Teil V

Literaturverzeichnis

Literaturverzeichnis

[1] J. Wilcox, K. Smith, S. Schwartz, D. Gordon. Localization of tissue factor in the normal vessel wall and in the atherosclerotic plaque. *Proc Natl Acad Sci USA* 86: 2839–2843, 1989.

[2] V. Bom, R. Bertina. The contribution of Ca^{2+}, phospholipids and tissue factor apoprotein to the activation of human blood–coagulation factor X by activated factor VII. *Biochem J* 265: 327–336, 1990.

[3] T. Nakagaki, D. Foster, K. Berkner, W. Kisiel. Initiation of the extrinsic pathway of blood coagulation: evidence for the tissue factor dependent autoactivation of human coagulation factor VII. *Biochemistry* 30: 10819–10824, 1991.

[4] P. Neuenschwander, M. Fiore, J. Morrissey. Factor VII autoactivation proceeds via interaction of distinct protease–cofactor and zymogen–cofactor complexes. Implications of a two–dimensional enzyme kinetic mechanism. *J Biol Chem* 268: 21489–21492, 1993.

[5] E. Davie, K. Fujikawa, W. Kisiel. The coagulation cascade: initiation, maintenance, and regulation. *Biochemistry* 30: 10363–10370, 1991.

[6] W. Ruf, T. Edgington. Structural biology of tissue factor, the initiator of thromobogenesis in vivo. *FASEB J* 8: 385–390, 1994.

[7] J. Morrissey, H. Fakhrai, T. Edgington. Molecular cloning of the cDNA for tissue factor, the cellular receptor for the initiation of the coagulation protease cascade. *Cell* 50: 129–135, 1987.

[8] E. Scarpati, D. Wen, G. Broze, J. Miletich, R. Flandermayer, N. Siegel, J. Sadler. Human tissue factor: cDNA sequence and chromosome localization of the gene. *Biochemistry* 26: 5234–5238, 1987.

[9] E. K. Spicer, R. Horton, L. Bloem, R. Bach, K. R. Williams, A. Guha, J. Kraus, T. C. Lin, Y. Nemerson, W. H. Konigsberg. Isolation of cDNA clones coding for human tissue factor: primary structure of the protein and cDNA. *Proc Natl Acad Sci USA* 84: 5148–5152, 1987.

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

[11] J. F. Bazan. Structural design and molecular evolution of a cytokine receptor superfamily. *Proc Natl Acad Sci USA* 87: 6934–6938, 1990.

[12] Y. A. Muller, M. H. Ultsch, A. M. de Vos. The crystal structure of the extracellular domain of human tissue factor refined to 1.7 Å resolution. *J Mol Biol* 256: 144–159, 1996.

[13] J. A. Rottingen, T. Enden, E. Camerer, J. G. Iversen, H. Prydz. Binding of human factor VIIa to tissue factor induces cytosolic Ca^{2+} signals in J82 cells, transfected COS-1 cells, Madin-Darby canine kidney cells and in human endothelial cells induced to synthesize tissue factor. *J Biol Chem* 270: 4650–4660, 1995.

[14] M. E. Bromberg, W. H. Konigsberg, J. F. Madison, A. Pawashe, A. Garen. Tissue factor promotes melanoma metastasis by a pathway independent of blood coagulation. *Proc Natl Acad Sci USA* 92: 8205–8209, 1995.

[15] M. E. Bromberg, R. Sundaram, R. J. Homer, A. Garen, W. H. Konigsberg. Role of tissue factor in metastasis: functions of the cytoplasmic and extracellular domains of the molecule. *Thromb Haemost* 82: 88–92, 1999.

[16] K. Abe, M. Shoji, J. Chen, A. Bierhaus, I. Danave, C. Micko, K. Casper, D. L. Dillehay, P. P. Nawroth, F. R. Rickles. Regulation of vascular endothelial growth factor production and angiogenesis by the cytoplasmic tail of tissue factor. *Proc Natl Acad Sci USA* 96: 8663–8668, 1999.

[17] J. J. Badimon, M. Lettino, V. Toschi, V. Fuster, M. Berrozpe, J. H. Chesebro, L. Badimon. Local inhibition of tissue factor reduces the thrombogenicity of disrupted human atherosclerotic plaques: effects of tissue factor pathway inhibitor on plaque thrombogenicity under flow conditions. *Circulation* 99: 1780–1787, 1999.

