

VII

Bibliografia

Abdulaev NG. Building a stage for interhelical play in rhodopsin. *Trends Biochem Sci.* 2003; 28:399-402.

abu Alla S, Quitterer U, Grigoriev S, Maidhof A, Haasemann M, Jarnagin K, Muller-Esterl W. Extracellular domains of the bradykinin B2 receptor involved in ligand binding and agonist sensing defined by anti-peptide antibodies. *J Biol Chem.* 1996; 271:1748-55.

Acharya S, Saad Y, Karnik SS. Transducin-alpha C-terminal peptide binding site consists of C-D and E-F loops of rhodopsin. *J Biol Chem.* 1997; 272: 6519-24.

Albeck A, Friedman N, Ottolenghi M, Sheves M, Einterz CM, Hug SJ, Lewis JW, Klier DS. Photolysis intermediates of the artificial visual pigment cis-5,6- dihydro-isorhodopsin. *Biophys J.* 1989; 55: 233-41.

Alberts B, Johnson A, Lewis M, Raff K, Roberts K, Walter P. Molecular Biology of the Cell, New York, NY 10001-2299. 1994.

al-Jandal N, Farrar GJ, Kiang AS, Humphries MM, Bannon N, Findlay JB, Humphries P, Kenna PF. A novel mutation within the rhodopsin gene (Thr-94-Ile) causing autosomal dominant congenital stationary night blindness. *Hum Mutat.* 1999; 15: 75-81.

Alkorta I, Du P. Sequence divergence analysis for the prediction of seven-helix membrane protein structures: II. A 3-D model of human rhodopsin. *Protein Eng.* 1994; 7: 1231-8.

Altenbach C, Yang K, Farrens DL, Farahbakhsh ZT, Khorana HG, Hubbel WL. Structural features and light-dependent changes in the cytoplasmic interhelical E-F loop region of rhodopsin: a site-directed spin-labeling study. *Biochemistry.* 1996; 35: 12470-8.

Alvarez R, Domínguez M, Pazos Y, Sussman F, de Lera AR. (9Z)- and (11Z)-8-methylretinals for artificial visual pigment studies: stereoselective synthesis, structure, and binding models. *Chem Eur J.* 2003; 9: 5821-31.

Andrés A, Kosoy A, Garriga P, Manyosa J. Mutations at position 125 in transmembrane helix III of rhodopsin affect the structure and signalling of the receptor. *Eur J Biochem.* 2001; 268: 5696-5704.

Andrés A, Garriga P, Manyosa J. Altered functionality in rhodopsin point mutants associated with retinitis pigmentosa. *Biochem Biophys Res Commun.* 2003; 303: 294-301.

- Archer E, Maigret B, Escrieut C, Pradyrol L, Fourmy D. Rhodopsin crystal: new template yielding realistic models of G-protein-coupled receptors?. *Trends Pharmacol Sci*. 2003; 24: 36-40.
- Arimoto R, Kisseelev OG, Makara GM, Marshall GR. Rhodopsin-transducin interfaces: studies with conformationally constrained peptides. *Biophys J*. 2001; 81: 3285-93.
- Arnis S, Hofmann KP. Two different forms of metarhodopsin II: Schiff base deprotonation precedes proton uptake and signaling state. *Proc Natl Acad Sci USA*. 1993; 90: 7849-53.
- Arnis S, Fahmy K, Hofmann KP, Sakmar TP. A conserved carboxylic acid group mediates light-dependent proton uptake and signaling by rhodopsin. *J Biol Chem*. 1994; 269:23879-81.
- Baenziger JE, Miller KW, McCarthy MP, Rothschild KJ. Probing conformational changes in the nicotinic acetylcholine receptor by Fourier transform infrared difference spectroscopy. *Biophys J*. 1992; 62: 64-6.
- Ballesteros JA, Weinstein H. Integrated methods for the construction of three dimensional models and computational probing of structure-function relations in G-protein coupled receptors. *Methods Neurosci*. 1995; 25: 366-428.
- Ballesteros J, Kitanovic S, Guarnieri F, Davies P, Fromme BJ, Konvicka K, Chi L, Millar RP, Davidson JS, Weinstein H, Sealfon SC. Functional microdomains in G-protein-coupled receptors. The conserved arginine-cage motif in the gonadotropin-releasing hormone receptor. *J Biol Chem*. 1998; 273: 10445-53.
- Ballesteros J, Palczewski K. G protein-coupled receptor drug discovery: implications from the crystal structure of rhodopsin. *Curr Opin Drug Discov Devel*. 2001a; 4: 561-74.
- Ballesteros JA, Shi L, Javitch JA. Structural mimicry in G protein-coupled receptors: implications of the high-resolution structure of rhodopsin for structure-function analysis of rhodopsin-like receptors. *Mol Pharmacol*. 2001b; 60: 1-19.
- Bartl FJ, Ritter E, Hofmann KP. FTIR spectroscopy of complexes formed between metarhodopsin II and C-terminal peptides from the G-protein alpha- and gamma-subunits. *FEBS Letters*. 2000; 473: 259-64.
- Bartl FJ, Fritze O, Ritter E, Herrmann R, Kuksa V, Palczewski K, Hofmann KP, Ernst OP. Partial agonism in a G protein-coupled receptor: role of the retinal ring structure in rhodopsin activation. *J Biol Chem*. 2005; 280: 34259-67.
- Becker OM, Shacham S, Marantz Y, Noiman S. Modeling the 3D structure of GPCRs: Advances and application to drug discovery. *Curr Opin Drug Discovery*. 2003; 6: 353-61.
- Berson EL. Nutrition and retinal degeneration. *Int Ophthalmol Clin*. 2000; 40: 93-111.

- Berson EL, Rosner B, Weigel-DiFranco C, Dryja TP, Sandberg MA. Disease progression in patients with dominant retinitis pigmentosa and rhodopsin mutations. *Investig Ophthalmol Vis Sci.* 2002; 43: 3027-3036.
- Birdsall NJ. Cloning and structure-function of the H-2 histamine-receptor. *Trends Pharmacol Sci.* 1991;12: 9-10.
- Bissantz C. Conformational changes of G protein-coupled receptors during their activation by agonist binding. *J Recept Signal Transduct Res.* 2003; 23: 123-53.
- Bissantz C, Bernard P, Hibert M, Rognan D. Protein-Based Virtual Screening of Chemical Databases.II. Are Homology Models of G-Protein Coupled Receptors Suitable Targets?. *Proteins.* 2003; 50: 5-25.
- Blin N, Yun J, Wess J. Mapping of single amino acid residues required for selective activation of Gq/11 by the m₃ muscarinic acetylcholine receptor. *J Biol Chem.* 1995; 270: 17741-8.
- Bockaert J, Pin JP. Molecular tinkering of G protein-coupled receptors: an evolutionary success. *EMBO J.* 1999;18:1723-9.
- Bohacek R, McMardin C. Modern computational chemistry and drug discovery: structure generating programs. *Curr Opin Chem Biol.* 1997; 1: 157-61.
- Bosch L, Ramon E, del Valle LJ, Garriga P. Structural and functional role of helices I and II in rhodopsin. A novel interplay evidenced by mutations at Gly-51 and Gly-89 in the transmembrane domain. *J Biol Chem.* 2003; 278: 20203-9.
- Bosch L, Iarricchio L, Garriga P. New prospects for drug discovery from structural studies of rhodopsin. *Curr Pharm Des.* 2005; 11: 2243-56.
- Bosch L, Cordomi A, Dominguez M, Toledo D, Morillo M, Perez JJ, Alvarez R, de Lera AR, Garriga P. A methyl group at C7 of 11-cis-retinal allows chromophore formation but affects rhodopsin activation. *Vision Res.* 2006;46:4472-81.
- Braiman MS, Rothschild KJ. Fourier transform infrared techniques for probing membrane protein structure. *Annu Rev Biophys Biophys Chem.* 1988;17:541-70.
- Breikers G, Bovee-Geurts PH, DeCaluwe GL, DeGrip WJ. A structural role for Asp83 in the photoactivation of rhodopsin. *Biol Chem.* 2001; 382:1263-70.
- Brink CB. Protean behavior by agonists: agonist-directed trafficking of receptor signaling. *Tips.* 2002; 23: 454-5.
- Brink CB, Harvey BH, Bodenstein J, Venter DP, Oliver DW. Recent advances in drug action and therapeutics: Relevance of novel concepts in G-protein-coupled receptor and signal transduction pharmacology. *Br J Clin Pharmacol.* 2004; 57: 373-87.

