

LECTURE #5: SIGNAL TRANSDUCTION— RECEPTORS AND ADAPTORS

Assigned (Required) Reading is (1) - (4):

•General Background (in your Reader):

(1) Hubbard SR, Miller WT (2007) Receptor tyrosine kinases: mechanisms of activation and signaling. *Curr. Opin. Cell Biol.* 19: 117-123.

(2) Pawson T (2007) Dynamic control of signaling by modular adaptor proteins. *Curr. Opin. Cell Biol.* 19: 112-116.

(3) Seet BT, Dikic I, Zhou MM, Pawson T (2006) Reading protein modifications with interaction domains. *Nature Rev. Mol. Cell. Biol.* 7: 473-483.

•Papers for Friday Discussion Session (30 Nov.)

(4a) Cherezov V, Rosenbaum DM, Hanson MA, Rasmussen SG, Thian FS, Kobilka TS, Choi HJ, Kuhn P, Weis WI, Kobilka BK, Stevens RC (2007) High-resolution crystal structure of an engineered human beta2-adrenergic G protein-coupled receptor. *Science* 318: 1258-1265.

(4b) Rosenbaum DM, Cherezov V, Hanson MA, Rasmussen SG, Thian FS, Kobilka TS, Choi HJ, Yao XJ, Weis WI, Stevens RC, Kobilka BK (2007) GPCR engineering yields high-resolution structural insights into beta2-adrenergic receptor function. *Science* 318: 1266-1273.

Bacterial chemotaxis and prokaryotic two-component signaling systems:

Gao R, Mack TR, Stock AM (2007) Bacterial response regulators: versatile regulatory strategies from common domains. *Trends Biochem. Sci.* 32: 225-234.

Khorchid A, Ikura M. (2006) Bacterial histidine kinase as signal sensor and transducer. *Int J Biochem Cell Biol.* 38: 307-312.

Wolanin PM, Stock JB (2004) Bacterial chemosensing: cooperative molecular logic. *Curr. Biol.* 14: R486-R487.

Bijlsma JJ, Groisman EA (2003) Making informed decisions: regulatory interactions between two-component systems. *Trends Microbiol.* 11: 359-366.

Ogura M, Tanaka T (2002) Recent progress in *Bacillus subtilis* two-component regulation. *Front Biosci.* 7: d1815-d1824.

Bourret RB, Stock AM (2002) Molecular information processing: lessons from bacterial chemotaxis. *J. Biol. Chem.* 277: 9625-9628.

Hwang I, Chen HC, Sheen J (2002) Two-component signal transduction pathways in Arabidopsis. *Plant Physiol.* 129: 500-515.

Klumpp S, Krieglstein J (2002) Phosphorylation and dephosphorylation of histidine residues in proteins. *Eur J Biochem.* 269: 1067-1071.

Falke JJ, Hazelbauer GL (2001) Transmembrane signaling in bacterial chemoreceptors. *Trends Biochem. Sci.* 26: 257-265.

Foussard M, Cabantous S, Pedelacq J, Guillet V, Tranier S, Mourey L, Birck C, Samama J. (2001) The molecular puzzle of two-component signaling cascades. *Microbes Infect.* 3: 417-424.

Hoch JA, Varughese KI (2001) Keeping signals straight in phosphorelay signal transduction. *J. Bacteriol.* 183: 4941-4949.

Santos JL, Shiozaki K (2001) Fungal histidine kinases. *Sci STKE.* Sep 4, 2001; 2001 (98): RE1.

Receptor classification:

Hendrickson WA (2005) Transduction of biochemical signals across cell membranes. *Quart. Rev. Biophys.* 38: 321-330.

Watling KJ (Ed.) (2002) *The Sigma-RBI Handbook of Receptor Classification and Signal Transduction*, Sigma-RBI Press, Inc., Natick, MA, 231pp.

Bernardo R (1999) Molecular and functional diversity of ion channels and receptors. *Ann. NY Acad Sci.* 868: 1-774.

Alexander, S.P.H. and J.A. Peters (1997) *Catalog of Receptors and Ion Channels*, 8th Ed. Supplement to *Trends Pharmacol. Sci.*

Receptor-tyrosine kinases—

Wiesner S, Wybenga-Groot LE, Warner N, Lin H, Pawson T, Forman-Kay JD, Sicheri F. (2006) A change in conformational dynamics underlies the activation of Eph receptor tyrosine kinases. *EMBO J.* 25: 4686-4696.

