

Scott, D. L., White, S. P., Browning, J. L., Rosa, J. J., Gelb, M. H. & Sigler, P. B. (1991). *Structures of free and inhibited human secretory phospholipase A2 from inflammatory exudate. Science*, **254**, 1007–1010.

Sha, B. & Luo, M. (1997). *Structure of a bifunctional membrane-RNA binding protein, influenza virus matrix protein M1. Nature Struct. Biol.* **4**, 239–244.

Shah, S. A., Shen, B. W. & Brunger, A. T. (1997). *Human ornithine aminotransferase complexed with L-canaline and gabaculine: structural basis for substrate recognition. Structure*, **5**, 1067–1075.

Sharma, A., Hanai, R. & Mondragon, A. (1994). *Crystal structure of the amino-terminal fragment of vaccinia virus DNA topoisomerase I at 1.6 Å resolution. Structure*, **2**, 767–777.

Sharma, V., Grubmeyer, C. & Sacchettini, J. C. (1998). *Crystal structure of quinolinic acid phosphoribosyltransferase from Mycobacterium tuberculosis: a potential TB drug target. Structure*, **6**, 1587–1599.

Sherry, B., Mosser, A. G., Colonno, R. J. & Rueckert, R. R. (1986). *Use of monoclonal antibodies to identify four neutralization immunogens on a common cold picornavirus, human rhinovirus 14. J. Virol.* **57**, 246–257.

Sherry, B. & Rueckert, R. (1985). *Evidence for at least two dominant neutralization antigens on human rhinovirus 14. J. Virol.* **53**, 137–143.

Shi, D., Morizono, H., Ha, Y., Aoyagi, M., Tuchman, M. & Allewell, N. M. (1998). *1.85-Å resolution crystal structure of human ornithine transcarbamoylase complexed with N-phosphonacetyl-L-ornithine. Catalytic mechanism and correlation with inherited deficiency. J. Biol. Chem.* **273**, 34247–34254.

Shi, W., Li, C. M., Tyler, P. C., Furneaux, R. H., Cahill, S. M., Girvin, M. E., Grubmeyer, C., Schramm, V. L. & Almo, S. C. (1999). *The 2.0 Å structure of malarial purine phosphoribosyltransferase in complex with a transition-state analogue inhibitor. Biochemistry*, **38**, 9872–9880.

Shi, W., Schramm, V. L. & Almo, S. C. (1999). *Nucleoside hydrolase from Leishmania major. Cloning, expression, catalytic properties, transition state inhibitors, and the 2.5-Å crystal structure. J. Biol. Chem.* **274**, 21114–21120.

Shieh, H. S., Kurumbail, R. G., Stevens, A. M., Stegeman, R. A., Sturman, E. J., Pak, J. Y., Wittwer, A. J., Palmier, M. O., Wiegand, R. C., Holwerda, B. C. & Stallings, W. C. (1996). *Three-dimensional structure of human cytomegalovirus protease. Nature (London)*, **383**, 279–282.

Sielecki, A. R., Hayakawa, K., Fujinaga, M., Murphy, M. E. P., Fraser, M., Muir, A. K., Carilli, C. T., Lewicki, J. A., Baxter, J. D. & James, M. N. G. (1989). *Structure of recombinant human renin, a target for cardiovascular-active drugs, at 2.5-Å resolution. Science*, **243**, 1346–1351.

Silva, A. M., Lee, A. Y., Gulnik, S. V., Maier, P., Collins, J., Bhat, T. N., Collins, P. J., Cachau, R. E., Luker, K. E., Gluzman, I. Y., Francis, S. E., Oksman, A., Goldberg, D. E. & Erickson, J. W. (1996). *Structure and inhibition of plasmepsin II, a hemoglobin-degrading enzyme from Plasmodium falciparum. Proc. Natl Acad. Sci. USA*, **93**, 10034–10039.

Silvian, L. F., Wang, J. & Steitz, T. A. (1999). *Insights into editing from an ile-tRNA synthetase structure with tRNAile and mupirocin. Science*, **285**, 1074–1077.