Buss V, Kolster K, Terstegen F, Vahrenhorst R. Absolute sense of twist of the C12-C13 bond of the retinal chromophore in rhodopsin - semiempirical and nonempirical calculations of chiroptical cata. *Angew Chem Int Ed.* 1998; 37: 1893-5.

Buss V. Inherent chirality of the retinal chromophore in rhodopsin - a nonempirical theoretical analysis of chiroptical data. *Chirality.* 2001;13: 13-23.

Cacace A, Banks M, Spicer T, Civoli F, Watson J. An ultra-HTS process for the identification of small molecules modulators of orphan G-protein-coupled receptors. *Drug Discov Today.* 2003; 17: 785-92.

Cascieri MA, Shiao LL, Mills SG, MacCoss M, Swain CJ, Yu H, Ber E, Sadowski S, Wu MT, Strader CD, et al. Characterization of the interaction of diacylpiperazine antagonists with the human neurokinin-1 receptor: Identification of a common binding site for structurally dissimilar antagonists. *Mol Pharmacol.* 1995; 47: 660-5.

Chabre M, Cone R, Saibil H. Is rhodopsin dimeric in native retinal rods?. *Nature.* 2003; 426: 30-31.

Chambers JJ, Nichols DE. A homology-based model of the human 5-HT_{2A} receptor derived from an in silico activated G-protein coupled receptor. *J Comput Aided Mol Des.* 2002; 16: 511-20.

Chan WK, Nakanishi K, Ebrey TG, Honig B. Properties of 14-methylretinal, 13-desmethyl-14-methylretinal, and visual pigments formed therefrom *J Am Chem.* 1974; 96: 3642-4.

Chen CY, Cordeaux Y, Hill SJ, King JR. Modelling of signalling via G-protein coupled receptors: pathway-dependent agonist potency and efficacy. *Bull Math Biol.* 2003; 65: 933-58.

Choi G, Landin J, Galan JF, Birge RR, Albert AD, Yeagle PL. Structural studies of metarhodopsin II, the activated form of the G-protein coupled receptor, rhodopsin. *Biochemistry.* 2002; 41: 7318-24.

Christopoulos A. Allosteric binding sites on cell-surface receptors: novel targets for drug discovery. *Nat Rev Drug Discov.* 2002; 1: 198-210.

Chuang JZ, Vega C, Jun W, Sung CH. Structural and functional impairment of endocytic pathways by retinitis pigmentosa mutant rhodopsin-arrestin complexes. *J Clin Invest.* 2004; 114: 131-40.

Cohen GB, Oprian DD, Robinson PR. Mechanism of activation and inactivation of opsin: role of Glu113 and Lys296. *Biochemistry.* 1992; 31:12592-601.

Cone RA. Rotational diffusion of rhodopsin in the visual receptor membrane. *Nature New Biol.* 1972; 236: 39-43.

- Crocker E, Eilers M, Ahuja S, Hornak V, Hirshfeld A, Sheves M, Smith SO. Location of Trp265 in metarhodopsin II: implications for the activation mechanism of the visual receptor rhodopsin. *J Mol Biol.* 2006; 357: 163-72.
- Cuatrecasas P, Wilcheck M, Anfinsen CD. Selective enzyme purification by affinity chromatography. *Proc Natl Acad Sci USA.* 1968; 636-43.
- Davidson FF, Loewen PC, Khorana HG. Structure and function in rhodopsin: replacement by alanine of cysteine residues 110 and 187, components of a conserved disulfide bond in rhodopsin, affects the light-activated metarhodopsin II state. *Proc Natl Acad Sci USA.* 1994; 91: 4029-33.
- del Valle LJ, Ramon E, Cañavate X, Dias P, Garriga P. Zinc-induced decrease of the thermal stability and regeneration of rhodopsin. *J Biol Chem.* 2003; 278: 4719-24.
- Dejneka NS, Rex TS, Bennet J. Gene therapy and animal models for retinal disease. *Dev Ophthalmol.* 2003; 37: 188-98.
- Deretic D, Schmerl S, Hargrave PA, Arendt A, McDowell JH. Regulation of sorting and post-Golgi trafficking of rhodopsin by its C-terminal sequence QVS(A)PA. *Proc Natl Acad Sci USA.* 1998; 95: 10620-5.
- Dixon JS. Evaluation of the CASP2 docking section. *Proteins.* 1997; (Suppl 1): 198-204.
- Doi T, Molday RS, Khorana HG. Role of the intradiscal domain in rhodopsin assembly and function. *Proc Natl Acad Sci USA.* 1990; 87: 4991-5.
- Dratz EA, Furstenau JE, Lambert CG, Thireault DL, Rarick H, Schepers T, Pakhlevanians S, Hamm HE. NMR structure of a receptor-bound G-protein peptide. *Nature* 1993; 363: 276-81.
- Drews J. Drug discovery: A historical Perspective. *Science.* 2000; 287: 1960-64
- Dryja TP, Hahn LB, Cowley GS, McGee TL, Berson EL. Mutation spectrum of the rhodopsin gene among patients with autosomal dominant retinitis pigmentosa. *Proc Natl Acad Sci USA.* 1991; 88: 9370-4.
- Dryja TP, Berson EL, Rao VR, Oprian DD. Heterogeneous missense in the rhodopsin gene as a cause of Congenital Stationary Night Blindness. *Nat Genet.* 1993; 4: 280-2.
- Dryja TP, Li T. Molecular genetics of retinitis pigmentosa. *Hum Mol Genet.* 1995; 4: 1739-43.
- Dunham TD, Farrens DL. Conformational changes in rhodopsin. Movement of helix f detected by site-specific chemical labeling and fluorescence spectroscopy. *J Biol Chem.* 1999; 274: 1683-90.