Pawson T (2002) Regulation and targets of receptor tyrosine kinases. *Eur J Cancer.* 38(Suppl 5): S3-S10.

Schlessinger J (2002) Ligand-induced, receptor-mediated dimerization and activation of EGF receptor. *Cell* 110: 669-672.

Zwick E, Bange J, Ullrich A (2002) Receptor tyrosine kinases as targets for anticancer drugs. *Trends Mol Med.* 8: 17-23.

Hubbard SR (2002) Autoinhibitory mechanisms in receptor tyrosine kinases. *Front Biosci.* 7: d330-d340.

Rebay I (2002) Keeping the receptor tyrosine kinase signaling pathway in check: lessons from *Drosophila*. *Dev Biol.* 251: 1-17.

De Meyts P, Whittaker J (2002) Structural biology of insulin and IGF1 receptors: implications for drug design. *Nature Rev Drug Discov.* 1: 769-783.

Cutforth T, Harrison CJ (2002) Ephs and ephrins close ranks. *Trends Neurosci.* 25: 332-334.

Wilkinson DG (2001) Multiple roles of EPH receptors and ephrins in neural development. *Nature Rev Neurosci.* 2: 155-164.

Schlessinger J. (2000) Cell signaling by receptor tyrosine kinases. *Cell* 103: 211-225.

Simon MA (2000) Receptor tyrosine kinases: specific outcomes from general signals. *Cell* 103: 13-15.

Raabe T. (2000) The sevenless signaling pathway: variations of a common theme. *Biochim Biophys A.* 1496: 151-163.

Receptor-tyrosine phosphatases—

Majeti R, Weiss A (2001) Regulatory mechanisms for receptor protein tyrosine phosphatases. *Chem Rev.* 101: 2441-2448

Bixby JL (2001) Ligands and signaling through receptor-type tyrosine phosphatases. *IUBMB Life.* 51: 157-163.

Li L, Dixon JE. (2000) Form, function, and regulation of protein tyrosine phosphatases and their involvement in human diseases. *Semin Immunol.* 12: 75-84.

Avraham H, Avraham S, Taniguchi Y. (2000) Receptor protein tyrosine phosphatases in hematopoietic cells. *J Hematother. Stem Cell Res.* 9: 425-432.

den Hertog J, Blanchetot C, Buist A, Overvoorde J, van der Sar A, Tertoolen LG. (1999) Receptor protein-tyrosine phosphatase signalling in development. *Int. J. Dev. Biol.* 43: 723-733. Review.

Receptor-serine/threonine kinases—

Attisano L, Wrana JL (2002) Signal transduction by the TGF-beta superfamily. *Science* 296: 1646-1647.

Miyazono K, Kusanagi K, Inoue H (2001) Divergence and convergence of TGF-beta/BMP signaling. *J Cell Physiol.* 187: 265-276.

Huse M, Muir TW, Xu L, Chen YG, Kuriyan J, Massague J (2001) The TGF beta receptor activation process: an inhibitor- to substrate-binding switch. *Mol Cell.* 8: 671-682.

Ethier JF, Findlay JK (2001) Roles of activin and its signal transduction mechanisms in reproductive tissues. *Reproduction* 121: 667-675.

Shi Y (2001) Structural insights on Smad function in TGFbeta signaling. *Bioessay* 23: 223-232.

Nakayama T, Cui Y, Christian JL (2000) Regulation of BMP/Dpp signaling during embryonic development. *Cell Mol Life Sci.* 57: 943-956.

Receptor-guanylate cyclases—

Potter LR, Hunter T (2001) Guanylyl cyclase-linked natriuretic peptide receptors: structure and regulation. *J Biol Chem.* 276: 6057-6060.

Silberbach M, Roberts CT Jr. (2001) Natriuretic peptide signalling: molecular and cellular pathways to growth regulation. *Cell Signal.* 13: 221-231.

Tamura N, Chrisman TD, Garbers DL (2001) The regulation and physiological roles of the guanylyl cyclase receptors. *Endocr J.* 48Z: 611-634.