[18] D. Kirchhofer, P. Moran, N. Chiang, J. Kim, M. A. Riederer, C. Eigenbrot, R. F. Kelley. Epitope location on tissue factor determines the anticoagulant potency of monoclonal anti-tissue factor antibodies. *Thromb Haemost* 84: 1072–1081, 2000.

[19] W. Ruf, T. S. Edgington. An anti-tissue factor monoclonal antibody which inhibits TF·VIIa complex is a potent anticoagulant in plasma. *Thromb Haemost* 66: 529–533, 1991.

[20] W. Ruf, A. Rehemtulla, T. S. Edgington. Antibody mapping of tissue factor implicates two different exon-encoded regions in function. *Biochem J* 278: 729–733, 1991.

[21] M. Huang, R. Syed, E. A. Stura, M. J. Stone, R. S. Stefanko, W. Ruf, T. S. Edgington, I. A. Wilson. The mechanism of an inhibitory antibody on TF–initiated blood coagulation revealed by the crystal structures of human tissue factor, Fab 5G9 and TF·5G9 complex. *J Mol Biol* 275: 873–894, 1998.

[22] D. Kirchhofer, M. T. Lipari, P. Moran, C. Eigenbrot, R. F. Kelley. The tissue factor region that interacts with substrates factor IX and Factor X. *Biochemistry* 39: 7380–7387, 2000.

[23] S. Roy, P. E. Hass, J. H. Bourell, W. J. Henzel, G. A. Vehar. Lysine residues 165 and 166 are essential for the cofactor function of tissue factor. *J Biol Chem* 266: 22063–22066, 1991.

[24] W. Ruf, D. J. Miles, A. Rehemtulla, T. S. Edgington. Cofactor residues lysine 165 and 166 are critical for protein substrate recognition by the tissue factor–factor VIIa protease complex. *J Biol Chem* 267: 6375–6381, 1992.

[25] D. Kirchhofer, C. Eigenbrot, M. T. Lipari, P. Moran, M. Peek, R. F. Kelley. The tissue factor region that interacts with factor Xa in the activation of factor VII. *Biochemistry* 40: 675–682, 2001.

[26] S. Dittmar, W. Ruf, T. S. Edgington. Influence of mutations in tissue factor on the fine specificity of macromolecular substrate activation. *Biochem J* 321: 787–793, 1997.

[27] L. Presta, P. Sims, Y. G. Meng, P. Moran, S. Bullens, S. Bunting, J. Schoenfeld, D. Lowe, J. Lai, P. Rancatore, M. Iverson, A. Lim, V. Chisholm, R. F. Kelley, M. Riederer, D. Kirchhofer. Generation of a humanized, high affinity anti–tissue

factor antibody for use as a novel antithrombotic therapeutic. *Thromb Haemost* 85: 379–389, 2001.

[28] C. Chothia, A. Lesk. Canonical structures for the hypervariable regions of immunoglobulins. *J Mol Biol* 196: 901–917, 1987.

[29] L. Riechmann, M. Clark, H. Waldmann, G. Winter. Reshaping human antibodies for therapy. *Nature* 332: 323–327, 1988.

[30] C. Kettleborough, J. Saldanha, V. Heath, C. Morrison, M. Bendig. Humanization of a mouse monoclonal antibody by CDR–grafting: the importance of framework residues on loop conformation. *Prot Engineer* 4: 773–783, 1991.

[31] G. Studnicka, S. Soares, M. Better, R. Williams, R. Nadell, A. Horwitz. Human–engineered monoclonal antibodies retain full specific binding activity by preserving non–CDR complementarity–modulating residues. *Prot Engineer* 7: 805–814, 1994.

[32] A. Tramontano, C. Chothia, A. M. Lesk. Framework residue 71 is a major determinant of the position and conformation of the second hypervariable region in the VH domains of immunoglobulins. *J Mol Biol* 215: 175–182, 1990.

[33] J. Xiang, Y. Sha, Z. Jia, L. Prasad, L. T. Delbaere. Framework residues 71 and 93 of the chimeric B72.3 antibody are major determinants of the conformation of heavy-chain hypervariable loops. *J Mol Biol* 253: 385–390, 1995.

