University of Pennsylvania
CHEMISTRY 700-001: Chemical Biology
Fall Semester 2009

Instructor: E. James Petersson (ejpetersson@sas.upenn.edu)
Office hours by appointment.

Reading: The course will draw from the primary literature. The following texts may be useful for review of 1) physical organic chemistry principles, 2) understanding organic reaction mechanisms, 3) biochemical reaction mechanisms, 4) biological pathways, 5) basic biophysics.
1) Dougherty and Anslyn, *Modern Physical Organic Chemistry*
2) Carey and Sundberg, *Advanced Organic Chemistry*
3) Lehninger, *Principles of Biochemistry*
4) Alberts *et al*, *Molecular Biology of the Cell*
5) Fersht, *Structure and Mechanism in Protein Science*

Course Outline: This course will focus on current topics in Chemical Biology, particularly experiments in which 1) chemical synthesis enables one to probe or control biological systems in novel ways or 2) manipulation of biological systems facilitates novel chemical syntheses. As the goal of the course is to familiarize students with innovative recent experimental approaches and to stimulate them to conceive of their own new methodology, students will be responsible for delivering presentations on topics selected from the literature and generating several novel research proposal ideas, one of which will be elaborated into a full proposal. The prepared seminar will allow students to explore topics not covered in Prof. Petersson's lectures or to research one of those topics in more depth. The proposal will be evaluated for creativity, feasibility, and impact.

Seminar Dates: Oct. 27: Topic selection and scheduling of student seminars.

Students must submit an outline of their student seminar two weeks before their scheduled seminar date and meet to discuss a draft of the seminar one week in advance.

Proposal Dates:
Oct. 1: First one page preproposal due.
Oct. 15: Second preproposal due.
Nov. 3: Third preproposal due.
Nov. 19: Final preproposal due.
Nov. 23–25: Student meetings to select full proposal topic.
Dec. 10: Full six-page proposal due.

Extra class sessions will be scheduled during reading period for oral presentations of the final proposals.

Exams: Three take-home exams will be given during the term, due one week after distribution. (Oct. 15, Nov. 19., Dec. 12).

Date	Topic
10-Sep	**Overview** Outline of topics to be covered in the course and those available as in-class seminar topics. Discussion of chemical and biological background of course.
15-Sep	**Sequence-specific DNA Recognition by "Small" Molecules** From non-specific intercalators (ethidium bromide) and DNA damage agents (enediynes) to sequence-specific polymers like polyamides and peptide nucleic acids (PNAs). Dervan, *Biorg. Med. Chem*. **9**, 2215-2235 (2001) Hannon, *Chem. Soc. Rev*. **36**, 280-295 (2007)
17-Sep	**Unnatural DNA** The synthesis and enzymatic incorporation of unnatural nucleic acids into DNA backbones as stucture probes (e.g. sequencing) or for engineering purposes. Piccirilli, *Nature* **343**, 33-37 (1990) Kool, *Angew. Chem. Int. Ed.* **39**, 990-1009 (2000) Hirao, *Curr. Opin. Chem. Biol.* **10**, 622-627 (2006) Eschenmoser, *Science* **284**, 2118-2124 (1999)
22-Sep	**RNA Aptamers, Ribozymes, and Selection** Non-coding RNAs, some discussion of the mechanism of natural RNA enzymes; focus on selection of sequences for function. Doudna, *Nature* **418**, 222-228 (2002) Mayer, *Angew. Chem. Int. Ed*. **48**, 2672-2689 (2009)
24-Sep	**Modified RNAi and Riboswitches** The basic mechanism of RNA interference (RNAi), delivery of interfering RNA to cells. Naturally occurring riboswitches as drug targets, and ways in which they can be introduced for gene control. Gallivan, *Curr. Opin. Chem. Biol.* **11**, 612-619 (2007) Blount, *Nat. Biotechnol.* **24**, 1558-1564 (2006) Whitehead, *Nat. Rev. Drug Disc.* **8**, 129-138 (2009)
29-Sep	**Unnatural Amino Acid Mutagenesis Methodolgy** Review of ribosomal function. Sense codon reassignment and nonsense suppression. Compare and contrast three methods for ribosomal unnatural amino acid incorporation: chemical synthesis, ribozyme aminoacylation, 21st synthetase Noren, *Science* **244**, 182-188 (1989) Murakami, *Nat. Meth.* **3**, 357-359 (2006) Wang, *Angew. Chem. Int. Ed.* **44**, 34-66 (2005)
1-Oct	**Unnatural Amino Acid Applications** Use of unnatural amino acids in biological experiment both *in vitro* and *in vivo*, combination with ribosomal manipulation for expanded amino acid coding Wang, *Chem. Biol.* **16**, 323-336 (2009) Mendel, *Ann. Rev. Biophys. Biomol. Struct.* **24**, 435-462 (1995)
6-Oct	**DNA- and mRNA-Templated Chemical Synthesis** Nucleic acid polymers are used to direct complex organic syntheses in both water and organic solvent. PCR amplification is also used to analyze reactions. Takahashi, *Trends Biochem. Sci.* **28**, 159-165 (2003) Wrenn, *Ann. Rev. Biochem*. **76**, 31-349 (2007)
8-Oct	**Chemical Protein Synthesis** Brief discussion of solid-phase synthesis methodology, focus on segment ligation chemistry and semi-synthetic approaches Kent, *Chem. Soc. Rev*. **38**, 338-351 (2009) Flavell, *Acc. Chem. Res*. **42**, 107-116 (2009) Hackenberger, *Angew. Chem. Int. Ed.* **47**, 10030-10074 (2008)