Sinning, I., Kleywegt, G. J., Cowan, S. W., Reinemer, P., Dirr, H. W., Huber, R., Gilliland, G. L., Armstrong, R. N., Ji, X., Board, P. G., Olin, B., Mannervik, B. & Jones, T. A. (1993). *Structure determination and refinement of human alpha class glutathione transferase A1-1, and a comparison with the mu and pi class enzymes. J. Mol. Biol.* **232**, 192–212.

Sixma, T. K., Pronk, S. E., Kalk, K. H., Wartna, E. S., van Zanten, B. A. M., Witholt, B. & Hol, W. G. J. (1991). *Crystal structure of a cholera toxin-related heat-labile enterotoxin from E. coli. Nature (London)*, **351**, 371–377.

Skinner, R., Abrahams, J. P., Whisstock, J. C., Lesk, A. M., Carrell, R. W. & Wardell, M. R. (1997). *The 2.6 Å structure of antithrombin indicates a conformational change at the heparin binding site. J. Mol. Biol.* **266**, 601–609.

Skinner, R., Chang, W. S. W., Jin, L., Pei, X. Y., Huntington, J. A., Abrahams, J. P., Carrell, R. W. & Lomas, D. A. (1998). *Implications for function and therapy of a 2.9 Å structure of binary-complexed antithrombin. J. Mol. Biol.* **283**, 9–14.

Smith, A. D., Geisler, S. C., Chen, A. A., Resnick, D. A., Roy, B. M., Lewi, P. J., Arnold, E. & Arnold, G. F. (1998). *Human rhinovirus type 14:human immunodeficiency virus type 1 (HIV-1) V3 loop chimeras from a combinatorial library induce potent neutralizing antibody responses against HIV-1. J. Virol.* **72**, 651–659.

Somers, W., Ultsch, M., DeVos, A. M. & Kossiakoff, A. A. (1994). *The X-ray structure of a growth hormone–prolactin receptor complex. Nature (London)*, **372**, 478–481.

Song, L., Hobaugh, M. R., Shustak, C., Cheley, S., Bayley, H. & Gouaux, J. E. (1996). *Structure of staphylococcal alpha-hemolysin, a heptameric transmembrane pore. Science*, **274**, 1859–1866.

Souza, D. H., Garratt, R. C., Araujo, A. P., Guimaraes, B. G., Jesus, W. D., Michels, P. A., Hannaert, V. & Oliva, G. (1998). *Trypanosoma cruzi glycosomal glyceraldehyde-3-phosphate dehydrogenase: structure, catalytic mechanism and targeted inhibitor design. FEBS Lett.* **424**, 131–135.

Spraggon, G., Everse, S. J. & Doolittle, R. F. (1997). *Crystal structures of fragment D from human fibrinogen and its crosslinked counterpart from fibrin. Nature (London)*, **389**, 455–462.

Spraggon, G., Phillips, C., Nowak, U. K., Ponting, C. P., Saunders, D., Dobson, C. M., Stuart, D. I. & Jones, E. Y. (1995). *The crystal structure of the catalytic domain of human urokinase-type plasminogen activator. Structure*, **3**, 681–691.

Spurlino, J. C., Smallwood, A. M., Carlton, D. D., Banks, T. M., Vavra, K. J., Johnson, J. S., Cook, E. R., Falvo, J., Wahl, R. D., Pulvino, T. A., Wendoloski, J. J. & Smith, D. L. (1994). *1.56-Å structure of mature truncated human fibroblast collagenase. Proteins*, **19**, 98–109.

Stams, T., Spurlino, J. C., Smith, D. L., Wahl, R. C., Ho, T. F., Qoronfleh, M. H., Banks, T. M. & Rubin, B. (1994). *Structure of human neutrophil collagenase reveals large S1′ specificity pocket. Nature Struct. Biol.* **1**, 119–123.

Stein, P. E., Boodhoo, A., Armstrong, G. D., Cockle, S. A., Klein, M. H. & Read, R. J. (1994). *The crystal structure of pertussis toxin. Structure*, **2**, 45–57.