[34] P. Carter, L. Presta, C. M. Gorman, J. B. Ridgway, D. Henner, W. L. Wong, A. M. Rowland, C. Kotts, M. E. Carver, H. M. Shepard. Humanization of an anti–p185HER2 antibody for human cancer therapy. *Proc Natl Acad Sci USA* 89: 4285–4289, 1992.

[35] L. G. Presta, H. Chen, S. J. O'Connor, V. Chisholm, Y. G. Meng, L. Krummen, M. Winkler, N. Ferrara. Humanization of an anti–vascular endothelial growth factor monoclonal antibody for the therapy of solid tumors and other disorders. *Cancer Res* 57: 4593–4599, 1997.

[36] M. Banfield, D. King, A. Mountain, R. Brady. VL:VH domain rotations in engineered antibodies: crystal structures of the Fab fragments from two murine antitumor antibodies and their engineered human constructs. *Proteins* 29: 161–171, 1997.

[37] I. A. Wilson, R. L. Stanfield. Antibody–antigen interactions: new structures and new conformational changes. *Curr Op Struct Biol* 4: 857–867, 1994.

[38] D. R. Davies, G. H. Cohen. Interactions of protein antigens with antibodies. *Proc Natl Acad Sci USA* 93: 7–12, 1996.

[39] L. L. Conte, C. Chothia, J. Janin. The atomic structure of protein–protein recognition sites. *J Mol Biol* 285: 2177–2198, 1999.

[40] S. Jones, J. M. Thornton. Principles of protein–protein interactions. *Proc Natl Acad Sci USA* 93: 13–20, 1996.

[41] S. E. Mylvaganam, Y. Paterson, E. D. Getzoff. Structural basis for the binding of an anti–cytochrome c antibody to its antigen: crystal structures of FabE8–cytochrome c complex to 1.8 Å resolution and FabE8 to 2.26 Å resolution. *J Mol Biol* 281: 301–322, 1998.

[42] Y. Li, H. Li, S. J. Smith-Gill, R. A. Mariuzza. Three–dimensional structures of the free and antigen–bound Fab from monoclonal antilysozyme antibody HyHEL–63. *Biochemistry* 39: 6296–6309, 2000.

[43] M. M. Fiore, P. F. Neuenschwander, J. H. Morrissey. An unusual antibody that blocks tissue factor/factor VIIa function by inhibiting cleavage only of macromolecular substrates. *Blood* 80: 3127–3134, 1992.

[44] L. R. Paborsky, B. M. Fendly, K. L. Fisher, R. M. Lawn, B. J. Marks, G. McCray, K. M. Tate, G. A. Vehar, C. M. Gorman. Mammalian cell transient expression of tissue factor for the production of antigen. *Prot Engineer* 3: 547–553, 1990.

[45] S. Gill, P. von Hippel. Calculation of the protein extinction coefficients from amino acid sequence data. *Anal Biochem* 182: 319–326, 1989.

[46] U. Laemmli. Cleavage of structural proteins during the assembly of the head of bacteriophage T4. *Nature* 227: 680–685, 1970.

[47] Y. A. Muller, M. H. Ultsch, R. F. Kelley, A. M. de Vos. Structure of the extracellular domain of human tissue factor: Location of the factor VIIa binding site. *Biochemistry* 33: 10864–10870, 1994.

[48] L. R. Paborsky, K. M. Tate, R. J. Harris, D. G. Yansura, L. Band, G. McCray, C. M. Gorman, D. P. O'Brien, J. Y. Chang, J. R. Swartz, V. Fung, J. Thomas,

G. Vehar. Purification of recombinant human tissue factor. *Biochemistry* 28: 8072–8077, 1989.

[49] Z. M. Mackinnon, R. EMBL Nucleotide Sequence Database. *Nucleic Acids Res* 29: 17–21, 2001.

[50] G. Jacobs, P. Stockwell, M. Schrieber, W. Tate, C. Brown. Transterm: A database of messenger RNA components and signals. *Nuc Acids Res* 28: 293–295, 2000.

[51] A. Ducruix, R. Giege. Crystallization of nucleic acids and proteins. A practical approach. Oxford University Press, 1992.