13-Oct	**Manipulation of Protein Folding and Protein-Protein Interations** Fundamentals of protein-protein interactions (both inter- and intramolecular), strategies for synthetic control of secondary, tertiary, and quaternary structure. Nilsson, *Chem. Rev.* **101**, 3153-3163 (2001) Garner, *Org. Biomol. Chem.* **5**, 3577-3585 (2007)
15-Oct	**Foldamers** Non-biological polymers that adopt specific folded shapes in solution like biomolecules. β-peptides, peptoids, modified nucleic acids, polyarylalkynes. Gellman, *Acc. Chem. Res.* **31**, 173-180 (1998) Goodman, *Nat. Chem. Biol.* **29**, 252-262 (2007)
20-Oct	**Biomolecule Labeling Technologies** Site-specific protein, polysaccharide, and nucleic acid modification with synthetic molecules, focus on chemoenzymatic routes and "bioorthogonal" reactions. Carrico, *Chem. Soc. Rev.* **37**, 1423-1431 (2008) Lavis, *ACS Chem. Biol.* **3**, 142-155 (2008) Foley, *Curr. Opin. Chem. Biol.* **11**, 12-19 (2007) Goncalves, *Chem. Rev.* **109**, 190-212 (2009)
22-Oct	**Engineering Small Molecule Biosynthesis** Redirection of biosynthetic pathways through directed evolution, application of unnatural substrates, or genetic engineering of multi-enzyme complexes. Walsh, *Acc. Chem. Res*. **41**, 4-10 (2008) Keasling, *ACS Chem. Biol.* **3**, 64-76 (2008)
27-Oct	**Monitoring Biomolecule Interactions** Small molecules and proteins engineered to detect transient interactions and output a signal (typically fluorescent or chemiluminescent). Villalobos, *Annu. Rev. Biomed. Eng.* **9**, 321-349 (2007) Giepmans, *Science* **312**, 217-224 (2006)
29-Oct	**Monitoring Small Molecule Chemical Messengers** Proteins, nucleic acids, or small molecules designed to report on the concentrations of small (< 1 kD) molecule concentrations in living cells. Miller, *Curr. Opin. Chem. Biol.* **11**, 620-625 (2007) Que, *Chem. Rev.* **108**, 1517-1549 (2008)
3-Nov	**"Bump and Hole" Chemical Genetics** Small molecule synthesis used in conjunction with genetic manipulation to understand signaling pathways and identify targets for pharmaceuticals. Alaimo, *Curr. Opin. Chem. Biol.* **5**, 360-367 (2001) Buskirk, *Chem. Biol.* **12**, 151-161 (2005)
5-Nov	**Photochemical Control of Cell Signaling** Techniques for incorporating photochemical triggers, either through chemical synthesis or the genetic manipulation of photo-responsive proteins. Lee, *ACS Chem. Biol.* **4**, 409-427 (2009) Gorostiza, *Science* **322**, 395-399 (2008)
10-Nov	**Geometric Control with Surfaces and Microfluidics** Precise control of surface geometry and solution flow for studying cellular interactions in defined environments; focus on applications not fabrication. Mrksich, *Chem. Soc. Rev.* **29**, 267-273 (2000) Kastrup, *Acc. Chem. Res.* **41**, 549-558 (2008)
12-Nov	**Proteomics and Metabolomics** Mass spectrometry and array-based technologies used to document changes in protein expression and activity in response to extracellular stimuli. Cravatt, *Annu. Rev. Biochem*. **77**, 383-414 (2008) Cravatt, *Nature* **450**, 991-1000 (2007)

17-Nov	Student Seminars
19-Nov	Student Seminars
24-Nov	Student Seminars
1-Dec	Student Seminars
3-Dec	Student Seminars
8-Dec	Student Seminars
10-Dec	Student Seminars