Stein, P. E., Boodhoo, A., Tyrrell, G. J., Brunton, J. L. & Read, R. J. (1992). *Crystal structure of the cell-binding B oligomer of verotoxin-1 from E. coli. Nature (London)*, **355**, 748–750.

Stewart, L., Redinbo, M. R., Qiu, X., Hol, W. G. J. & Champoux, J. J. (1998). *A model for the mechanism of human topoisomerase I. Science*, **279**, 1534–1541.

Stubbs, M. T., Laber, B., Bode, W., Huber, R., Jerala, R., Lenarcic, B. & Turk, V. (1990). *The refined 2.4 Å X-ray crystal structure of recombinant human stefin B in complex with the cysteine proteinase papain: a novel type of proteinase inhibitor interaction. EMBO J.* **9**, 1939–1947.

Stuckey, J. A., Schubert, H. L., Fauman, E. B., Zhang, Z. Y., Dixon, J. E. & Saper, M. A. (1994). *Crystal structure of Yersinia protein tyrosine phosphatase at 2.5 Å and the complex with tungstate. Nature (London)*, **370**, 571–575.

Sugio, S., Kashima, A., Mochizuki, S., Noda, M. & Kobayashi, K. (1999). *Crystal structure of human serum albumin at 2.5 Å resolution. Protein Eng.* **12**, 439–446.

Suguna, K., Bott, R. R., Padlan, E. A., Subramanian, E., Sheriff, S., Cohen, G. H. & Davies, D. R. (1987). *Structure and refinement at 1.8 Å resolution of the aspartic proteinase from Rhizopus chinensis. J. Mol. Biol.* **196**, 877–900.

Sundstrom, M., Hallen, D., Svensson, A., Schad, E., Dohlsten, M. & Abrahmsen, L. (1996). *The co-crystal structure of staphylococcal enterotoxin type A with Zn^{2+} at 2.7 Å resolution. Implications for major histocompatibility complex class II binding. J. Biol. Chem.* **271**, 32212–32216.

Symersky, J., Patti, J. M., Carson, M., House-Pompeo, K., Teale, M., Moore, D., Jin, L., Schneider, A., DeLucas, L. J., Hook, M. & Narayana, S. V. (1997). *Structure of the collagen-binding domain from a Staphylococcus aureus adhesin. Nature Struct. Biol.* **4**, 833–838.

Taylor, P., Page, A. P., Kontopidis, G., Husi, H. & Walkinshaw, M. D. (1998). *The X-ray structure of a divergent cyclophilin from the nematode parasite Brugia malayi. FEBS Lett.* **425**, 361–366.

Testa, B. (1994). *Drug metabolism*. In *Burger's Medicinal Chemistry and Drug Discovery*, 5th ed., edited by M. E. Wolf, Vol. 1. New York: John Wiley & Sons.

Tews, I., Perrakis, A., Oppenheim, A., Dauter, Z., Wilson, K. S. & Vorgias, C. E. (1996). *Bacterial chitobiase structure provides insight into catalytic mechanism and the basis of Tay–Sachs disease. Nature Struct. Biol.* **3**, 638–648.

Thayer, M. M., Flaherty, K. M. & McKay, D. B. (1991). *Three-dimensional structure of the elastase of Pseudomonas aeruginosa at 1.5-Å resolution. J. Biol. Chem.* **266**, 2864–2871.

Thieme, R., Pai, E. F., Schirmer, R. H. & Schulz, G. E. (1981). *Three-dimensional structure of glutathione reductase at 2 Å resolution. J. Mol. Biol.* **152**, 763–782.

Thompson, S. K., Halbert, S. M., Bossard, M. J., Tomaszek, T. A., Levy, M. A., Zhao, B., Smith, W. W., Abdel-Meguid, S. S., Janson, C. A., D'Alessio, K. J., McQueney, M. S., Amegadzie, B. Y., Hanning, C. R., DesJarlais, R. L., Briand, J., Sarkar, S. K., Huddleston, M. J., James, C. F., Carr, S. A., Garges, K. T., Shu, A., Heys, J. R., Bradbeer, J., Zembryki, D. & Veber, D. F. (1997). *Design of potent and selective*

human cathepsin K inhibitors that span the active site. Proc. Natl Acad. Sci. USA, **94**, 14249–14254.

