Foundations in Biomedical Sciences IV:
Mechanisms of Cell Communication

Spring 2012
Tuesdays, Thursdays, and Fridays, 9:30 am to 11:20 am
Fridays, 12:15 pm to 1:45 pm

Course description

The fourth module of the Foundations in Biomedical Sciences course will focus on the mechanisms of cell communication. This module will begin by discussing overarching concepts before examining the specific types of molecules that initiate and transduce signals. Examples of cell signaling and subsequent cellular responses will then be considered in different contexts to provide a framework on which future learning can be applied. As the module progresses, the complexity of the systems explored will increase from individual cells to multicellular environments such as tissues, organs and organisms. In addition, normal processes as well as the dysregulation of cell-cell communication in disease will be studied.

The course will be aimed towards first year Ph.D. students in the Division of Graduate Medical Sciences. The class will be taught by members of the Division in a variety of Departments utilizing a combination of traditional lectures and discussion sections focusing on primary research. There will be a total of 7 hours of class time per week. Supplementary study materials will be made available using Blackboard (www.blackboard.bu.edu) to aid students in the review of the material. Reading materials will be taken primarily from the scientific literature and will utilize examples of classical studies as well as recent works. Students will be evaluated on their performance on a quiz, problem set, and examination along with active participation in discussion sections.

Course Learning Objectives

At the end of this module students will be able to:

1. Describe the biochemical basis of ligand-receptor interactions

2. Explain in lay language how extracellular signals are interpreted by cells

3. Give examples of how cells communicate with their neighbors to form multicellular structures

4. Compare the mechanisms of tissue maintenance with the breakdown of tissue homeostasis

5. Relate how the dysregulation of normal signaling can lead to disease

Course Managers

Karen Symes, Ph.D.
Associate Professor
Department of Biochemistry
K-408, 617-638-4077
symes@bu.edu

Tien Hsu, Ph.D.
Professor
Department of Medicine
X-440, 617-638-7599
tienh@bu.edu

Additional Participating Faculty

Isabel Dominguez, Ph.D., Assistant Professor, Dept. Medicine, X-438
617-414-1829
isdoming@bu.edu

Katya Ravid, DSc., Ph.D., Professor, Depts. Medicine and Biochemistry, W-601
617-638-5053
kravid@bu.edu

Konstantin Kandror, Ph.D., Professor, Dept. Biochemistry, K-123
617-638-5049
kkandror@bu.edu

Stella Martin, Ph.D., Research Associate, Dept. Pharmacology and Experimental Therapeutics, L-601
617-638-5323
scmartin@bu.edu

Caryn Navarro, Ph.D., Assistant Professor, Dept. Medicine, L-310C
617-638-4278
cnavarro@bu.edu

Nader Rahimi, Ph.D., Associate Professor, Dept. Pathology and Laboratory of Medicine
670 Albany, 5th floor
617-638-5011
nrahimi@bu.edu

Grading:

Quiz	10%
Final Exam	50%
Problem Set	20%
Breakout Sessions	20%
Total	100%

Recommended reference materials to supplement reading of the literature include:

Alberts, B., Johnson, A., Lewis, J., Raff, M., Roberts, K., Walter, P. *Molecular Biology of the Cell.* 5th ed. Garland Science, 2007. Chapters 15-23