- Fahmy K, Sakmar TP. Regulation of the rhodopsin-transducin interaction by a highly conserved carboxylic acid group. *Biochemistry*. 1993; 32: 7229-36.
- Fahmy K, Zvyaga TA, Sakmar TP, Siebert F. Spectroscopic evidence for altered chromophore--protein interactions in low-temperature photoproducts of the visual pigment responsible for congenital night blindness. *Biochemistry*. 1996; 35: 15065-73.
- Fahmy K, Sakmar TP, Siebert F. Transducin-depend protonation of glutamic acid 134 in rhodopsin. *Biochemistry*. 2000; 39: 10607-12.
- Farrar GJ, Findlay JB, Kumar-Singh R, Kenna P, Humphries MM, Sharpe E, Humphries P. Autosomal dominant retinitis pigmentosa: a novel mutation in the rhodopsin gene in the original 3q linked family. *Hum Mol Genet*. 1992; 1: 769-71.
- Farrar GJ, Kenna PF, Humphries P. On the genetics of retinitis pigmentosa and on mutation-independent approaches to therapeutic intervention. *EMBO J*. 2002; 21: 857-64.
- Farrens DL, Khorana HG. Structure and function in rhodopsin. Measurement of the rate of metarhodopsin II decay by fluorescence spectroscopy. *J Biol Chem*. 1995; 270: 5073-6.
- Farrens DL, Altenbach C, Yang K, Hubbell WL, Khorana HG. Requirement of rigid-body motion of transmembrane helices for light activation of rhodopsin. *Science*. 1996; 274: 768-70.
- Faurobert E, Otto-Bruc A, Chardin P, Chabre M. Tryptophan W207 in transducin T alpha is the fluorescence sensor of the G protein activation switch and is involved in the effector binding. *EMBO J*. 1993; 12: 4191-8.
- Ferretti L, Karnik SS, Khorana HG, Nassal M, Oprian DD. Total synthesis of gene for bovine rhodopsin. *Proc Natl Acad Sci USA*. 1986; 83: 599-603.
- Filipek S, Teller DC, Palczewski K, Stenkamp R. The crystallographic model of rhodopsin and its use in studies of other G-protein-coupled Receptors. *Annu Rev Biophys Biomol Struct*. 2003a; 32: 375-97.
- Filipek S, Stenkamp RE, Teller DC, Palczewski K. G-protein-coupled receptor rhodopsin: a prospectus. *Ann Rev Physiol*. 2003b; 65: 851-79.
- Fiser A, Sanchez R, Melo F, Sali A. Comparative protein structure modeling. In: Computational Biochemistry and Biophysics. Becker OM, MacKerell AD Jr, Roux B, Watanabe M (Eds), Marcel Dekker, New York, NY, USA 2001; 275-312.
- Fishkin N, Berova N, Nakanishi K. Primary events in dim light vision: a chemical and spectroscopic approach towards understanding protein/chromophore interactions in rhodopsin. *Chem Rec*. 2004; 4: 120-35.
- Fodale V, Quattrone D, Trecroci C, Caminiti V, Santamaria LB. Alzheimer's disease and anaesthesia: implications for the central cholinergic system. *Br J Anaesth*. 2006; 97: 445-52.

- Fong TM, Huang RR, Yu H, Strader CD. Mapping the ligand binding site of the NK1 receptor. *Regul Pept.* 1993; 46: 43-8.
- Fotiadis D, Liang Y, Filipek S, Saperstein DA, Engel A, Palczewski K. Rhodopsin dimers in native disc membranes. *Nature.* 2003a 421: 127-8.
- Fotiadis D, Liang Y, Filipek S, Saperstein DA, Engel A, Palczewski K. Is rhodopsin dimeric in native retinal rods?. *Nature.* 2003b; 426: 31.
- Franke RR, Sakmar TP, Oprian DD, Khorana HG. A single amino acid substitution in Rhodopsin (Lysine 248—Leucine) prevents activation of transducin. *J Biol Chem.* 1988; 268: 2119-22.
- Fritze O, Filipek S, Kuksa V, Palczewski K, Hofmann KP, Ernst OP. Role of the conserved NPXXY(X)5,6F motif in the rhodopsin ground state and during activation. *Proc Natl Acad Sci USA.* 2003; 100: 2290-5.
- Fryxell KJ, Meyerowitz EM. An opsin gene that is expressed only in the R7 photoreceptor cell of *Drosophila*. *EMBO J.* 1987; 6: 443-451.
- Fujimoto Y, Ishihara J, Maki S, Fujioka N, Wang T, Furuta T, Fishkin N, Borhan B, Berova N, Nakanishi K. On the bioactive conformation of the rhodopsin chromophore: Absolute sense of Twist around the 6-s-cis bond. *Chemistry.* 2001; 7: 4198-204.
- Fujimoto Y, Fishkin N, Pescitelli G, Decatur J, Berova N, Nakanishi K. Solution and biologically relevant conformations of enantiomeric 11-cis-locked cyclopropyl retinals. *J Am Chem Soc.* 2002;124: 7294-7302.
- Fukuda MN, Papermaster DS, Hargrave PA. Structural analysis of carbohydrate moiety of bovine rhodopsin. *Methods Enzymol.* 1982; 81: 214-23.
- Fung BK, Hurley JB, Stryer L. Flow of information in the light-triggered cyclic nucleotide cascade of vision. *Proc Natl Acad Sci USA.* 1981; 78: 152-6.
- Gales C, Kowalski-Chauvel A, Dufour MN, Seva C, Moroder L, Pradayrol L, Vaysse N, Fourmy D, Silvente-Poirot S. Mutation of Asn-391 within the conserved NPXXY motif of the cholecystokinin B receptor abolishes Gq protein activation without affecting its association with the receptor. *J Biol Chem.* 2002; 275: 17321-17327.
- Garcia PD, Onrust R, Bell SM, Sakmar TP, Bourne HR. Transducin-alpha C-terminal mutations prevent activation by rhodopsin: a new assay using recombinant proteins expressed in cultured cells. *EMBO J.* 1995; 14: 4460-9.
- Garriga P, Liu X, Khorana HG. Structure and function in rhodopsin: correct folding and misfolding in point mutants at and in proximity to the site of the retinitis pigmentosa mutation Leu-125-->Arg in the transmembrane helix C. *Proc Natl Acad Sci USA.* 1996; 93: 4560-4.

Garriga P, Manyosa J. The eye photoreceptor protein rhodopsin. Structural implications for retinal disease. *FEBS Lett.* 2002; 528: 17-22.

Gartner W, Towner P. Invertebrate visual pigments. *Photochem Photobiol.* 1995; 62: 1-16.

George SR, O'Dowd BF, Lee SP. G-protein-coupled receptors oligomerization and its potential for drug discovery. *Nat Rev Drug Discov.* 2002; 1: 808-20.

Gerber BO, Meng EC, Dotsch V, Baranski TJ, Bourne HR. An activation switch in the ligand binding pocket of the C5a receptor. *J Biol Chem.* 2001; 276: 3394-400.

Gether U, Kobilka BK. G protein-coupled receptors. II. Mechanism of agonist activation. *J Biol Chem.* 1998; 273: 17979-82.

Gether U. Uncovering Molecular Mechanisms involved in activation of G Protein-Coupled Receptors. *Endocr Rev.* 2000; 21: 90-113.

Gether U, Asmar F, Meinild AK, Rasmussen SG. Structural basis for activation of G-protein-coupled receptors. *Pharmacol Toxicol.* 2002; 91: 304-12.

Green SA, Spasoff AP, Coleman RA, Johnson M, Liggett SB. Sustained activation of a G protein-coupled receptor via 'anchored' agonist binding. Molecular localization of the salmeterol exosite within the 2-adrenergic receptor. *J Biol Chem.* 1996; 271: 24029 – 35.

Gripentrog JM, Jesaitis AJ, Miettinen HM. A single amino acid substitution (N297A) in the conserved NPXXY sequence of the human N-formyl peptide receptor results in inhibition of desensitization and endocytosis, and a dose-dependent shift in p42/44 mitogen-activated protein kinase activation and chemotaxis. *Biochem J.* 2000; 352: 399-407.

Govaerts C, Lefort A, Costagliola S, Wodak SJ, Ballesteros JA, Van Sande J, Pardo L, Vassart G. A conserved Asn in transmembrane helix 7 is an on/off switch in the activation of the thyrotropin receptor. *J Biol Chem.* 2001; 276: 22991-9.

Gutiérrez-de-Terán H, Centeno NB, Pastor M, Sanz F. Novel approaches for modeling of the A1 adenosine receptor and its agonist binding sites. *Proteins.* 2004; 54: 705-15.

Halazy S *et al.* Serotonin dimers: application of the bivalent ligand approach to the design of a new potent and selective 5-HT(1B/1D) agonists. *J Med Chem.* 1996; 39: 4920-7.

Hamaguchi N, True TA, Saussy DL, Jeffs PW. Phenylalanine in the second membrane-spanning domain of α_{1A} -adrenergic receptor determines subtype selectivity of dihydropyridine antagonists. *Biochemistry.* 1996; 35: 14312-7.

Hamaguchi N, True TA, Goetz AS, Strouffer MJ, Lybrand TP, Jeffs PW. α_{1A} Adrenergic receptor subtype determinants for 4-piperidyl oxazole antagonists. *Biochemistry.* 1998; 37: 5730-7.