Cytokine receptors—

Wang X, Rickert M, Garcia KC (2005) Structure of the quaternary complex of interleukin-2 with its α , β , and γ_c receptors. *Science* 310: 1159-1163.

Frank SJ (2002) Receptor dimerization in GH and erythropoietin action--it takes two to tango, but how? *Endocrinology* 143: 2-10.

Strous G, Gent (2002) Dimerization, ubiquitylation and endocytosis go together in growth hormone receptor function. *FEBS Lett* 529: 102-109.

Grotzinger J (2002) Molecular mechanisms of cytokine receptor activation. *Biochim Biophys Acta* 1592: 215-223.

Jequier E (2002) Leptin signaling, adiposity, and energy balance. *Ann N Y Acad Sci.* 967: 379-388.

Levy DE, Darnell JE Jr. (2002) Stats: transcriptional control and biological impact. *Nat Rev Mol Cell Biol.* 3: 651-662.

Zhu T, Goh EL, Graichen R, Ling L, Lobie PE (2001) Signal transduction via the growth hormone receptor. *Cell Signal.* 13: 599-616.

Ihle JN (2001) The Stat family in cytokine signaling. *Curr Opin Cell Biol.* 13: 211-217.

Constantinescu SN, Ghaffari S, Lodish HF. (1999) The erythropoietin receptor: structure, activation and intracellular signal transduction. *Trends Endocrinol Metab.* 10: 18-23.

Tartaglia LA. (1997) The leptin receptor. *J. Biol. Chem.* 272: 6093-6096.

Toll family receptors—

Hargreaves DC, Medzhitov R. (2005) Innate sensors of microbial infection. *J Clin Immunol.* 25: 503-510.

- Underhill DM. (2004) Toll-like receptors and microbes take aim at each other. *Curr Opin Immunol.* 16: 483-487.
- Armant MA, Fenton MJ (2002) Toll-like receptors: a family of pattern-recognition receptors in mammals. *Genome Biol.* 3: 3011.1-3011.6.
- O'Neill LA (2002) Toll-like receptor signal transduction and the tailoring of innate immunity: a role for Mal? *Trends Immunol.* 23: 296-300.
- Aderem A, Ulevitch RJ (2000) Toll-like receptors in the induction of the innate immune response. *Nature.* 406: 782-787.
- Anderson KV (2000) Toll signaling pathways in the innate immune response. *Curr Opin Immunol.* 12: 13-19.
- G-protein coupled receptors—*
- Iyengar R (2005) Structure of G protein-coupled receptors and G proteins. *Sci STKE.* 2005 Mar 22; 2005(276):tr10.
- Lefkowitz RJ, Shenoy SK (2005) Transduction of receptor signals by beta-arrestins. *Science* 308: 512-517.
- Lefkowitz RJ (2004) Historical review: a brief history and personal retrospective of seven-transmembrane receptors. *Trends Pharmacol. Sci.* 25: 413-422.
- Pierce KL, Premont RT, Lefkowitz RJ (2002) Seven-transmembrane receptors. *Nature Rev. Mol. Cell. Biol.* 3: 639-650.
- Hall RA, Lefkowitz RJ (2002) Regulation of G protein-coupled receptor signaling by scaffold proteins. *Circ Res.* 91: 672-680.
- Onuffer J, Horuk R (2002) Chemokines, chemokine receptors and small-molecule antagonists: recent developments. *Trends Pharmacol Sci.* 23(10): 459-467.
- George SR, O'Dowd BF, Lee SP (2002) G-protein-coupled receptor oligomerization and its potential for drug discovery. *Nature Rev Drug Discov.* 1: 808-820.
- Parnot C, Miserey-Lenkei S, Bardin S, Corvol P, Clauser E (2002) Lessons from constitutively active mutants of G protein-coupled receptors. *Trends Endocrinol Metab.* 13: 336-343.
- El Far O, Betz H (2002) G-protein-coupled receptors for neurotransmitter amino acids: C-terminal tails, crowded signalosomes. *Biochem J.* 365: 329-336.
- Meng EC, Bourne HR (2001) Receptor activation: what does the rhodopsin structure tell us? *Trends Pharmacol Sci.* 22: 587-593.
- Devi LA (2001) Heterodimerization of G-protein-coupled receptors: pharmacology, signaling and trafficking. *Trends Pharmacol Sci.* 22: 532-537.
- Milligan G, White JH (2001) Protein-protein interactions at G-protein-coupled receptors. *Trends Pharmacol Sci* 22: 513-518.
- Marinissen MJ, Gutkind JS (2001) G-protein-coupled receptors and signaling networks: emerging paradigms. *Trends Pharmacol Sci.* 22: 368-376.
- Horuk R (2001) Chemokine receptors. *Cytokine Growth Factor Rev.* 12: 313-335.
- Ram PT, Iyengar R (2001) G protein coupled receptor signaling through the Src and Stat3 pathway: role in proliferation and transformation. *Oncogene* 20: 1601-1606.