Dates	Class	Instructor
January 10	**Lecture 1:** Introduction to basic concepts of cell communication. —How do cells signal to one another: extracellular signals, contact-dependant signaling, paracrine signaling, autocrine signaling, gap junctions —How are extracellular signals received and processed by cells: ligand-receptor interactions, receptor domains, signaling cascades, feedback loops. *1. Yaffe (2002) Phosphotyrosine-Binding Domains In Signal Transduction. Nature Rev. Molecular Cell Biology 3:177-186* *2. Pawson et al (2001) SH2 domains, interaction modules and cellular wiring. Trends in Cell Biology 11:504-511* *3. Bhattacharyya et al (2006) Domains, Motifs, and Scaffolds: The Role of Modular Interactions in the Evolution and Wiring of Cell Signaling Circuits. Annu. Rev. Biochem.75:655–80.*	Rahimi
January 12	**Lecture 2:** Introduction to cell signaling – part 1 —The signaling mechanisms of receptor tyrosine kinases (RTKs): receptor dimerization, transautophosphorylation, docking sites and signaling effectors, cytoplasmic tyrosine kinases, Ras superfamily, phosphotases, attenuation of signaling —The signaling mechanisms of serine/threonine kinase receptors: TGF-beta receptor, SMADS —JAK/STAT: fast track to the nucleus *1. Lemmon and Schlessinger (2010) Cell signaling by receptor tyrosine kinases. Cell. 141:1117-1134.* *2. Xu and Huang (2010) Receptor tyrosine kinase coactivation networks in cancer. Cancer Res. 70:3857-3860.* *3. Heldin and Moustakas (2011) Role of Smads in TGFβ signaling. Cell Tissue Res. Jun 4. [Epub ahead of print]*	Kandror
January 13	**Lecture 3:** Introduction to cell signaling – part 2 —The signaling mechanisms of seven-transmembrane receptors in the context of rhodopsins and olfactory receptors: G-protein-coupled receptors, structure, ligands, G-proteins, signal amplification, desensitization	Kandror

	1. Rosenbaum (2009) The structure and function of G-protein-coupled receptors. Nature 459:356-363	
January 13	***Discussion Session #IV-1*** *Two classical receptor tyrosine kinase papers will be discussed in the context of modern technology:* *1. Yarden and Schlessinger (1987) Epidermal growth factor induces rapid, reversible aggregation of the purified epidermal growth factor receptor. Biochemistry. 26:1443-1451.* *2. Kazlauskas and Cooper. 1989. Autophosphorylation of the PDGF receptor in the kinase insert region regulates interactions with cell proteins. Cell 58:1121-1133.* *Problem set will be handed out to be reviewed, discussed and returned in #IV-3*	
January 17	**Lecture 4:** Introduction to cell signaling – part 3 —Second messengers: cAMP signaling, phospholipase C signaling, Ca^{2+}, CaM Kinase, direct activation of ion channels, stimulation of transcription *1. Lipp and Reither (2011) Protein Kinase C: The "Masters" of Calcium and Lipid. Cold Spring Harb Perspect Biol. Published in Advance May 31, 2011*	Kandror
January 19	**Lecture 5:** The regulation of cell life and death —How a loss of cell cycle control can lead to cancer —Cell death and senescence: Apoptosis pathways, ER stress, Necrosis *1. Bueno and Malumbres (2011) MicroRNAs and the cell cycle. Biochim Biophys Acta. 1812:592-601.* *2. Brady et al. (2011) Distinct p53 Transcriptional Programs Dictate Acute DNA-Damage Responses and Tumor Suppression. Cell. 145:571-83.* *3. Ren et al (2010) BID, BIM, and PUMA are essential for activation of the BAX- and BAK-dependent cell death program. Science 330:1390-1393.*	Ravid
January 20	**Lecture 6:** Control of cell movement —How RhoGTPases form the functional link between	Symes

	extracellular signals and the cytoskeleton —How cell movements can be directed: Chemotaxis, Dictyostelium, cAMP signaling, Drosophila border cell migration, PDGF/VEGF signaling —What happens when cell movements are not regulated: Metastasis *1. Wang et al (2011) Signaling mechanisms for chemotaxis Dev Growth Differ. 53:495-502.* *2. Sanz-Moreno et al. (2008). Rac activation and inactivation control plasticity of tumor cell movement. Cell 135:510-523*	
January 20	***Discussion Session #IV-2*** *In class quiz.* *Discussion of the research articles assigned for lectures 5 and 6 with emphasis on understanding the big picture in relation to cell communication and also the methodologies used.*	
January 24	**Lecture 7:** Creating tissue boundaries and organizing different cell types (Martin) —How boundaries of different cell types within a tissue are established: Notch signaling and contact inhibition. —How neurons make connections using repelling and attracting signals: Semaphorin signaling and guidance cues. *1. Pierfelice et al (2011) Notch in the Vertebrate Nervous System: An Old Dog with New Tricks. Neuron 69: 840-855* *2. Mehlen et al (2011) Novel roles for Slits and netrins: axon guidance cues as anticancer targets? Nat. Rev. Cancer 11:188-197.* *3. Derijck et al (2010) Semaphorin signaling: molecular switches at the midline. Trends in Cell Biology 20:568–576.*	Martin
January 26	**Lecture 8:** Epithelial morphogenesis —How epithelium, the "cover sheet" of all organs, develops during embryonic development: formation and maintenance of cell-cell junctions; establishment of polarity of epithelial cells. —What happens when the epithelial structure is broken down: Epithelial-to-mesenchymal transition in development and disease.	Martin