Hamm HE, Deretic D, Arendt A, Hargrave PA, König B, Hofmann KP. Site of G protein binding to rhodopsin mapped with synthetic peptides from the alpha subunit. *Science*. 1988; 241: 832-5.

Han M, Smith SO. NMR constraints on the location of the retinal chromophore in rhodopsin and bathorhodopsin. *Biochemistry*. 1995; 34: 1425-32.

Han M, Smith SO, Sakmar TP. Constitutive activation of opsin by mutation of methionine 257 on transmembrane helix 6. *Biochemistry*. 1998; 37: 8253-61.

Heck M, Hofmann KP. G-protein-effector coupling: a real-time light-scattering assay for transducin-phosphodiesterase interaction. *Biochemistry*. 1993; 32: 8220-7.

Heck M, Schadel SA, Maretzki D, Bartl FJ, Ritter E, Palczewski K, Hofmann KP. Signaling states of rhodopsin. Formation of the storage form, metarhodopsin III, from active metarhodopsin II. *J Biol Chem*. 2003; 278: 3162-9.

Heckenlively JR, Boughman JA, Friedman LH. Pedigree analysis. In Heckenlively JR. Retinitis pigmentosa. Philadelphia PA, Lippincott. 1988, pp 6-24.

Herrmann R, Heck M, Henklein P, Henklein P, Kleuss C, Hofmann KP, Ernst OP. Sequence of interactions in receptor-G protein coupling. *J Biol Chem*. 2004; 279: 24283-90.

Hillion J, Canals M, Torvinen M, Casado V, Scott R, Terasmaa A, Hansson A, Watson S, Olah ME, Mallol J, Canela EI, Zoli M, Agnati LF, Ibanez CF, Lluis C, Franco R, Ferre S, Fuxe K. Coaggregation, cointernalization, and codesensitization of adenosine A_{2A} receptors and dopamine D₂ receptors. *J Biol Chem*. 2002; 277: 18091-7.

Hubbell WL, Altenbach C, Khorana HG. Rhodopsin structure, dynamics, and activation: a perspective from crystallography, site-directed spin labeling, sulfhydryl reactivity, and disulfide cross-linking. *Adv Protein Chem*. 2003; 63: 243-90.

Hwa J, Garriga P, Liu X, Khorana HG. Structure and function in rhodopsin: packing of the helices in the transmembrane domain and folding to a tertiary structure in the intradiscal domain are coupled. *Proc Natl Acad Sci USA*. 1997; 94: 10571-6.

Ishiguro M. A mechanism of primary photoactivation reactions of rhodopsin: modeling of the intermediates in the rhodopsin photocycle. *J Am Chem Soc*. 2000; 122: 444-51.

Jacobson SG, Kemp CM, Sung CH, Nathans J. Retinal function and rhodopsin levels in autosomal dominant retinitis pigmentosa with rhodopsin mutants. *Am J Ophthalmol*. 1991; 112: 256-71.

Jacoby E, Fauchere JL, Raimbaud E, Ollivier S, Michel A, Spedding M. A three binding site hypothesis for the interaction of ligands with monoamine G protein-coupled receptors: Implications for combinatorial ligand design. *Quant Struct Act Relatsh*. 1999; 18: 561-72.

Jager F, Fahmy K, Sakmar TP, Siebert F. Identification of glutamic acid 113 as the Schiff base proton acceptor in the metarhodopsin II photointermediate of rhodopsin. *Biochemistry*. 1994a; 33: 10878-82.

Jager F, Jager S, Krutle O, Friedman N, Sheves M, Hofmann KP, Siebert F. Interactions of the beta-ionone ring with the protein in the visual pigment rhodopsin control the activation mechanism. An FTIR and fluorescence study on artificial vertebrate rhodopsins. *Biochemistry*. 1994b; 33: 7389-97.

Jang GF, Kuksa V, Filipek S, Barti E, Ritter E, Gelb M, Hofmann PK, Palczewski K. Mechanism of rhodopsin activation as examined with ring-constrained retinal analogues and the crystal structure of the ground state protein. *J Biol Chem*. 2001; 276: 26148-53.

Janz JM, Fay JF, Farrens DL. Stability of dark state rhodopsin is mediated by a conserved ion pair in intradiscal loop E-2. *J Biol Chem*. 2003; 278: 16982-16991.

Janz JM, Farrens DL. Rhodopsin activation exposes a key hydrophobic binding site for the transducin α -subunit C terminus. *J Biol Chem*. 2004; 279: 29767-73.

Ji H, Zheng W, Zhang Y, Catt KJ, Sandberg K. Genetic transfer of a nonpeptide antagonist binding site to a previously unresponsive angiotensin receptor. *Proc Natl Acad Sci USA*. 1995; 92: 9240-4.

Kakitani H, Kakitani T, Yomosa S. Molecular mechanism for the initial process of visual excitation. II. Theoretical analysis of optical activity in rhodopsin and bathorhodopsin. *J Phys Soc Jpn*. 1977; 42: 996-1004.

Kalloniatis M, Fletcher EL. Retinitis pigmentosa: understanding the clinical presentation, mechanisms and treatment options. *Clin Exp Optom*. 2004; 87: 65-80.

Kaplan HJ, Tezel TH, Berger AS, Wolf ML, Del Priore LV. Human photoreceptor transplantation in retinitis pigmentosa. A safety study. *Arch Ophthalmol*. 1997; 115: 1168-72.

Karnik SS, Sakmar TP, Chen HB, Khorana HG. Cysteine residues 110 and 187 are essential for the formation of correct structure in bovine rhodopsin. *Proc Natl Acad Sci USA*. 1988; 85: 8459-63.

Kaushal S, Ridge KD, Khorana HG. Structure and function in rhodopsin. The role of Asparagine-linked glycosylation. *Proc Natl Acad Sci USA*. 1994a; 4024-28.

Kaushal S, Khorana HG. Structure and function in rhodopsin. 7. Point mutations associated with autosomal dominant retinitis pigmentosa. *Biochemistry*. 1994b; 33: 6121-8.

Kelleher DJ, Johnson GL. Transducin inhibition of light-dependent rhodopsin phosphorylation: evidence for beta gamma subunit interaction with rhodopsin. *Mol Pharmacol*. 1988; 34: 452-60.

Kelleher DJ, Johnson GL. Characterization of rhodopsin kinase purified from bovine rod outer segments. *J Biol Chem.* 1990 Feb 15; 265: 2632-9.

Kenakin T. Ligand-selective receptors conformations revisited: the promise and the problem. *Tips.* 2003; 24: 346-54.

Kim JM, Hwa J, Garriga P, Reeves PJ, RajBhandary UL, Khorana HG. Light-driven activation of beta 2-adrenergic receptor signaling by a chimeric rhodopsin containing the beta 2-adrenergic receptor cytoplasmic loops. *Biochemistry.* 2005; 44: 2284-92.

Klabunde T, Hessler G. Drug design strategies for targeting G-protein-coupled receptors. *Chembiochem.* 2002; 3: 928-44.

Klein-Seetharaman J, Getmanova EV, Loewen MC, Reeves PJ, Khorana HG. NMR spectroscopy in studies of light-induced structural changes in mammalian rhodopsin: applicability of solution (¹⁹F) NMR. *Proc Natl Acad Sci USA.* 1999; 96: 13744-9.

Konig B, Arendt A, McDowell JH, Kahlert M, Hardgrave PA, Hofmann KP. Three cytoplasmic loop of rhodopsin interact with transducin. *Proc Natl Acad Sci.* 1989; 86: 6878-82.

Kosteins E, Conklin BR, Wess J. Molecular basis of Receptor/G protein coupling selectivity studied by coexpression of wild type and mutant m₂ muscarinic receptors with mutant GalFAQ subunits. *Biochemistry.* 1997; 36: 1487-95

Kota P, Reeves PJ, Rajbhandary UL, Khorana HG. Opsin is present as dimers in COS1 cells: identification of amino acids at the dimeric interface. *Proc Natl Acad Sci USA.* 2006; 103: 3054-9.