Pierce KL, Luttrell LM, Lefkowitz RJ (2001) New mechanisms in heptahelical receptor signaling to mitogen-activated protein kinase cascades. *Oncogene* 20: 1532-1539.

Coughlin SR. (2000) Thrombin signalling and protease-activated receptors. *Nature* 407: 258-264.

Missale C, Nash SR, Robinson SW, Jaber M, Caron MG. (1998) Dopamine receptors: from structure to function. *Physiol. Rev.* 78: 189-225.

Adaptor proteins, scaffold proteins, linker proteins, anchoring proteins:

General Background—

Bhattacharyya RP, Remenyi A, Yeh BJ, Lim WA (2006) Domains, motifs, and scaffolds: the role of modular interactions in the evolution and wiring of cell signaling circuits. *Annu. Rev. Biochem.* 75: 655-680.

Pawson T (2004) Specificity in signal transduction: from phosphotyrosine-SH2 domain interactions to complex cellular systems. *Cell* 116: 191-203.

Pawson T, Nash P (2003) Assembly of cell regulatory systems through protein interaction domains. *Science* 300: 445-452.

Morrison DK, Davis RJ (2003) Regulation of map kinase signaling modules by scaffold proteins in mammals. *Annu Rev Cell Dev Biol* 19: 91-118.

Pawson T, Raina M, Nash P (2002) Interaction domains: from simple binding events to complex cellular behavior. *FEBS Lett.* 513: 2-10.

Aasland R, Abrams C, Ampe C, Ball LJ, Bedford MT, Cesareni G, Gimona M, Hurley JH, Jarchau T, Lehto VP, Lemmon MA, Linding R, Mayer BJ, Nagai M, Sudol M, Walter U, Winder SJ. (2002) Normalization of nomenclature for peptide motifs as ligands of modular protein domains. *FEBS Lett.* 513: 141-144.

Smith FD, Scott JD (2002) Signaling complexes: junctions on the intracellular information super highway. *Curr Biol.* 12: R32-R40.

Lim W (2002) The modular logic of signaling proteins: building allosteric switches from simple binding domains *Curr Opin Struct Biol.* 12: 61-68.

Burack WR, Cheng AM, Shaw AS (2002) Scaffolds, adaptors and linkers of TCR signaling: theory and practice. *Curr Opin Immunol.* 14: 312-316.

Samelson LE (2002) Signal transduction mediated by the T cell antigen receptor: the role of adapter proteins. *Annu Rev Immunol.* 20: 371-394

Sims TN, Dustin M (2002) The immunological synapse: integrins take the stage. *Immunol Rev.* 2002 186: 100-117.

Liu Y, Rohrschneider LR (2002) The gift of Gab. *FEBS Lett.* 515: 1-7.

Buday L, Wunderlich L, Tamas P (2002) The Nck family of adapter proteins. Regulators of actin cytoskeleton. *Cell Signal* 14: 723-731.

Kapiloff MS (2002) Contributions of protein kinase A anchoring proteins to compartmentation of cAMP signaling in the heart. *Mol Pharmacol.* 62: 193-199.

Fagni L, Worley PF, Ango F (2002) Homer as both a scaffold and transduction molecule. *Sci STKE* Jun 18, 2002; 2002 (137): RE8. R

Blume-Jensen P, Hunter T (2001) Oncogenic kinase signalling. *Nature* 411: 355-365

Catling AD, Eblen ST, Schaeffer HJ, Weber MJ (2001) Scaffold protein regulation of mitogen-activated protein kinase cascade. *Methods Enzymol.* 332: 368-387.