	1. Yang and Weinberg (2008) Epithelial-Mesenchymal Transition: At the Crossroads of Development and Tumor Metastasis. Developmental Cell 14:818-829. *2. Kalluri and Weinberg (2009) The basics of epithelial-mesenchymal transition. J. Clin. Invest. 119:1420- 1428.* *3. Chaffer, et al. (2011) A Perspective on Cancer Cell Metastasis. Science 331:1559-1564.*	
January 27	**Lecture 9:** Organizing an embryo —How different body parts are determined during embryonic development, part 1: Axis determination in invertebrates Drosophila D/V and A/P axis; RNA localization and the concept of the morphogen. — How different body parts are determined during embryonic development, part 2: Axis determination in vertebrates (wnt signaling and growth factors). *1. St. Johnston and Nusslein-Volhard (1992) The origin of pattern and polarity in the Drosophila embryo. Cell 68:201-219.* *2. Lynch and Roth (2011) The evolution of dorsal–ventral patterning mechanisms in insects. Genes & Dev. 25:107-118* *3. Plouhinec and De Robertis (2009) Systems Biology of the Self-regulating Morphogenetic Gradient of the Xenopus Gastrula Cold Spring Harb Perspect Biol. 1:a001701*.	Navarro
January 27	***Discussion Session #IV-3*** *Problem set review.* *Papers for #IV-4 will be distributed. Each student will write a lay abstract based on one of the assigned papers.* *1. Stone et al. (1996) The tumour-suppressor gene patched encodes a candidate receptor for Sonic hedgehog. Nature 384:129-34.* *2. Nonaka et al. (1998) Randomization of left-right asymmetry due to loss of nodal cilia generating leftward flow of extraembryonic fluid in mice lacking KIF3B motor protein. Cell 95:829-37.*	

January 31	Lecture 10: Stem cells —What is a stem cell —Properties and maintenance of stem cells. —The ultimate totipotent cells: Germ cell formation. *1. Sareen and Svendsen (2010) Stem cell biologists sure play a mean pinball. Nature Biotechnology 28:333–335* *2. Cinalli et al. (2008) Germ cells are forever. Cell 132:559-62.*	Navarro
February 2	**Lecture 11:** Cell differentiation —How cells diverge from common progenitors: Wnt signaling and hedgehog signaling. —How the differentiation process can go wrong: Wnt signaling in cancer progression and the role of hedgehog signaling in basal cell carcinoma. *1. Barker (2011) The canonical Wnt/beta-catenin signalling pathway. Methods Mol Biol. 468:5-15.* *2. Takebe (2011) Targeting cancer stem cells by inhibiting Wnt, Notch, and Hedgehog pathways. Nat Rev Clin Oncol. 8:97-106.*	Dominguez
February 3	**Lecture 12:** Forming complex structures — Organ building: how cells respond to morphogens and signaling pathways to make a three-dimensional structure, the heart *1. Vincent and Buckingham (2010). How to make a heart: the origin and regulation of cardiac progenitor cells. Curr Top Dev Biol. 90:1-41.* *2. Takeuchi JK, Bruneau (2009). Directed transdifferentiation of mouse mesoderm to heart tissue by defined factors. Nature 459:708-11.*	Dominguez
February 3	***Discussion Session #IV-4*** *In class presentation of lay abstract and critique*	
February 7	**MODULE IV FINAL EXAM**	