Lander ES et al. Initial sequencing and analysis of the human genome. *Nature.* 2001; 409: 860-921

Lehmann N, Alexiev U, Fahmy K. Linkage Between the Intramembrane H-bond Network Around Aspartic Acid 83 and the Cytosolic Environment of Helix 8 in Photoactivated Rhodopsin. *J Mol Biol.* 2007; 366:1129-41.

Lemaitre V, Yeagle P, Watts A. Molecular dynamics simulations of retinal in rhodopsin: from the dark-adapted state towards lumirhodopsin. *Biochemistry.* 2005; 44: 12667-80.

Lewis JW, Pinkas I, Sheves M, Ottolenghi M, Kliger DS. Structural changes in early photolysis intermediates of rhodopsin from time-resolved spectral measurements of artificial pigments sterically hindered along the chromophore chain. *J Am Chem Soc.* 1995; 117: 918-23.

Liang Y, Fotiadis D, Filipek S, Saperstein DA, Palczewski K, Engel A. Organization of the G-protein-coupled receptors rhodopsin and opsin in native membranes. *J Biol Chem.* 2003; 278: 21655-62.

Li J, Edwards PC, Burghammer M, Villa C, Schertler GFX. Structure of bovine rhodopsin in a trigonal crystal form. *J Mol Biol.* 2004; 343; 1409-38.

- Liu X, Garriga P, Khorana HG. Structure and function in rhodopsin: correct folding and misfolding in two point mutants in the intradiscal domain of rhodopsin identified in retinitis pigmentosa. *Proc Natl Acad Sci USA*. 1996a; 93: 4554-9.
- Liu J, Blin N, Conklin BR, Wess J. Molecular mechanisms involved in muscarinic acetylcholine receptor-mediated G protein activation studied by insertion mutagenesis. *J Biol Chem*. 1996b; 271: 6172-8.
- Liu W, Eilers M, Patel AB, Smith SO. Helix packing moments reveal diversity and conservation in membrane protein structure. *J Mol Biol*. 2004; 337: 713-29.
- Lou J, Hashimoto M, Berova N, Nakanishi K. Enantioselective binding of an 11-*cis*-locked cyclopropyl retinal. The conformation of retinal in bovine rhodopsin. *Org Lett*. 1999; 1: 51-4.
- Lu B, Kwan T, Kurimoto Y, Shatos M, Lund RD, Young MJ. Transplantation of EGF-responsive neurospheres from GFP transgenic mice into the eyes of rd mice. *Brain Res*. 2002a; 943: 292-300.
- Lu ZL, Saldanha JW, Hulme EC. Seven-transmembrane receptors: crystals clarify. *Trends Pharmacol Sci*. 2002b; 23: 140-6.
- Macke JP, Davenport CM, Javcobson SG, Hennessey JC, Gonzalez-Fernandez F, Conway BP, Keckenlively J, Palmer R, Maumenee IH, Sieving P, Gouras P, Good W, Nathans J. Identification of novel rhodopsin mutations responsible for retinitis pigmentosa: implications for the structure and function of rhodopsin. *Am J Hum Genet*. 1993; 53: 80-89.
- Maggio R, Scarselli M, Novi F, Millan MJ, Corsini GU. Potent activation of dopamine D3/D2 heterodimers by the antiparkinsonian agents, S32504, pramipexole and ropinirole. *J Neurochem*. 2003; 87: 631-41.
- Mandel M, Higa A. Calcium dependent bacteriophage DNA infection. *J Mol Biol*. 1970; 53: 154-9.
- Manivet P, Schneider B, Smith JC, Choi DS, Maroteaux L, Kellermann O, Launay JM. The serotonin binding site of human and murine 5-HT_{2B} receptors. Molecular modeling and site-directed mutagenesis. *J Biol Chem*. 2002; 277: 17170-78.
- Marin EP, Krishna G, Zyaga TA, Isele J, Siebert F, Sakmar TP. The amino terminus of the fourth cytoplasmic loop of rhodopsin modulates rhodopsin-transducin interaction. *J Biol Chem*. 2000; 275: 1930-6.
- Martin EL, Rens-Domiano S, Schatz PJ, Hamm HE. Potent peptide analogues of a G protein receptor-binding region obtained with a combinatorial library. *J Biol Chem*. 1996; 271: 361-6.
- Marvin C, Gershengorn, Osman R. Insights into G protein-coupled receptor function using molecular models. *Endocrinology*. 2001; 142: 2-10.

Mason JS, Morize I, Menard PR, Cheney DL, Hulme C, Labaudiniere RF. New 4-point pharmacophore method for molecular similarity and diversity applications: overview of the method and applications, including a novel approach to the design of combinatorial libraries containing privileged substructures. *J Med Chem.* 1999; 42: 3251–64.

Matthews RG, Hubbard R, Brown PK, Wald G. Tautomeric forms of metarhodopsin. *J Gen Physiol.* 1963; 47: 215–40.

McDowell JH, Nawrocki JP, Hargrave PA. Phosphorylation sites in bovine rhodopsin. *Biochemistry.* 1993; 32:4968-74.

Mendes HF, van der Spuy J, Chapple JP, Cheetham ME. Mechanisms of cell death in rhodopsin retinitis pigmentosa: implications for therapy. *TRENDS Mol Med.* 2005; 11: 177-85

Meng EC, Bourne HR. Receptor activation: what does the rhodopsin structure tell us?. *Trends Pharmacol Sci.* 2001; 22: 587-93.

Meyer CK, Bohme M, Ockenfels A, Gartner W, Hofmann KP, Ernst OP. Signaling states of rhodopsin. Retinal provides a scaffold for activating proton transfer switches. *J Biol Chem.* 2000; 275:19713-8.

Miggiano GA, Falsini B. Diet and management of degenerative diseases of the retina (retinitis pigmentosa). *Clin Ter.* 2004;155:347-51.

Milligan G. G protein-coupled receptor dimerization: Function and ligand pharmacology. *Mol Pharmacol.* 2004; 66: 1-7.

Mirzaegan T, Diehl F, Ebi B, Bhakta S, Polsky I, McCarley D, Mulkins M, Weatherhead GS, Lapierre JM, Dankwardt J, Morgans D Jr, Wilhelm R, Jarnagin K. Identification of the binding site for a novel class of CCR2b chemokine receptor antagonists: Binding to a common chemokine receptor motif within the helical bundle. *J Biol Chem.* 2000; 275: 25562-71.

Mirzaegan T, Benko G, Filipek S, Palczewski K. Sequence analyses of G-protein-coupled receptors: similarities to rhodopsin. *Biochemistry.* 2003; 42: 2759-67.

Mitchell DC, Kibelbek J, Litman BJ. Effect of phosphorylation on receptor conformation: the metarhodopsin I in equilibrium with metarhodopsin II equilibrium in multiply phosphorylated rhodopsin. *Biochemistry.* 1992; 31: 8107-11.

Miura SI, Karnik SS. Constitutive activation of angiotensin II type 1 receptor alters the orientation of transmembrane Helix-2. *J Biol Chem.* 2002; 277: 24299-24305.

Miura SI, Zhang J, Boros J, Karnik SS. TM2-TM7 interaction in coupling movement of transmembrane helices to activation of the angiotensin II type-1 receptor. *J Biol Chem.* 2003; 278: 3720-5.