[52] J. Jancarik, S. Kim. Sparse matrix sampling: a screening method for crystallization of proteins .

[53] R. Cudney, S. Patel, K. Weisgraber, Y. Newhouse, A. McPherson. Screening and optimization strategies for macromolecular crystal growth. *Acta Crystallogr* D50: 414–423, 1994.

[54] R. Sousa. Use of glycerol, polyols and other protein structure stabilizing agents in protein crystallization. *Acta Crystallogr* D51: 271–277, 1995.

[55] S. Trakhanov, F. Quiocho. Influence of divalent cations on protein crystallization. *Protein Sci* 4: 1914–1919, 1995.

[56] H. Michel. Crystallization of Membrane Proteins. CRC Press, Boston, 1991.

[57] A. Riboldi-Tunicliffe, R. Hilgenfeld. Cryocrystallography with oil — an old idea revisited. *J Appl Crystallogr* 32: 1003–1005, 1999.

[58] J. Drenth. Principles of protein X–ray crystallography. Springer Verlag, New York, 1999.

[59] M. Rossmann, D. Blow. The detection of sub–units within the crystallographic asymmetric unit. *Acta Crystallogr* 15: 24–31, 1962.

[60] CCP4. The CCP4 suite: programs for protein crystallography. *Acta Crystallogr* 760–763, 1994.

[61] J. Navaza, E. Vernoslova. On the fast translation function for molecular replacement. *Acta Crystallogr* 445–449, 1995.

[62] A. Wilson. *Acta Cryst* 3: 397–398.

[63] G. Stout, L. Jensen. X-ray structure determination. A practical guide. Macmillan Company, New York, 1968.

[64] R. Engh, R. Huber. Accurate bond and angle parameters for X–ray protein structure refinement. *Acta Crystallogr* 392–400, 1991.

[65] R. J. Read. Improved Fourier coefficients for maps using partial structures with errors. *Acta Crystallogr* 140–149, 1986.

[66] R. Read. Structure–factor probabilities for related structures. *Acta Crystallogr* 900–912, 1990.

[67] Z. Otwinowski, W. Minor. Processing of X–ray diffraction data collected in oscillation mode. *Methods in Enzymology* 276: 307–326, 1997.

[68] W. Kabsch. Evaluation of single crystal X–ray diffraction data from a position sensitive detector. *J Appl Crystallogr* 21: 916–924, 1988.

[69] R. Ravelli, R. Sweet, J. Skinner, A. Duisenberg, J. Kroon. STRATEGY: a program to optimize the starting spindle angle and scan range for X–ray data collection. *J Appl Crystallogr* 30: 551–554, 1997.

[70] A. T. Brunger, P. D. Adams, G. M. Clore, W. L. DeLano, P. Gros, R. W. Grosse-Kunstleve, J. S. Jiang, J. Kuszewski, M. Nilges, N. S. Pannu, R. J. Read, L. M. Rice, T. Simonson, G. L. Warren. Crystallography & NMR system: a new software suite for macromolecular structure determination. *Acta Crystallogr* 905–921, 1998.

[71] T. A. Jones, J. Zou, S. W. Cowan, M. Kjeldgaard. Improved methods for building protein models in electron density maps and the location of errors in these models. *Acta Crystallogr* 110–119, 1991.

[72] R. A. Laskowski, M. W. MacArthur, D. S. Moss, J. M. Thornton. PROCHECK: a program to check the stereochemical quality of protein structures. *J Appl Crystallogr* 26: 283–291, 1993.

[73] G. Vriend. WHAT IF: A molecular modeling and drug design program. *J Mol Graph* 8: 52–56, 1990.

[74] E. A. Kabat, T. T. Wu, M. Redi-Miller, H. M. Perry, K. S. Gottesman. Sequences of proteins of immunological interest, 4th edition. National Institute of Health, Bethesda, Maryland, 1987.

[75] K. Diederichs. Structural superposition of proteins with unknown alignment and detection of topological similarity using a six–dimensional search algorithm. *Proteins* 23: 187–195, 1995.

[76] B. Lee, F. Richards. The interpretation of protein structures: estimation of static accessibility. *J Mol Biol* 55: 379–400, 1971.