Thylefors, B., Negrel, A. D., Pararajasegaram, R. & Dadzie, K. Y. (1995). *Global data on blindness. Bull. WHO*, **73**, 115–121.

Tiffany, K. A., Roberts, D. L., Wang, M., Paschke, R., Mohsen, A. W., Vockley, J. & Kim, J. J. (1997). *Structure of human isovaleryl-CoA dehydrogenase at 2.6 Å resolution: structural basis for substrate specificity. Biochemistry*, **36**, 8455–8464.

Toney, M. D., Hohenester, E., Cowan, S. W. & Jansonius, J. N. (1993). *Dialkylglycine decarboxylase structure: bifunctional active site and alkali metal sites. Science*, **261**, 756–759.

Tong, L., Pav, S., White, D. M., Rogers, S., Crane, K. M., Cywin, C. L., Brown, M. L. & Pargellis, C. A. (1997). *A highly specific inhibitor of human p38 MAP kinase binds in the ATP pocket. Nature Struct. Biol.* **4**, 311–316.

Tong, L., Qian, C., Massariol, M. J., Bonneau, P. R., Cordingley, M. G. & Lagace, L. (1996). *A new serine-protease fold revealed by the crystal structure of human cytomegalovirus protease. Nature (London)*, **383**, 272–275.

Tran, P. H., Korszun, Z. R., Cerritelli, S., Springhorn, S. S. & Lacks, S. A. (1998). *Crystal structure of the DpnM DNA adenine methyltransferase from the Dpnii restriction system of Streptococcus pneumoniae bound to S-adenosylmethionine. Structure*, **6**, 1563–1575.

Tskovsky, Y. V., Patskovska, L. N. & Listowsky, I. (1999). *Functions of His107 in the catalytic mechanism of human glutathione s-transferase hGSTM1a-1a. Biochemistry*, **38**, 1193–1202.

Turner, B. G. & Summers, M. F. (1999). *Structural biology of HIV. J. Mol. Biol.* **285**, 1–32.

Umland, T. C., Wingert, L. M., Swaminathan, S., Furey, W. F., Schmidt, J. J. & Sax, M. (1997). *Structure of the receptor binding fragment HC of tetanus neurotoxin. Nature Struct. Biol.* **4**, 788–792.

Van Duyne, G. D., Standaert, R. F., Karplus, P. A., Schreiber, S. L. & Clardy, J. (1991). *Atomic structure of FKBP-FK506, an immunophilin–immunosuppressant complex. Science*, **252**, 839–842.

Van Duyne, G. D., Standaert, R. F., Karplus, P. A., Schreiber, S. L. & Clardy, J. (1993). *Atomic structures of the human immunophilin FKBP-12 complexes with FK506 and rapamycin. J. Mol. Biol.* **229**, 105–124.

Van Duyne, G. D., Standaert, R. F., Schreiber, S. L. & Clardy, J. (1991). *Atomic structure of the rapamycin human immunophilin FKBP-12 complex. J. Am. Chem. Soc.* **113**, 7433–7434.

Varghese, J. N., Laver, W. G. & Colman, P. M. (1983). *Structure of the influenza virus glycoprotein antigen neuraminidase at 2.9 Å resolution. Nature (London)*, **303**, 35–40.

Varney, M. D., Palmer, C. L., Romines, W. H. R., Boritzki, T., Margosiak, S. A., Almassy, R., Janson, C. A., Bartlett, C., Howland, E. J. & Ferre, R. (1997). *Protein structure-based design, synthesis, and biological evaluation of 5-thia-2,6-diamino-4(3H)-oxopyrimidines: potent inhibitors of glycinamide ribonucleotide transformylase with potent cell growth inhibition. J. Med. Chem.* **40**, 2502–2524.

Vath, G. M., Earhart, C. A., Rago, J. V., Kim, M. H., Bohach, G. A., Schlievert, P. M. & Ohlendorf, D. H. (1997). *The structure of the superantigen exfoliative toxin A suggests a novel regulation as a serine protease. Biochemistry*, **36**, 1559–1566.