- Molday RS, MacKenzie D. Monoclonal antibodies to rhodopsin: characterization, cross-reactivity, and application as structural probes. *Biochemistry*. 1983; 12: 4517-23.
- Molday RS. Photoreceptor membrane proteins, phototransduction, and retinal degenerative diseases. *Invest Ophthalmol & Vis Sci*. 1998; 39: 2493-513.
- Moritz OL, Tam BM, Hurd LL, Peranen J, Deretic D, Papermaster DS. Mutant rab8 Impairs docking and fusion of rhodopsin-bearing post-Golgi membranes and causes cell death of transgenic Xenopus rods. *Mol Biol Cell*. 2001; 12: 2341-51.
- Morizumi T, Imai H, Shichida Y. Two-step mechanism of interaction of rhodopsin intermediates with the C-terminal region of the transducin alpha-subunit. *J Biochem*. 2003; 134: 259-67.
- Nakanishi K, Crouch R. Application of artificial pigments to structure determination and study of photoinduced transformations of retinal proteins. *Isr J Chem*. 1995; 35: 253-72.
- Nathans J. Determinants of visual pigment absorbance: identification of the retinylidene Schiff base counterion in bovine rhodopsin. *Biochemistry*. 1990; 29: 9746-52.
- Nicolas C, Ghedira I, Stiemer R, Teufel B, Hecquet C, Faure JP, Mirshahi M. Identification of visual arrestin (S-antigen) in retinal pigmented epithelial cells. *Curr Eye Res*. 2000; 21: 677-83.
- Nikiforovich GV, Marshall GR. Three-dimensional model for meta-II rhodopsin, an activated G-protein-coupled receptor. *Biochemistry*. 2003; 42: 9110-20.
- O'Brien PJ, Zatz M. Acylation of bovine rhodopsin by [³H]palmitic acid. *J Biol Chem*. 1984; 259: 5054-7.
- Ohguro H, Van Hooser JP, Milam AH, Palczewski K. Rhodopsin phosphorylation and dephosphorylation in vivo. *J Biol Chem*. 1995; 270: 14259-62.
- Okada T, Ernst OP, Palczewski K, Hofman KP. Activation of rhodopsin: new insights from structural and biochemical studies. *Trends Biochem Sci*. 2001; 26: 318-24.
- Okada T, Fujiyoshi Y, Silow M, Navarro J, Landau EM, Shichida Y. Functional role of internal water molecules in rhodopsin revealed by X-ray crystallography. *Proc Natl Acad Sci USA*. 2002; 99: 5982-7.
- Okada T, Sugihara M, Bondar AN, Elstner M, Entel P, Buss V. The retinal conformation and its environment in rhodopsin in light of a new 2.2 angstrom crystal structure. *J Mol Biol*. 2004; 342: 571-83.
- Oprian DD, Molday RS, Kaufman RJ, Khorana HG. Expression of synthetic bovine rhodopsin gene in monkey kidney cells. *Proc Natl Acad Sci USA*. 1987; 84: 8874-8.

Osawa S, Weiss ER. The effect of carboxyl-terminal mutagenesis of Gt alpha on rhodopsin and guanine nucleotide binding *J Biol Chem.* 1995; 270: 31052-58.

Osman R, Colson A-O, Perlman JH, Laakkonen LJ, Gershengorn MC. Mapping binding sites for peptide G protein-coupled receptors: The receptor for thyrotropin-releasing hormone. In: Wess J (ed) Structure/Function of G-Protein Coupled Receptors. John Wiley & Sons, New York. 1999; 59-84.

Padron-Garcia JA, Crespo-Otero R, Hernandez-Rodriguez EW, Garriga P, Montero LA, Garcia-Pineiro JC. Patterns of retinal light absorption related to retinitis pigmentosa mutants from in silico model structures of rhodopsin. *Proteins.* 2004; 57: 392-9.

Palczewski K, Kumada T, Hori T, Behnke CA, Motoshima H, Fox BA, Le Trong I, Teller DC, Okada T, Stenkamp RE, Yamamoto M, Miyano M. Crystal structure of rhodopsin: A G protein-coupled receptor. *Science.* 2000; 289: 739-45

Papermaster DS, Dreyer WJ. Rhodopsin content in the outer segment membranes of bovine and frog retinal rods. *Biochemistry.* 1974; 13: 2438-46.

Pardo L, Deupi X, Dölker N, López-Rodríguez ML, Campillo M. The Role of Internal Water Molecules in the Structure and Function of the Rhodopsin Family of G-protein-Coupled Receptors. *ChemBioChem.* 2006; 8: 19-24.

Patel AB, Crocker E, Eilers M, Hirshfeld A, Sheves M, Smith SO. Coupling of retinal isomerization to the activation of rhodopsin. *Proc Natl Acad Sci USA.* 2004; 101: 10048-53.

Patel AB, Crocker E, Reeves PJ, Getmanova EV, Eilers M, Khorana HG, Smith SO. Changes in interhelical hydrogen bonding upon rhodopsin activation. *J Mol Biol.* 2005; 347: 803-12.

Pepperberg DR, Crouch RK. An illuminating new step in visual-pigment regeneration. *The Lancet.* 2001; 358: 2098-9.

Peralta EG, Ashkenazi A, Winslow JW, Smith DH, Ramachandran J, Capon DJ. Distinct primary structures, ligand-binding properties and tissue-specific expression of four human muscarinic acetylcholine receptors. *EMBO J.* 1987; 6: 3923-9.

Perez DM, Hwa J, Gaivin R, Mathur M, Brown F, Graham RM. Constitutive activation of a single effector pathway: evidence of multiple activation states of a G protein-coupled receptor. *Mol Pharmacol.* 1996; 49:112-22.

Phillips WJ, Cerione RA. The intrinsic fluorescence of the alpha subunit of transducin. Measurement of receptor-dependent guanine nucleotide exchange. *J Biol Chem.* 1988; 263: 15498-505.

Piggott MA, Owens J, O'Brien J, Colloby S, Fenwick J, Wyper D, Jaros E, Johnson M, Perry RH, Perry EK. Muscarinic receptors in basal ganglia in dementia with Lewy bodies, Parkinson's disease and Alzheimer's disease. *J Chem Neuroanat.* 2003; 25: 161-73.

Prioleau C, Visiers I, Ebersole BJ, Weinstein H, Sealfon SC. Conserved helix 7 tyrosine acts as a multistate conformational switch in the 5HT2C receptor. Identification of a novel "locked-on" phenotype and double revertant mutations. *J Biol Chem.* 2002; 277: 36577-36584.

Ramon E, del Valle LJ, and Garriga P. Unusual thermal and conformational properties of the rhodopsin congenital night blindness mutant Thr-94-Ile. *J Biol Chem.* 2003a; 278: 6427-32.

Ramon E, Marron J, del Valle L, Bosch L, Andres A, Manyosa J, Garriga P. Effect of dodecyl maltoside detergent on rhodopsin stability and function. *Vision Res.* 2003b; 43: 3055-61.

Ramon E, del Valle LJ, Garriga P. Molecular Biology of Retinitis Pigmentosa: Therapeutic Implications. *Current Pharmacogenomics.* 2004; 2: 1-5.

Ramon E, Cordomí A, Bosch L, Zernii EY, Senin II, Manyosa J, Philippov PP, Pérez JJ, Garriga P. Critical role of electrostatic interactions of amino acids at the cytoplasmic region of helices 3 and 6 in rhodopsin conformational properties and activation. *J Biol Chem.* 2007. In Press.

Randall CE, Lewis JW, Hug SJ, Björling SC, Eisner-Shanas I, Ottolenghi M, Sheves Friedman N, Kliger DS. A new photolysis intermediate in artificial and native visual pigments. *J Am Chem Soc.* 1991; 113: 3473-85.

Rando R. Polyenes and vision. *Chem Biol.* 1996; 3: 255-62.

Rao RV, Cohen GB, Oprian DD. Rhodopsin mutation G90D and a molecular mechanism for congenital night blindness. *Nature.* 1994; 367: 639-42.

Rath P, Delange F, DeGrp WJ, Rothschild. Hydrogen bonding changes of internal water molecules in rhodopsin during metarhodopsin I and Metarhodopsin II formation. *Biochem J.* 1998; 329: 713-7.

Rattner A, Sun H, Nathans J. Molecular genetics of human retinal disease. *Annu Rev Genet.* 1999; 33: 89-131.