Feller SM (2001) Crk family adaptors-signalling complex formation and biological roles. *Oncogene*. 20: 6348-6371.

Hadari YR, Gotoh N, Kouhara H, Lax I, Schlessinger J (2001) Critical role for the docking-protein FRS2 alpha in FGF receptor-mediated signal transduction pathways. *Proc Natl Acad Sci USA* 98: 8578-8583.

Elion EA (2001) The Ste5p scaffold. *J Cell Sci*. 114: 3967-3978.

Li W, Fan J, Woodley DT (2001) Nck/Dock: an adapter between cell surface receptors and the actin cytoskeleton. *Oncogene* 20: 6403-6417.

Ravichandran KS (2001) Signaling via Shc family adapter proteins. *Oncogene* 20: 6322-6330.

Pawson T, Nash P (2000) Protein-protein interactions define specificity in signal transduction. *Genes Dev*. 14: 1027-1047.

Ferrell JE Jr (2000) What do scaffold proteins really do? *Sci STKE*. 2000 Oct 3, 2000; 2000 (52): PE1.

Myung PS, Boerthe NJ, Koretzky GA. (2000) Adapter proteins in lymphocyte antigen-receptor signaling. *Curr Opin Immunol*. 12: 256-266.

Songyang Z (1999) Recognition and regulation of primary-sequence motifs by signaling modular domains. *Prog Biophys Mol Biol* 71: 359-372.

Whitmarsh AJ, Davis RJ (1998) Structural organization of MAP-kinase signaling modules by scaffold proteins in yeast and mammals. *Trends Biochem Sci*. 23: 481-485.

Lee CH, Cowburn D, Kuriyan J (1998) Peptide recognition mechanisms of eukaryotic signaling modules. *Methods Mol Biol*. 84: 3-31.

White MF (1998) The IRS-signaling system: a network of docking proteins that mediate insulin and cytokine action. *Recent Prog Horm Res*. 53: 119-138.

Bray D. (1998) Signaling complexes: biophysical constraints on intracellular communication. *Annu. Rev. Biophys. Biomol. Struct*. 27: 59-75.

Modular recognition domains and their targets:

Domains that recognize phosphorylated determinants on proteins:

SH2 domains—

Yaffe MB (2002) Phosphotyrosine-binding domains in signal transduction. *Nat Rev Mol Cell Biol*. 3: 177-186.

Sawyer TK, Bohacek RS, Dalgarno DC, Eyermann CJ, Kawahata N, Metcalf CA 3rd, Shakespeare WC, Sundaramoorthi R, Wang Y, Yang MG (2002) SRC homology-2 inhibitors: peptidomimetic and nonpeptide. *Mini Rev Med Chem*. 2: 475-488.

Vetter SW, Zhang ZY (2002) Probing the phosphopeptide specificities of protein tyrosine phosphatases, SH2 and PTB domains with combinatorial library methods. *Curr Protein Pept Sci*. 3: 365-397.

Garcia-Echeverria C (2001) Antagonists of the Src homology 2 (SH2) domains of Grb2, Src, Lck and ZAP-70. *Curr Med Chem* 8: 1589-1604.

PTB Domains—

Yan KS, Kuti M, Zhou MM (2002) PTB or not PTB -- that is the question. *FEBS Lett*. 513: 67-70.

Vetter SW, Zhang ZY (2002) Probing the phosphopeptide specificities of protein tyrosine phosphatases, SH2 and PTB domains with combinatorial library methods. *Curr Protein Pept Sci*. 3: 365-397.

Guy GR, Yusoff P, Bangarusamy D, Fong CW, Wong ES (2002) Dockers at the crossroads. *Cell Signal*. 14: 11-20.

Forman-Kay JD, Pawson T (1999) Diversity in protein recognition by PTB domains. *Curr Opin Struct Biol* 9: 690-695.

Borg JP, Margolis B (1998) Function of PTB domains. *Curr Top Microbiol Immunol.* 228: 23-38.

14-3-3 Proteins—

Yaffe MB (2002) How do 14-3-3 proteins work?-- Gatekeeper phosphorylation and the molecular anvil hypothesis. *FEBS Lett.* 513: 53-57.