Veerapandian, P. (1997). Editor. *Structure-Based Drug Design.* New York: Marcel-Dekker.

Velanker, S. S., Ray, S. S., Gokhale, R. S., Suma, S., Balaram, P. & Murthy, M. R. (1997). *Triosephosphate isomerase from Plasmodium falciparum: the crystal structure provides insights into antimalarial drug design. Structure*, **5**, 751–761.

Vellieux, F. M., Hajdu, J., Verlinde, C. L., Groendijk, H., Read, R. J., Greenhough, T. J., Campbell, J. W., Kalk, K. H., Littlechild, J. A., Watson, H. C. & Hol, W. G. J. (1993). *Structure of glycosomal glyceraldehyde-3-phosphate dehydrogenase from Trypanosoma brucei determined from Laue data. Proc. Natl Acad. Sci. USA*, **90**, 2355–2359.

Verlinde, C. L. M. J. & Hol, W. G. J. (1994). *Structure-based drug design: progress, results and challenges. Structure*, **2**, 577–587.

Vigers, G. P., Anderson, L. J., Caffes, P. & Brandhuber, B. J. (1997). *Crystal structure of the type-I interleukin-1 receptor complexed with interleukin-1beta. Nature (London)*, **386**, 190–194.

Villeret, V., Tricot, C., Stalon, V. & Dideberg, O. (1995). *Crystal structure of Pseudomonas aeruginosa catabolic ornithine transcarbamoylase at 3.0-Å resolution: a different oligomeric organization in the transcarbamoylase family. Proc. Natl Acad. Sci. USA*, **92**, 10762–10766.

Vondrasek, J., van Buskirk, C. P. & Wlodawer, A. (1997). *Database of three-dimensional structure of HIV proteinases. Nature Struct. Biol.* **4**, 8.

Waksman, G., Shoelson, S. E., Pant, N., Cowburn, D. & Kuriyan, J. (1993). *Binding of a high affinity phosphotyrosyl peptide to the Src SH2 domain: crystal structures of the complexed and peptide-free forms. Cell*, **72**, 779–790.

Walker, N. P. C., Talanian, R. V., Brady, K. D., Dang, L. C., Bump, N. J., Ferenz, C. R., Franklin, S., Ghayur, T., Hackett, M. C., Hammill, L. D., Herzog, L., Hugunin, M., Houy, W., Mankovich, J. A., McGuiness, L., Orlewicz, E., Paskind, M., Pratt, C. A., Reis, P., Summani, A., Terranova, M. & Welch, J. P. (1994). *Crystal structure of the cysteine protease interleukin-1 beta-converting enzyme: a (p20/p10)2 homodimer. Cell*, **78**, 343–352.

Walsh, C. T., Fisher, S. L., Park, I. S., Prahalad, M. & Wu, Z. (1996). *Bacterial resistance to vancomycin: five genes and one missing hydrogen bond tell the story. Chem. Biol.* **3**, 21–28.

Walter, M. R., Windsor, W. T., Nagabhushan, T. L., Lundell, D. J., Lunn, C. A., Zauodny, P. J. & Narula, S. K. (1995). *Crystal structure of a complex between interferon-gamma and its soluble high-affinity receptor. Nature (London)*, **376**, 230–235.

Wang, A. H., Ughetto, G., Quigley, G. J. & Rich, A. (1987). *Interactions between an anthracycline antibiotic and DNA: molecular structure of daunomycin complexed to d(CpGpTpApCpG) at 1.2 Å resolution. Biochemistry*, **26**, 1152–1163.

Warner, P., Green, R. C., Gomes, B. & Strimpler, A. M. (1994). *Non-peptidic inhibitors of human leukocyte elastase. 1. The design and synthesis of pyridone-containing inhibitors. J. Med. Chem.* **37**, 3090–3099.

Watanabe, K., Hata, Y., Kizaki, H., Katsube, Y. & Suzuki, Y. (1997). *The refined crystal structure of Bacillus cereus oligo-1,6-glucosidase at 2.0 Å resolution: structural characterization of proline-substitution sites for protein thermostabilization. J. Mol. Biol.* **269**, 142–153.