[77] D. A. Case, M. Karplus. Dynamics of ligand binding to heme proteins. *J Mol Biol* 132: 343–368, 1979.

[78] H. M. Berman, J. Westbrook, Z. Feng, G. Gilliland, T. N. Bhat, H. Weissig, I. N. Shindyalov, P. E. Bourne. The protein data bank. *Nucleic Acids Res* 28: 235–242., 2000.

[79] UCLA Workshop. 1993.

[80] L. Z. Song, J. E. Gouaux. Membrane protein crystallization: application of sparse matrices to the alpha–hemolysin heptamer. *Methods Enzymol* 60–74, 1997.

[81] C. Ostermeier, H. Michel. Crystallization of membrane proteins. *Curr Op Struct Biol* 7: 697–701, 1997.

[82] J. Rosenbusch. The critical role of detergents in the crystallization of membrane proteins. *J Struct Biol* 104: 134–138, 1990.

[83] R. M. Garavito, D. Picot, P. J. Loll. Strategies for crystallizing membrane proteins. *J Bioenerg Biomembr* 28: 13–27, 1996.

[84] E. Pebay-Peyroula, G. Rummel, J. Rosenbusch, E. Landau. X–ray structure of bacteriorhodopsin at 2.5 Å resolution from microcrystals grown in lipidic cubic phases. *Science* 277: 1676–1681, 1997.

[85] H. Luecke, B. Schobert, H. Richter, J. Cartailler, K. Lanyi. Structure of bacteriorhodopsin at 1.55 Å resolution. *J Mol Biol* 291: 899–911, 1999.

[86] E. M. Landau, J. P. Rosenbusch. Lipidic cubic phases: a novel concept for the crystallization of membrane proteins. *Proc Natl Acad Sci USA* 93: 14532–14535, 1996.

[87] G. Rummel, A. Hardmeyer, C. Widmer, M. L. Chiu, P. Nollert, K. P. Locher, I. Pedruzzi, E. M. Landau, J. P. Rosenbusch. Lipidic cubic phases: new matrices for the three–dimensional crystallization of membrane proteins. *J Struct Biol* 121: 82–91, 1998.

[88] E. Gouaux. It's not just a phase: crystallization and X–ray structure determination of bacteriorhodopsin in lipidic cubic phases. *Structure* 6: 5–10, 1998.

[89] A. Ferguson, E. Hofmann, J. Coulton, K. Diedrichs, W. Welte. Siderophore–mediated iron transport: crystal structure of FhuA with bound lipopolysaccharide. *Science* 282: 2215–2220, 1998.

[90] G. Ramachandran, V. Sasisekharan. Conformation of polypeptides and proteins. *Adv Protein Chem* 23: 283.

[91] S. Chacko, E. W. Silverton, S. J. Smith-Gill, D. R. Davies, K. A. Shick, K. A. Xavier, R. C. Willson, P. D. Jeffrey, C. Y. Chang, L. C. Sieker, S. Sheriff. Refined structures of bobwhite quail lysozyme uncomplexed and complexed with the HyHEL–5 Fab fragment. *Proteins* 26: 55–65, 1996.

[92] Y. A. Muller, Y. Chen, H. W. Christinger, B. Li, B. C. Cunningham, H. B. Lowman, A. M. de Vos. VEGF and the Fab fragment of a humanized neutralizing antibody: crystal structure of the complex at 2.4 Å resolution and mutational analysis of the interface. *Structure* 6: 1153–1167, 1998.

[93] E. G. Hutchinson, J. M. Thornton. A revised set of potentials for beta-turn formation in proteins. *Protein Sci* 3: 2207–2216, 1994.

[94] B. C. Braden, H. Souchon, J. L. Eisele, G. A. Bentley, T. N. Bhat, J. Navaza, R. J. Poljak. Three–dimensional structures of the free and the antigen–complexed Fab from monoclonal anti–lysozyme antibody D44.1. *J Mol Biol* 243: 767–781, 1994.

[95] K. Harlos, D. M. A. Martin, D. P. O'Brien, E. Y. Jones, D. I. Stuart, I. Polikarpov, A. Miller, E. G. D. Tuddenham, C. W. G. Boys. Crystal structure of the extracellular region of human tissue factor. *Nature* 370: 662–666, 1994.