Truong AB, Masters SC, Yang H, Fu H (2002) Role of the 14-3-3 C-terminal loop in ligand interaction. *Proteins* 49: 321-3

Masters SC, Subramanian RR, Truong A, Yang H, Fujii K, Zhang H, Fu H (2002) Survival-promoting functions of 14-3-3 proteins. *Biochem Soc Trans* 30: 360-365.

Tzivion G, Shen YH, Zhu J (2001) 14-3-3 proteins; bringing new definitions to scaffolding. *Oncogene* 20: 6331-6338.

Fu H, Subramanian RR, Masters SC (2000) 14-3-3 proteins: structure, function, and regulation. *Annu Rev Pharmacol Toxicol* 40: 617-647.

Forkhead-associated (HA) domains—

Durocher D, Jackson SP (2002) The FHA domain. *FEBS Lett.* 513: :58-66.

Yaffe MB, Smerdon SJ. (2001) PhosphoSerine/threonine binding domains: you can't pSERious? *Structure (Camb).* 9: R33-R38.

Li J, Lee GI, Van Doren SR, Walker JC (2000) The FHA domain mediates phosphoprotein interactions. *J Cell Sci.* 113: 4143-4149.

WW domains—

Lu PJ, Zhou XZ, Liou YC, Noel JP, Lu KP (2002) Critical role of WW domain phosphorylation in regulating phosphoserine binding activity and Pin1 function. *J Biol Chem* 277: 2381-2384.

Sudol M, Sliwa K, Russo T (2001) Functions of WW domains in the nucleus. *FEBS Lett.* 490: 190-195.

Yaffe MB, Elia AE. (2001) Phosphoserine/threonine-binding domains. *Curr Opin Cell Biol.* 13: 131-138.

Verdecia MA, Bowman ME, Lu KP, Hunter T, Noel JP (2000) Structural basis for phosphoserine-proline recognition by group IV WW domains. *Nat Struct Biol.* 2000 Aug;7(8):639-43.

SH3 domains—

Liu Q, Berry D, Nash P, Pawson T, McGlade CJ, Li SS (2003) Structural basis for specific binding of the Gads SH3 domain to an RxxK motif-containing SLP-76 peptide: a novel mode of peptide recognition. *Mol Cell* 11: 471-481.

Cesareni G, Panni S, Nardelli G, Castagnoli L (2002) Can we infer peptide recognition specificity mediated by SH3 domains? *FEBS Lett.* 513: 38-44.

Mayer BJ (2001) SH3 domains: complexity in moderation. *J Cell Sci.* 114: 1253-1263.

Kay BK, Williamson MP, Sudol M (2000) The importance of being proline: the interaction of proline-rich motifs in signaling proteins with their cognate domains. *FASEB J.* 14: 231-241.

Buday L. (1999) Membrane-targeting of signalling molecules by SH2/SH3 domain-containing adaptor proteins. *Biochim Biophys A.* 1422: 187-204.

WW domains—

Macias MJ, Wiesner S, Sudol M (2002) WW and SH3 domains, two different scaffolds to recognize proline-rich ligands. *FEBS Lett.* 513: 30-37.

Ilsley JL, Sudol M, Winder SJ (2002) The WW domain: linking cell signalling to the membrane cytoskeleton. *Cell Signal.* 14: 183-189.

EVH1 domains—

Ball LJ, Jarchau T, Oschkinat H, Walter U (2002) EVH1 domains: structure, function and interactions. *FEBS Lett.* 513: 45-52.

Paunola E, Mattila PK, Lappalainen P (2002) WH2 domain: a small, versatile adapter for actin monomers. *FEBS Lett.* 513: 92-97.

Beneken J, Tu JC, Xiao B, Nuriya M, Yuan JP, Worley PF, Leahy DJ. (2000) Structure of the Homer EVH1 domain-peptide complex reveals a new twist in polyproline recognition. *Neuron.* 26: 143-154.

Prehoda KE, Lee DJ, Lim WA (1999) Structure of the enabled/VASP homology 1 domain-peptide complex: a key component in the spatial control of actin assembly. *Cell* 97: 471-480.

Other domains that mediate protein-protein interactions:

PDZ domains—

Hung AY, Sheng M (2002) PDZ domains: structural modules for protein complex assembly. *J Biol Chem.* 277: 5699-5702.