Riek RP, Rigoutsos I, Novotny J, Graham RM. Non-alpha-helical elements modulate polytopic membrane protein architecture. *J Mol Biol.* 2001; 306: 349-62.

Ridge KD, Lu Z, Liu X, Khorana HG. Structure and function in rhodopsin. Separation and characterization of the correctly folded and misfolded opsins produced on expression of an opsin mutant gene containing only the native intradiscal cysteine codons. *Biochemistry.* 1995; 34: 3261-7.

Ritter E, Zimmermann K, Heck M, Hofmann KP, Bartl FJ. Transition of rhodopsin into the active metarhodopsin II state opens a new light-induced pathway linked to Schiff base isomerization. *J Biol Chem.* 2004; 279: 48102-11.

- Robinson PR, Cohen GB, Zhukovsky EA, Oprian DD. Constitutively active mutants of rhodopsin. *Neuron*. 1992; 9:719-25.
- Rohrig UF, Guidoni L, Rothlisberger U. Early steps of the intramolecular signal transduction in rhodopsin explored by molecular dynamics simulations. *Biochemistry*. 2002; 41: 10799-809.
- Roof DJ, Heuser JE. Surfaces of rod photoreceptor disk membranes: integral membrane components. *J Cell Biol*. 1982; 95: 487-500.
- Rosemberg IM. Protein Analysis and Purification, Benchtop techniques; Massachussets General Hospital. 1996.
- Rothschild KJ, Zagaeski M, Cantore WA. Conformational changes of bacteriorhodopsin detected by Fourier transform infrared difference spectroscopy. *Biochem Biophys Res Commun*. 1981; 103: 483-9.
- Sagdullaev BT, Aramant RB, Seiler MJ, Woch G, McCall MA. Retinal transplantation-induced recovery of retinectal visual function in a rodent model of retinitis pigmentosa. *Invest Ophthalmol Vis Sci*. 2003; 44: 1686-95.
- Sakmar TP, Franke RR, Khorana HG. Glutamine acid-113 serves as the retinylidene Schiff base counterion in bovine rhodopsin. *Proc Natl Acad Sci USA*. 1989; 86: 8309-13.
- Sakmar TP. Rhodopsin: a prototypical G-protein-coupled receptor. *Prog Nucl Acids Res Mol Biol*. 1998; 59: 1-34.
- Sakmar TP. Structure of rhodopsin and the superfamily of seven-helical receptors: the same or not the same. *Curr Opin Cell Biol*. 2002; 14: 189-95.
- Sakmar TP, Menon ST, Marin EP, Awad ES. Rhodopsin: insights from recent structural studies. *Annu Rev Biophys Biomol Struct*. 2002; 31: 443-84.
- Saliba RS, Munro PM, Luthert PJ, Cheetham ME. The cellular fate of mutant rhodopsin: quality control, degradation and aggresome formation. *J Cell Sci*. 2002; 115: 2907-18.
- Samama P, Cotecchia S, Costa T, Kefkowitz RJ. A mutation-induced activated state of the β -adrenergic receptor: extending the TCM. *J Biol Chem*. 1993; 268: 4625-36.
- Saam J, Tajkhorshid E, Hayashi S, Schulten K. Molecular dynamics investigation of primary photoinduced events in the activation of rhodopsin. *Biophys J*. 2002; 83: 3097-112.
- Savarese TM, Fraser CM. *In vitro* mutagenesis and the search for structure-function relationships among G protein-coupled receptors. *Biochem J*. 1992; 283: 1-19.
- Scheer A, Fanelli F, Costa T, De Benedetti PG, Cotecchia S. The activation process of the 1- β -adrenergic receptor: potential role of protonation and hydrophobicity of a highly conserved aspartate. *Proc Natl Acad Sci USA*. 1997; 94: 808-13.

- Schertler GF, Villa C, Henderson R. Projection structure of rhodopsin. *Nature*. 1993; 362: 770-2.
- Seibert C, Harteneck C, Ernst OP, Schultz G, Hofmann KP. Activation of the rod G-protein Gt by the thrombin receptor (PAR1) expressed in Sf9 cells. *Eur J Biochem*. 1999; 266: 911-16.
- Shacham S *et al.* Modeling the 3D structure of GPCRs from sequence. *Med Res Rev*. 2001; 21: 472-83.
- Sheer A, Fanelli F, Costa T, De Benedetti PG, Cotecchia S. The activation process of the 1- β -adrenergic receptor: potential role of protonation and hydrophobicity of a highly conserved aspartate. *Proc Natl Acad Sci USA*. 1997; 94: 808-13.
- Sheikh SP, Zvyaga TA, Lichtarge O, Sakmar TP, Bourne HR. Rhodopsin activation blocked by metal-ion-binding sites linking transmembrane helices C and F. *Nature*. 1996 ; 383: 347-50.
- Shichida Y, Morizumi T. Mechanism of G-protein Activation by Rhodopsin. *Photochem Photobiol*. 2006. In Press.
- Shoichet B, McGovern S, Wei B, Irwin J. Lead discovery using molecular docking. *Curr Opin Chem Biol*.2002; 6: 439-46.
- Siebert C, Harteneck C, Ernst OP, Schultz G, Hofmann KP. Activation of the rod G-protein Gt by the thrombin receptor (PAR1) expressed in Sf9 cells. *Eur J Biochem*.1999; 266: 911-6.
- Simonds WF, Goldsmith PK, Codina J, Unson CG, Spiegel AM. Gi2 mediates alpha 2-adrenergic inhibition of adenylyl cyclase in platelet membranes: in situ identification with G alpha C-terminal antibodies. *Proc Natl Acad Sci USA*. 1989; 86: 7809-13.
- Smith WC, Dinculescu A, Peterson JJ, McDowell JH. The surface of visual arrestin that binds to rhodopsin. *Mol Vis*. 2004; 10: 392-8.
- Sieving PA, Richards JE, Naarendorf F, Bingham EL, Scott K, Alpern M. Dark-light: Model for nightblindness from the human rhodopsin Gly90-Asp mutations. *Proc natl Acad Sci USA*. 1995; 92: 880-4.
- Soudijn W, Van Wijngaarden I, Ijzerman AP. Allosteric modulation of G protein-coupled receptors. *Expert Opin Ther Pat*. 2001; 11: 1889-904.
- Spooner PJR, Sharples JM, Verhoeven MA, Lugtenburg J, Glaubitz C, Watts A. Relative Orientation between the β -ionone ring and the polyene chain for the chromophore of rhodopsin in native membranes. *Biochemistry*. 2002; 41: 7549-55.
- Spooner PJR, Sharples JM, Goodall SC, Seedorf H, Verhoeven MA, Lugtenburg J, Bovee-Geurts PHM, de Grip WJ, Watts A. Conformational Similarities in the β -ionone ring region of the rhodopsin chromophore in its ground state and after photoactivation to the metarhodopsin-I intermediate. *Biochemistry*. 2003; 42: 13371-8.