Weber, P. C. & Czarniecki, M. (1997). *Structure-based design of thrombin inhibitors*. In *Structure-Based Drug Design*, edited by P. Veerapandian, pp. 247–264. New York: Marcel Dekker.

Wei, A. Z., Mayr, I. & Bode, W. (1988). *The refined 2.3-Å crystal structure of human leukocyte elastase in a complex with a valine chloromethyl ketone inhibitor. FEBS Lett.* **234**, 367–373.

Weissenhorn, W., Carfi, A., Lee, K. H., Skehel, J. J. & Wiley, D. C. (1998). *Crystal structure of the Ebola virus membrane fusion subunit, GP2, from the envelope glycoprotein ectodomain. Mol. Cell*, **2**, 605–616.

Wery, J. P., Schevitz, R. W., Clawson, D. K., Bobbitt, J. L., Dow, E. R., Gamboa, G., Goodson, T. J., Hermann, R. B., Kramer, R. M., McClure, D. B., Mihelich, E. D., Putnam, J. E., Sharp, J. D., Stark, D. H., Teater, C., Warrick, M. W. & Jones, N. D. (1991). *Structure of recombinant human rheumatoid arthritic synovial fluid phospholipase A2 at 2.2-Å resolution. Nature (London)*, **352**, 79–82.

Weston, S. A., Camble, R., Colls, J., Rosenbrock, G., Taylor, I., Egerton, M., Tucker, A. D., Tunnicliffe, A., Mistry, A., Macia, F., de La Fortelle, E., Irwin, J., Bricogne, G. & Pauptit, R. A. (1998). *Crystal structure of the anti-fungal target N-myristoyl transferase. Nature Struct. Biol.* **5**, 213–221.

Whitlow, M., Howard, A. J., Stewart, D., Hardman, K. D., Kuyper, L. F., Baccanari, D. P., Fling, M. E. & Tansik, R. L. (1997). *X-ray crystallographic studies of Candida albicans dihydrofolate reductase. High resolution structure of the holoenzyme and an inhibited ternary complex. J. Biol. Chem.* **272**, 30289–30298.

Whittingham, J. L., Edwards, D. J., Antson, A. A., Clarkson, J. M. & Dodson, G. G. (1998). *Interactions of phenol and m-cresol in the insulin hexamer, and their effect on the association properties of B28 pro Asp insulin analogues. Biochemistry*, **37**, 11516–11523.

Whittle, P. J. & Blundell, T. L. (1994). *Protein structure-based drug design. Annu. Rev. Biophys. Biomol. Struct.* **23**, 349–375.

Wierenga, R. K., Kalk, K. H. & Hol, W. G. J. (1987). *Structure determination of the glycosomal triosephosphate isomerase from Trypanosoma brucei brucei at 2.4 Å resolution. J. Mol. Biol.* **198**, 109–121.

Wild, K., Bohner, T., Aubry, A., Folkers, G. & Schulz, G. E. (1995). *The three-dimensional structure of thymidine kinase from herpes simplex virus type 1. FEBS Lett.* **368**, 289–292.

Williams, J. C., Zeelen, J. P., Neubauer, G., Vriend, G., Backmann, J., Michels, P. A., Lambeir, A. M. & Wierenga, R. K. (1999). *Structural and mutagenesis studies of leishmania triosephosphate isomerase: a point mutation can convert a mesophilic enzyme into a superstable enzyme without losing catalytic power. Protein Eng.* **12**, 243–250.

Williams, P. A., Cosme, J., Sridhar, V., Johnson, E. F. & McRee, D. E. (2000). *Mammalian microsomal cytochrome P450 monooxygenase:*

structural adaptations for membrane binding and functional diversity. Mol. Cell, **5**, 121–131.

Williams, S. P. & Sigler, P. B. (1998). *Atomic structure of progesterone complexed with its receptor. Nature (London)*, **393**, 392–396.