Sheng M, Sala C (2001) PDZ domains and the organization of supramolecular complexes. *Annu Rev Neurosci.* 24: 1-29.

Harris BZ, Lim WA (2001) Mechanism and role of PDZ domains in signaling complex assembly. *J Cell Sci.* 114: 3219-3231.

LIM domains—

Khurana T, Khurana B, Noegel AA (2002) LIM proteins: association with the actin cytoskeleton. *Protoplasma* 219: 1-12.

Brown S, Coghill ID, McGrath MJ, Robinson PA (2001) Role of LIM domains in mediating signaling protein interactions. *IUBMB Life.* 51: 359-364.

Bach I (2000) The LIM domain: regulation by association. *Mech Dev.* 91: 5-17.

Jurata LW, Gill GN (1998) Structure and function of LIM domains. *Curr Top Microbiol Immunol.* 228: 75-113.

SAM domains—

Ramachander R, Kim CA, Phillips ML, Mackereth CD, Thanos CD, McIntosh LP, Bowie JU (2002) Oligomerization-dependent association of the SAM domains from *Schizosaccharomyces pombe* Byr2 and Ste4. *J Biol Chem.* 277: 39585-39593.

Wang WK, Bycroft M, Foster NW, Buckle AM, Fersht AR, Chen YW (2001) Structure of the C-terminal sterile alpha-motif (SAM) domain of human p73 alpha. *Acta Crystallogr D Biol Crystallogr.* 57: 545-551.

Stapleton D, Balan I, Pawson T, Sicheri F (1999) The crystal structure of an Eph receptor SAM domain reveals a mechanism for modular dimerization. *Nat Struct Biol.* 6: 44-49.

Thanos CD, Faham S, Goodwill KE, Cascio D, Phillips M, Bowie JU (1999) Monomeric structure of the human EphB2 sterile alpha motif domain. *J Biol Chem* 274: 37301-37306.

DEP domains—

Chen S, Hamm HE (2006) DEP domains: more than just membrane anchors. *Dev. Cell* 11: 436-438.

Ballon DR, Flanary PL, Gladue DP, Konopka JB, Dohlman HG, Thorner J (2006) DEP-domain-mediated regulation of GPCR signaling responses. *Cell* 126: 1079-1093.

Domains that Recruit Proteins to Membrane Lipids:

General Background—

Narayan K, Lemmon MA. (2006) Determining selectivity of phosphoinositide-binding domains. *Methods* 39: 122-133.

Toker A (2002) Phosphoinositides and signal transduction. *Cell Mol Life Sci* 59: 761-779.

Itoh T, Takenawa (2002) Phosphoinositide-binding domains. Functional units for temporal and spatial regulation of intracellular signalling. *Cell Signal* 14: 733-743.

Cantley LC (2002) The phosphoinositide 3-kinase pathway. *Science* 296: 1655-1657.

Hurley JH, Meyer T (2001) Subcellular targeting by membrane lipids. *Curr Opin Cell Biol.* 13: 146-152.

Katso R, Okkenhaug K, Ahmadi K, White S, Timms J, Waterfield MD (2001) Cellular function of phosphoinositide 3-kinases: implications for development, homeostasis, and cancer. *Annu Rev Cell Dev Biol* 17: 615-675.

PH Domains—

Yu JW, Mendrola JM, Audhya A, Singh S, Keleti D, DeWald DB, Murray D, Emr SD, Lemmon MA (2004) Genome-wide analysis of membrane targeting by *S. cerevisiae* pleckstrin homology domains. *Mol. Cell* 13: 677-688.

Lemmon MA, Ferguson KM, Abrams CS (2002) Pleckstrin homology (PH) domains and the cytoskeleton. *FEBS Letts.* 513: 71-76.

Maffucci T, Falasca M (2001) Specificity in pleckstrin homology (PH) domain membrane targeting: a role for a phosphoinositide-protein co-operative mechanism. *FEBS Lett.* 506: 173-179.

Lemmon MA, Ferguson KM (2001) Molecular determinants in pleckstrin homology domains that allow specific recognition of phosphoinositides. *Biochem Soc Trans.* 29: 377-384.

Fruman DA, Rameh LE, Cantley LC (1999) Phosphoinositide binding domains: embracing 3-phosphate. *Cell* 97: 817-820.