[96] S. Morrison, M. Johnson, L. Herzenberg, V. Oi. Chimeric human antibody molecules: mouse antigen–binding domains with human constant region domain. *Proc Acad Natl Sci USA* 81: 6851–6855, 1984.

[97] G. Boulianne, N. Hozumi, M. Shulman. Production of functional chimaeric mouse/human antibody. *Nature* 312: 643–646, 1984.

[98] M. Roguska, J. Pedersen, C. Keddy, A. Henry, S. Searle, J. Lambert, V. Goldmacher, W. Blättler, A. Rees, B. Guild. Humanization of murine monoclonal antibodies through variable domain resurfacing. *Proc Natl Acad Sci USA* 91: 969–973, 1994.

[99] P. Jones, P. Dear, J. Foote, M. Neuberger, G. Winter. Replacing the complementarity–determining regions in a human antibody with those from a mouse. *Nature* 321: 522–525, 1986.

[100] M. Verhoyen, C. Milstein, G. Winter. Reshaping human antibodies: grafting an antilysozyme activity. *Science* 239: 1534–1536, 1988.

[101] J. Foote, G. Winter. Antibody framework residues affecting the conformation of the hypervariable loops. *J Mol Biol* 224: 487–499, 1992.

[102] S. Gorman, M. Clark, E. Routledge, S. Cobbold, H. Waldmann. Reshaping a therapeutic CD4 antibody. *Proc Natl Acad Sci USA* 88: 4181–4185, 1991.

[103] W. Werther, T. Gonzalez, S. O'Connor, S. McCabe, B. Chan, T. Hotaling, M. Champe, J. Fox, P. Jardieu, P. Berman, L. Presta. Humanization of an anti–lymphocyte function–associated antigen (LFA–1) monoclonal antibody and reengineering of the humanized antibody for binding rhesus LFA–1. *J Immunol* 157: 4986–4995, 1996.

[104] L. Presta, S. Lahr, R. Shields, J. Porter, C. Gorman, B. Fendley, P. Jardieu. Humanization of an antibody directed against IgE. *J Immunol* 151: 2623–2632, 1993.

[105] C. Eigenbrot, T. Gonzalez, J. Mayeda, P. Carter, W. Werther, T. Hotaling, J. Fox, J. Kessler. X–ray structures of fragments from binding and nonbinding versions of a humanized anti–CD18 antibody: structural indications of the key role of VH residues 59 to 65. *Proteins* 18: 49–62, 1994.

[106] C. Eigenbrot, M. Randal, L. Presta, P. Carter, A. A. Kossiakoff. X–ray structures of the antigen–binding domains from three variants of humanized anti–p185HER2 antibody 4D5 and comparison with molecular modeling. *J Mol Biol* 229: 969–995, 1993.

[107] P. M. Alzari, M. B. Lascombe, R. J. Poljak. Three–dimensional structure of antibodies. *Annu Rev Immunol* 6: 555–580, 1988.

[108] A. F. Williams, A. N. Barclay. The immunoglobulin superfamily–domains for cell surface recognition. *Annu Rev Immunol* 6: 381–405, 1988.

[109] C. Chothia, E. Y. Jones. The molecular structure of cell adhesion molecules. *Annu Rev Biochem* 66: 823–862, 1997. Using Smart Source Parsing.

[110] P. Luzzati. Traitement statistique des erreurs dans la determination des structures cristallines. *Acta Crystallogr* 5: 802–810, 1952.

[111] Y. A. Muller, R. F. Kelley, A. M. de Vos. Hinge bending within the cytokine receptor superfamily revealed by the 2.4 Å crystal structure of the extracellular domain of rabbit tissue factor. *Protein Sci* 7: 1106–1115, 1998.

[112] R. L. Stanfield, M. Takimoto-Kamimura, J. M. Rini, A. T. Profy, I. A. Wilson. Major antigen–induced domain rearrangements in an antibody. *Structure* 1: 83–93, 1993.

[113] I. A. Wilson, R. L. Stanfield. Antibody–antigen interactions. *Curr Op Struct Biol* 3: 113–118, 1993.

[114] T. Steiner, G. Koellner. Hydrogen bonds with π–acceptors in proteins: frequencies and role in stabilizing local 3D structures. *J Mol Biol* 305: 535–557, 2001.