Wilson, D. K., Bohren, K. M., Gabbay, K. H. & Quiocho, F. A. (1992). *An unlikely sugar substrate site in the 1.65 Å structure of the human aldose reductase holoenzyme implicated in diabetic complications. Science*, **257**, 81–84.

Wilson, I. A., Skehel, J. J. & Wiley, D. C. (1981). *Structure of the haemagglutinin membrane glycoprotein of influenza virus at 3 Å resolution. Nature (London)*, **289**, 366–373.

Wilson, K. P., Fitzgibbon, M. J., Caron, P. R., Griffith, J. P., Chen, W., McCaffrey, P. G., Chambers, S. P. & Su, M. S. (1996). *Crystal structure of p38 mitogen-activated protein kinase. J. Biol. Chem.* **271**, 27696–27700.

Wireko, F. C. & Abraham, D. J. (1991). *X-ray diffraction study of the binding of the antisickling agent 12C79 to human hemoglobin. Proc. Natl Acad. Sci. USA*, **88**, 2209–2211.

Wlodawer, A., Miller, M., Jaskolski, M., Sathyanarayana, B. K., Baldwin, E., Weber, I. T., Selk, L. M., Clawson, L., Schneider, J. & Kent, S. B. (1989). *Conserved folding in retroviral proteases: crystal structure of a synthetic HIV-1 protease. Science*, **245**, 616–621.

Wlodawer, A. & Vondrasek, J. (1998). *Inhibitors of HIV-1 protease: a major success of structure-assisted drug design. Annu. Rev. Biophys. Biomol. Struct.* **27**, 249–284.

Wolf, E., Vassilev, A., Makino, Y., Sali, A., Nakatani, Y. & Burley, S. K. (1998). *Crystal structure of a GCN5-related N-acetyltransferase: Serratia marcescens aminoglycoside 3-N-acetyltransferase. Cell*, **94**, 439–449.

Worthylake, D. K., Wang, H., Yoo, S., Sundquist, W. I. & Hill, C. P. (1999). *Structures of the HIV-1 capsid protein dimerization domain at 2.6 Å resolution. Acta Cryst.* D**55**, 85–92.

Wynne, S. A., Crowther, R. A. & Leslie, A. G. (1999). *The crystal structure of the human hepatitis B virus capsid. Mol. Cell*, **3**, 771–780.

Xia, D., Henry, L. J., Gerard, R. D. & Deisenhofer, J. (1994). *Crystal structure of the receptor-binding domain of adenovirus type 5 fiber protein at 1.7 Å resolution. Structure*, **2**, 1259–1270.

Xie, X., Gu, Y., Fox, T., Coll, J. T., Fleming, M. A., Markland, W., Caron, P. R., Wilson, K. P. & Su, M. S. (1998). *Crystal structure of JNK3: a kinase implicated in neuronal apoptosis. Structure*, **6**, 983–991.

Xu, W., Harrison, S. C. & Eck, M. J. (1997). *Three-dimensional structure of the tyrosine kinase c-Src. Nature (London)*, **385**, 595–602.

Xue, Y., Bjorquist, P., Inghardt, T., Linschoten, M., Musil, D., Sjolin, L. & Deinum, J. (1998). *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. Structure*, **6**, 627–636.

Yan, Y., Li, Y., Munshi, S., Sardana, V., Cole, J. L., Sardana, M., Steinkuehler, C., Tomei, L., De Francesco, R., Kuo, L. C. & Chen, Z. (1998). *Complex of NS3 protease and NS4A peptide of BK strain hepatitis C virus: a 2.2 Å resolution structure in a hexagonal crystal form. Protein Sci.* **7**, 837–847.

Yang, J., Kloek, A. P., Goldberg, D. E. & Mathews, F. S. (1995). *The structure of Ascaris hemoglobin domain I at 2.2 Å resolution: molecular features of oxygen avidity. Proc. Natl Acad. Sci. USA*, **92**, 4224–4228.

Yang, X. & Moffat, K. (1995). *Insights into specificity of cleavage and mechanism of cell entry from the crystal structure of the highly specific Aspergillus ribotoxin, restrictocin. Structure*, **4**, 837–852.