PX Domains—

Ellson CD, Andrews S, Stephens LR, Hawkins PT (2002) The PX domain: a new phosphoinositide-binding module. *J Cell Sci.* 115: 1099-1105.

Xu Y, Seet LF, Hanson B, Hong W (2001) The Phox homology (PX) domain, a new player in phosphoinositide signalling. *Biochem J.* 360: 513-530.

Sato TK, Overduin M, Emr SD (2001) Location, location, location: membrane targeting directed by PX domains. *Science* 294: 1881-1885.

Simonsen A, Stenmark H (2001) PX domains: attracted by phosphoinositides. *Nature Cell Biol.* 3: E179-E182.

Wishart MJ, Taylor GS, Dixon JE (2001) Phoxy lipids: revealing PX domains as phosphoinositide binding modules. *Cell* 105: 817-820.

C2 Domains—

Benes CH, Wu N, Elia AE, Dharia T, Cantley LC, Soltoff SP. (2005) The C2 domain of PKCdelta is a phosphotyrosine binding domain. *Cell* 121: 271-280.

Nalefski EA, Falke JJ (2002) Use of fluorescence resonance energy transfer to monitor Ca(2+)-triggered membrane docking of C2 domains. *Methods Mol Biol.* 172: 295-303.

Bai J, Wang P, Chapman ER (2002) C2A activates a cryptic Ca(2+)-triggered membrane penetration activity within the C2B domain of synaptotagmin I. *Proc Natl Acad Sci USA* 99: 1665-1670.

Cho W (2001) Membrane targeting by C1 and C2 domains. *J Biol Chem.* 276: 32407-32410.

Rizo J, Sudhof TC (1998) C2-domains, structure and function of a universal Ca2+-binding domain. *J Biol Chem.* 273: 15879-15882.

ENTH Domains—

De Camilli P, Chen H, Hyman J, Panepucci E, Bateman A, Brunger AT (2002) The ENTH domain. *FEBS Lett.* 513: 11-18.

Itoh T, Koshiba S, Kigawa T, Kikuchi A, Yokoyama S, Takenawa (2001) Role of the ENTH domain in phosphatidylinositol-4,5-bisphosphate binding and endocytosis. *Science* 291: 1047-1051.

FYVE Domains—

Stenmark H, Aasland R, Driscoll PC (2002) The phosphatidylinositol 3-phosphate-binding FYVE finger. *FEBS Lett.* 513: 77-84.

Gillooly DJ, Simonsen A, Stenmark H (2001) Cellular functions of phosphatidylinositol 3-phosphate and FYVE domain proteins. *Biochem J.* 355: 249-258.

Misra S, Miller GJ, Hurley JH (2001) Recognizing phosphatidylinositol 3-phosphate. *Cell* 107: 559-562.

Kutateladze TG, Ogburn KD, Watson WT, de Beer T, Emr SD, Burd CG, Overduin M (1999) Phosphatidylinositol 3-phosphate recognition by the FYVE domain. *Mol Cell.* 3: 805-811.

Modeling of Signaling Networks:

Gordon A, Colman-Lerner A, Chin TE, Benjamin KR, Yu RC, Brent R (2007) Single-cell quantification of molecules and rates using open-source microscope-based cytometry. *Nature Methods* 4: 175-181.

Aldridge BB, Burke JM, Lauffenburger DA, Sorger PK (2006) Physicochemical modelling of cell signalling pathways. *Nature Cell Biol.* 8: 1195-1203.

Chen RE, Thorner J (2005) Systems biology approaches to cell signaling research. *Genome Biol.* 6: 235.1-235.5.

Papin JA, Hunter T, Palsson BO, Subramaniam S (2005) Reconstruction of cellular signalling networks and analysis of their properties. *Nature Rev. Mol. Cell Biol.* 6: 99-111.

Yildirim N, Hao N, Dohlman HG, Elston TC (2004) Mathematical modeling of RGS and G-protein regulation in yeast. *Methods Enzymol.* 389: 383-398.

Levchenko A (2003) Dynamical and integrative cell signaling: challenges for the new biology. *Biotechnol Bioeng.* 84: 773-782.

Ferrell JE, Xiong W (2001) Bistability in cell signaling: How to make continuous processes discontinuous, and reversible processes irreversible. *Chaos* 11: 227-232.