University of Pennsylvania
CHEM/BMB 751: Chemical Biology
Spring Semester 2020

Instructors: E. James Petersson (ejpetersson@sas.upenn.edu)
Office hours by appointment except during exams.

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) Voet and Voet, *Fundamentals of Biochemistry*
4) Alberts *et al*, *Molecular Biology of the Cell*
5) Kuriyan, *The Molecules of Life*

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 two novel research proposal ideas, one of which will be elaborated into a full proposal. The proposal will be evaluated for creativity, feasibility, and impact.

Student Papers: Students are responsible for leading discussion of one paper. Each student will lead discussion (or students may work together to compare/contrast papers) and present a question on the paper to the class.

Proposal Dates: Feb 8: First 1-2 page preproposal due
Mar 26: Second preproposal due
Apr 29/30: Student meetings to select full proposal topic
~May 1: Brief proposal presentations to the class
~May 11: Full six-page proposal due

Exams: Two take-home exams will be given during the term, due one class week after distribution. Any notes or literature may be used in answering exam questions (Feb 27/Mar 5, Apr 7/Apr 14).

Date	Topic
16-Jan	**Lecture 1: Overview** Outline of topics to be covered in the course. Discussion of chemical and biological background of course.
21-Jan	**Lecture 2: Sequence-specific DNA Recognition by "Small" Molecules** From non-specific intercalators (ethidium bromide) and DNA damage agents to sequence-specific polymers like polyamides and peptide nucleic acids (PNAs).
23-Jan	**Lecture 3: Unnatural DNA and RNA** The synthesis and enzymatic incorporation of unnatural nucleic acids into DNA/RNA backbones as structure probes (e.g. sequencing) or for engineering purposes.
28-Jan	**Lecture 4: RNA Aptamers, Ribozymes, and Riboswitches** Non-coding RNAs, some discussion of the mechanism of natural RNA enzymes; focus on selection of sequences for function; naturally occurring riboswitches as drug targets, and ways in which they can be introduced for gene control.
30-Jan	**Lecture 5: Gene Expression Modification Tools** The basic mechanism of RNA interference (RNAi), delivery of interfering RNA to cells; CRISPR/Cas and zinc finger/TALEN proteins for gene editing in vivo.
4-Feb	**Lecture 6: Engineering Protein Translation** Sense codon reassignment, nonsense suppression, and ribosome modification. Compare and contrast three methods for ribosomal unnatural amino acid incorporation: chemical synthesis, ribozyme aminoacylation, 21st synthetase.
6-Feb	**Lecture 7: Unnatural Amino Acid Applications** Use of unnatural amino acids in biological experiment both *in vitro* and *in vivo.*
8-Feb	**Preproposal 1 Due**
11-Feb	**No Lecture**
13-Feb	**Lecture 8: DNA- and mRNA-Templated Chemical Synthesis** Nucleic acid polymers used to direct complex organic syntheses in both water and organic solvent. PCR amplification used to analyze reactions.
18-Feb	**Lecture 9: Engineering Small Molecule Biosynthesis** Redirection of biosynthetic pathways through directed evolution, application of unnatural substrates, or genetic engineering of multi-enzyme complexes.
20-Feb	**Lecture 10: Chemical Protein Synthesis** Brief discussion of solid-phase synthesis methodology, focus on segment ligation chemistry and semi-synthetic approaches.
25-Feb	**Lecture 11: Manipulation of Protein Folding and Protein Interactions** Fundamentals of protein-protein interactions (both inter- and intramolecular), strategies for synthetic control of secondary, tertiary, and quaternary structure.
27-Feb	**Lecture 12: Foldamers** Non-biological polymers that adopt specific folded shapes in solution like biomolecules. β-peptides, peptoids, modified nucleic acids, polyarylalkynes.
27-Feb	**Exam 1 Distributed**
3-Mar	**Office Hours**
5-Mar	**Lecture 13: Biomolecule Labeling Technologies** Site-specific protein, polysaccharide, and nucleic acid modification with synthetic molecules, focus on chemoenzymatic routes and "bioorthogonal" reactions.
5-Mar	**Exam 1 Due**

17-Mar	**Lecture 14: Monitoring Biomolecule Interactions** Small molecules and proteins engineered to detect transient interactions and output a signal (typically fluorescent or chemiluminescent).
19-Mar	**Lecture 15: 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.
24-Mar	**Lecture 16: "Bump and Hole" Chemical Genetics** Small molecule synthesis used in conjunction with genetic manipulation to understand signaling pathways and identify targets for pharmaceuticals.
26-Mar	**Lecture 17: Photochemical Control of Cell Signaling** Techniques for incorporating photochemical triggers, either through chemical synthesis or the genetic manipulation of photo-responsive proteins.
26-Mar	**Preproposal 2 Due**
31-Mar	**Lecture 18: 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.
2-Apr	**Lecture 19: Proteomics and Metabolomics** Mass spectrometry and array-based technologies used to document changes in protein expression and activity in response to extracellular stimuli.
7-Apr	**Lecture 20: Optogenetics** Genetically-encoded devices that stimulate specific cellular pathways in response to light input enable in vivo studies with high temporal and spatial resolution.
7-Apr	**Exam 2 Distributed**
9-Apr	**Office Hours**
14-Apr	**Student Presentations 1**
14-Apr	**Exam 2 Due**
16-Apr	**Student Presentations 2**
21-Apr	**Student Presentations 3**
23-Apr	**Student Presentations 4**
28-Apr	**Student Presentations 5**
~1-May	**Proposal Presentations**
~11-May	**Final Proposal Due**