Yao, N., Hesson, T., Cable, M., Hong, Z., Kwong, A. D., Le, H. V. & Weber, P. C. (1997). *Structure of the hepatitis C virus RNA helicase domain. Nature Struct. Biol.* **4**, 463–467.

Yee, V. C., Pedersen, L. C., LeTrong, I., Bishop, P. D., Stenkamp, R. E. & Teller, D. C. (1994). *Three-dimensional structure of a transglutaminase: human blood coagulation factor XIII. Proc. Natl Acad. Sci. USA*, **91**, 7296–7300.

Yeh, J. I., Claiborne, A. & Hol, W. G. J. (1996). *Structure of the native cystein-sulfenic acid redox center of enterococcal NADH peroxidase refined at 2.8 Å resolution. Biochemistry*, **35**, 9951–9957.

Yoshimoto, T., Kabashima, T., Uchikawa, K., Inoue, T., Tanaka, N., Nakamura, K. T., Tsuru, M. & Ito, K. (1999). *Crystal structure of prolyl aminopeptidase from Serratia marcescens. J. Biochem. (Tokyo)*, **126**, 559–565.

Zaitseva, I., Zaitsev, V., Card, G., Moshkov, K., Bax, B., Ralph, A. & Lindley, P. (1996). *The X-ray structure of human serum ceruloplasmin at 3.1 Å: nature of the copper centres. J. Biol. Inorg. Chem.* **1**, 15–23.

Zdanov, A., Schalk-Hihi, C., Menon, S., Moore, K. W. & Wlodawer, A. (1997). *Crystal structure of Epstein–Barr virus protein BCRF1, a homolog of cellular interleukin-10. J. Mol. Biol.* **268**, 460–467.

Zhang, A., Geisler, S. C., Smith, A. D., Resnick, D. A., Li, M. L., Wang, C. Y., Looney, D. J., Wong-Staal, F., Arnold, E. & Arnold, G. F. (1999). *A disulfide-bound HIV-1 V3 loop sequence on the surface of human rhinovirus 14 induces neutralizing responses against HIV-1. J. Biol. Chem.* **380**, 365–374.

Zhang, H., Gao, Y. G., van der Marel, G. A., van Boom, J. H. & Wang, A. H. (1993). *Simultaneous incorporations of two anticancer drugs into DNA. The structures of formaldehyde-cross-linked adducts of daunorubicin-d(CG(araC)GCG) and doxorubicin-d(CA(araC)GTG) complexes at high resolution. J. Biol. Chem.* **268**, 10095–10101.

Zhang, R., Evans, G., Rotella, F. J., Westbrook, E. M., Beno, D., Huberman, E., Joachimiak, A. & Collart, F. R. (1999). *Characteristics and crystal structure of bacterial inosine-5′-monophosphate dehydrogenase. Biochemistry*, **38**, 4691–4700.

Zhang, R. G., Scott, D. L., Westbrook, M. L., Nance, S., Spangler, B. D., Shipley, G. G. & Westbrook, E. M. (1995). *The three-dimensional crystal structure of cholera toxin. J. Mol. Biol.* **251**, 563–573.

Zhang, X., Morera, S., Bates, P. A., Whitehead, P. C., Coffer, A. I., Hainbucher, K., Nash, R. A., Sternberg, M. J., Lindahl, T. & Freemont, P. S. (1998). *Structure of an XRCC1 BRCT domain: a new protein–protein interaction module. EMBO J.* **17**, 6404–6411.

Zhu, X., Kim, J. L., Newcomb, J. R., Rose, P. E., Stover, D. R., Toledo, L. M., Zhao, H. & Morgenstern, K. A. (1999). *Structural analysis of the lymphocyte-specific kinase Lck in complex with non-selective and Src family selective kinase inhibitors. Struct. Fold. Des.* **7**, 651–661.

Zuccola, H. J., Rozzelle, J. E., Lemon, S. M., Erickson, B. W. & Hogle, J. M. (1998). *Structural basis of the oligomerization of hepatitis delta antigen. Structure*, **6**, 821–830.