- Spooner PJR, Sharples JM, Goodall SC, Bovee-Geurts PHM, Verhoeven MA, Lugtenburg J, Pistorius AMA, de Grip WJ, Watts A. The ring of the rhodopsin chromophore in a hydrophobic activation switch within the binding pocket. *J Mol Biol.* 2004; 343: 719-30.
- Stojanovic A, Stitham J, Hwa J. Critical role of transmembrane segment zing binding in the structure and function of rhodopdin. *J Biol Chem.* 2004; 279:35932-41
- Stojanovic A, Hwa J. Rhodopsin and retinitis pigmentosa: shedding light on structure and function. *Receptors Channels.* 2002; 8: 33-50.
- Strosberg AD. Structure and function of the beta-3-adrenergic receptor. *Annu Rev Pharmacol Toxicol.* 1997; 37: 421-50.
- Stryer L. Cyclic GMP cascade of vision. *Annu Rev Neurosci.* 1986; 9: 87-119.
- Sung CH, Davenport CM, Hennessey JC, Maumenee IH, Jacobson SG, Heckenlively JR, Nowakowski R, Fishman G, Gouras P, Nathans J. Rhodopsin mutations in autosomal dominant retinitis pigmentosa. *Proc Natl Acad Sci USA.* 1991a; 88: 6481-5.
- Sung CH, Shneider BG, Agarwal N, Papermaster DS, Nathans J. Functional heterogeneity of mutant rhodopsins responsible for autosomal dominant retinitis pigmentosa. *Proc Natl Acad Sci USA.* 1991b; 88: 8840-4.
- Sung CH, Davenport C, Nathans J. Rhodopsin mutations responsible for autosomal dominant retinitis pigmentosa. Clustering of functional classes along the polypeptide chain. *J Biol Chem.* 1993; 268: 26645-26649.
- Sung CH, Makino C, Baylor D, Nathans J. A rhodopsin gene mutation responsible for autosomal dominant retinitis pigmentosa results in a protein that is defective in localization to the photoreceptor outer segment. *J Neurosci.* 1994; 14: 5818-33.
- Tachibanaki S, Imai H, Mizukami T, Okada T, Imamoto Y, Matsuda T, Fukada Y, Terakita A, Shichida Y. Presence of two rhodopsin intermediates responsible for transducin activation. *Biochemistry.* 1997; 36: 14173-80.
- Tachibanaki S, Imai H, Terakita A, Shichida Y. Identification of a new intermediate state that binds but not activates transducin in the bleaching process of bovine rhodopsin. *FEBS Lett.* 1998; 425: 126-30.
- Tam BM, Moritz OL, Hurd LB, Papermaster DS. Identification of an outer segment targeting signal in the COOH terminus of rhodopsin using transgenic *Xenopus laevis*. *J Cell Biol.* 2000; 151: 1369-80.
- Tame JRH. Scoring functions: a view from the bench. *J Comput Aided Mol Des.* 1999; 13: 99-108.

- Tan Q, Lou J, Borhan B, Karnaughova E, Berova N, Nakanishi K. Absolute sense of twist of the c12—c13 bond of the retinal chromophore in bovine rhodopsin based on exciton-coupled CD spectra of 11,12-dihydroretinal analogues. *Angew Chem Int Ed*. 1997; 36: 2089-93.
- Teller DC, Okada T, Behnke CA, Palczewski K, Stenkamp RE. Advances in determination of a high-resolution three-dimensional structure of rhodopsin, a model of G-protein-coupled receptors (GPCRs). *Biochemistry*. 2001; 40: 7761-72.
- Ter Laak AM, Timmerman H, Leurs R, Nederkoorn PH, Smit MJ, Donne-Op den Kelder GM. Modelling and mutation studies on the histamine H1-receptor agonist binding site reveal different binding modes for H1-agonists: Asp116 (TM3) has a constitutive role in receptor stimulation. *J Comput Aided Mol Des*. 1995; 9: 319-30.
- Themmen AP, Verhoef-Post M. LH receptors defects. *Semin Reprod Med*. 2002; 20: 199-204.
- Tota MR, Candelore MR, Dixon RA, Strader CD. Biophysical and genetic analysis of the ligand-binding site of the β -adrenoceptor. *Trends Pharmacol Sci*. 1991; 12: 4-6.
- Tucek S, Jakubik J, Dolezal V, el-Fakahany EE. Positive effects of allosteric modulators on the binding properties and the function of muscarinic acetylcholine receptors. *J Physiol Paris*. 1998; 92: 241-3.
- Underwood DJ, Strader CD, Rivero R, Patchett AA, Greenlee W, Prendergast K. Structural model of antagonist and agonist binding to the angiotensin II, AT1 subtype, G protein coupled receptor. *Chem Biol*. 1994; 1: 211-221.
- Unger VM, Hargrave PA, Baldwin JM, Schertler GF. Arrangement of rhodopsin transmembrane alpha-helices. *Nature*. 1997; 389: 203-6.
- Vaidehi N, Floriano WB, Trabanino R, Hall SE, Freddolino P, Choi EJ, Zamanakos G, Goddard WA 3rd. Prediction of structure and function of G protein-coupled receptors. *Proc Natl Acad Sci USA*. 2002; 99: 12622-27.
- van Soest S, Westerveld A, de Jong PT, Bleeker-Wagemakers EM, Bergen AA. Retinitis pigmentosa: defined from a molecular point of view. *Surv Ophthalmol*. 1999; 43: 321-34.
- Venter JC *et al*. The sequence of the human genome. *Science*. 2001; 291: 1304-50.
- Visiers I, Ballesteros JA, Weinstein H. Prokink: a protocol for numerical evaluation of helix distortions by proline. *Protein Eng*. 2000; 13: 603-6.
- Vogel R, Fan GB, Siebert F, Sheves M. Anions stabilize a metarhodopsin II-like photoproduct with a protonated Schiff base. *Biochemistry*. 2001; 40: 13342-52.

Vogel R, Siebert F. Fourier transform IR spectroscopy study for new insights into molecular properties and activation mechanisms of visual pigment rhodopsin. *Biopolymers*. 2003;72: 133-48.

Vogel R, Siebert F, Zhang XY, Fan G, Sheves M. Formation of Meta III during the decay of activated rhodopsin proceeds via Meta I and not via Meta II. *Biochemistry*. 2004; 43: 9457-66.

Vogel R, Siebert F, Lüdeke S, Hirshfeld A, Sheves M. Agonists and partial agonists of rhodopsin: retinals with ring modifications. *Biochemistry*. 2005; 44: 11684-99.

Vogel R, Lüdeke S, Siebert F, Sakmar TP, Hirshfeld A, Sheves M. Agonists and partial agonists of rhodopsin: retinal polyene methylation affects receptor activation. *Biochemistry*. 2006; 45: 1640-52.

Wang Q, Schoenlein RW, Peteanu LA, Mathies RA, Shank CV. vibrationally coherent photochemistry in the femtosecond primary event of vision. *Science*. 1994; 266: 422-24.

Waszkowycz B, Perkins TDJ, Sykes RA, Li J. Large-scale virtual screening for discovery leads in the postgenomics era. *IBM Systems Journal*. 2001; 40: 360-76.

Weiss J, Morgan P, Lutz M, Kenakin T. The cubic ternary complex receptor occupancy model. I. Model description. *J Theor Biol*. 1996a; 178: 151-67.

Weiss J, Morgan, P, Lutz M, Kenakin T. The cubic ternary complex receptor occupancy model. II. Understanding apparent affinity. *J Theor Biol*. 1996b; 178: 169-82.

Wise A, Gearing K, Rees S. Target validation of G-protein coupled receptors. *Drug Discov Today*. 2002; 7: 235-46.

Yamashita T, Terakita A, Shichida Y. Distinct roles of the second and third cytoplasmic loops of bovine rhodopsin in G-protein activation. *J Biol Chem*. 2000; 275: 34272-9.

Yan EC, Kazmi MA, Ganim Z, Hou JM, Pan D, Chang BS, Sakmar TP, Mathies RA. Retinal counterion switch in the photoactivation of the G protein-coupled receptor rhodopsin. *Proc Natl Acad Sci U S A*. 2003; 100: 9262-7.

Zeng FY, Hopp A, Soldner A, Wess J. Use of a disulfide cross-linking strategy to study muscarinic receptor structure and mechanisms of activation. *J Biol Chem*. 1999; 274: 16629-40.

Zhu L, Jang GF, Jastrzebska B, Filipek S, Pearce-Kelling SE, Aguirre GD, Stenkamp RE, Acland GM, Palczewski K. A Naturally Occurring Mutation of the Opsin Gene (T4R) in Dogs Affects Glycosylation and Stability of the G Protein-coupled Receptor. *J Biol Chem*. 2004; 279: 53828-39.

Zhukovsky EA, Oprian DD. Effect of carboxylic acid side chains on the absorption maximum of visual pigments. *Science*. 1989; 246: 928-30.