[115] T. Clackson, J. A. Wells. A hot spot of binding energy in a hormone-receptor interface. *Science* 267: 383–386, 1995.

[116] T. N. Bhat, G. A. Bentley, G. Boulot, M. I. Greene, D. Tello, W. Dall'Acqua, H. Souchon, F. P. Schwarz, R. A. Mariuzza, R. J. Poljak. Bound water molecules and conformational stabilization help mediate an antigen–antibody association. *Proc Natl Acad Sci USA* 91: 1089–1093, 1994.

[117] K. Huang, W. Lu, S. Anderson, J. Laskowski, M., M. N. James. Water molecules participate in proteinase–inhibitor interactions: crystal structures of Leu18, Ala18, and Gly18 variants of turkey ovomucoid inhibitor third domain complexed with *Streptomyces griseus* proteinase B. *Protein Sci* 4: 1985–1997, 1995.

[118] D. G. Covell, A. Wallqvist. Analysis of protein–protein interactions and the effects of amino acid mutations on their energetics. The importance of water molecules in the binding epitope. *J Mol Biol* 269: 281–297, 1997.

[119] T. N. Bhat, G. A. Bentley, T. O. Fischmann, G. Boulot, R. J. Poljak. Small rearrangements in structures of Fv and Fab fragments of antibody D1.3 on antigen binding. *Nature* 347: 483–485, 1990.

[120] B. C. Braden, E. R. Goldman, R. A. Mariuzza, R. J. Poljak. Anatomy of an antibody molecule: structure, kinetics, thermodynamics and mutational studies of the antilysozyme antibody D1.3. *Immunol Rev* 163: 45–57, 1998.

[121] W. Dall'Acqua, E. R. Goldman, W. Lin, C. Teng, D. Tsuchiya, H. Li, X. Ysern, B. C. Braden, Y. Li, S. J. Smith-Gill, R. A. Mariuzza. A mutational analysis of binding interactions in an antigen–antibody protein–protein complex. *Biochemistry* 37: 7981–7991, 1998.

[122] L. Prasad, E. B. Waygood, J. S. Lee, L. T. Delbaere. The 2.5 Å resolution structure of the Jel42 Fab fragment/HPr complex. *J Mol Biol* 280: 829–845, 1998.

[123] R. F. Kelley, K. E. Costas, M. P. O'Connell, R. A. Lazarus. Analysis of the factor VIIa binding site on human tissue factor: effects of tissue factor mutations on the kinetics and thermodynamics of binding. *Biochemistry* 34: 10383–10392, 1995.

[124] T. Hage, W. Sebald, P. Reinemer. Crystal structure of the interleukin-4/receptor alpha chain complex reveals a mosaic binding interface. *Cell* 97: 271–281, 1999.

[125] E. A. Padlan. On the nature of antibody combining sites: unusual structural features that may confer on these sites an enhanced capacity for binding ligands. *Proteins* 7: 112–124, 1990.

[126] I. S. Mian, A. R. Bradwell, A. J. Olson. Structure, function and properties of antibody binding sites. *J Mol Biol* 217: 133–151, 1991.

[127] F. A. Goldbaum, F. P. Schwarz, E. Eisenstein, A. Cauerhff, R. A. Mariuzza, R. J. Poljak. The effect of water activity on the association constant and the enthalpy of reaction between lysozyme and the specific antibodies D1.3 and D44.1. *J Mol Recognit* 9: 6–12, 1996.

[128] P. Y. S. Lam, P. K. Jadhav, C. J. Eyermann, C. N. Hodge, Y. Ru, L. T. Bacheler, J. L. Meek, M. J. Otto, M. M. Rayner, Y. N. Wong, C. Chang, P. Weber,

D. Jackson, T. Sharpe, S. Erickson-Vitanen. Rational design of potent, bioavailable, nonpeptide cyclic ureas as HIV protease inhibitors. *Science* 263: 380–384, 1994.

[129] Y. Chen, C. Wiesmann, G. Fuh, B. Li, H. W. Christinger, P. McKay, A. M. de Vos, H. B. Lowman. Selection and analysis of an optimized anti–VEGF antibody: crystal structure of an affinity–matured Fab in complex with antigen. *J Mol Biol* 293: 865–881, 1999.