# Course Syllabus for "CHEM1230: Chemical Biology"

*Instructor:*
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Geochem 331
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*General Information*: "CHEM 1230: Chemical Biology" is a survey course covering some of the ingenious methods that chemists have devised for studies of biological molecules and biological processes. There will be in-depth discussions of transformative experiments in the history of biology that employed chemical tools, as well coverage of some exciting new developments from the past decade.

Given the inter-disciplinary nature of the content, this course is open to students with backgrounds in the biological and/or the physical sciences. Familiarity with fundamental concepts of organic chemistry and biochemistry will be assumed.

*Course Materials:* The primary textbook for this course is "Introduction to Bioorganic Chemistry and Chemical Biology" by Weiss and Van Vrancken. For the lectures, the content of the text will be enhanced by information from the primary scientific literature and review articles. The instructor will provide all of the reference material in-class or via the course web site.

Additional Reading sources
Any modern-day biochemistry or organic chemistry text book
Blackburn, G.M. & Gait, M.J. Nucleic Acids in Chemistry and Biology
Branden, C. & Tooze, J. Introduction to Protein Structure.
Fersht, A. Structure and Mechanism in Protein Science.
McMurry, J. & Begley, T. The Organic Chemistry of Biological Pathways.
Walsh, C. T. Antibiotics: Actions, Origins, and Resistance
Walsh, C. T. Post-Translational Modification of Proteins: Expanding Nature's Inventory

*Course Activities:* This course includes lectures and in-class discussions.

*Course Goals:* Upon successful completion of this course, students will understand and be able to explain the following:

•The chemical bases of the "Central Dogma of Molecular Biology"
•The structures and reactivity of amino acids, proteins, nucleic acids, carbohydrates, lipids, steroids, enzyme co-factors, and other biological molecules.
•Chemical methods used to elucidate the structures of and synthesize DNA, RNA, proteins, and carbohydrates.
•Design and identification of small molecule ligands for biological macromolecules
•Development and application of small molecules for studies of biological processes (chemical genetics and diversity-oriented organic synthesis)
• Biosynthesis and engineering of natural products
• Contributions of key scientists working at the interface of chemistry and biology

*Assessments:* Final grades will be assigned based on the scores on weekly problem sets (20%), the final paper (20%), and three examinations (60%- 20% for each exam).

A problem set will be distributed each Wednesday and will be due on the following Wednesday before 5 pm.

Examination Schedule:

Wednesday, October 8 from 7-10 pm (location to be determined)
Wednesday, November 12 from 7-10 pm (location to be determined)
Saturday, December 13, 2014 from 2-5 pm (location to be determined)

The final paper is a 10-page (single spaced, not including figures) describing examples from the literature (within the past five years) wherein chemical methods were used to provide new insights into a biological molecule or phenomenon. Alternatively, the paper can provide a partial or complete career retrospective on an established chemical biologist. The topic and abstract must be submitted to Prof. Sello by December 3, 2014 for final approval. The final paper is due by 5 pm on December 17, 2014.

**Course Topics**

Overview of DNA Structure

- Chemistry and structure of nucleobases, deoxyribose, and phoshodiester backbone
- Base-pairing and aromatic p-stacking
- Packaging of DNA into Chromatin
- Natural and Non-natural DNA superstructures

Analysis of DNA Structure

- X-Ray Crystallography
- Electrophoresis
- Sequencing of DNA- Comparison of Maxim-Gilbert, Sanger, Illumina, and Nanopore methods

Synthesis of DNA

- DNA Replication
- Polymerase Chain Reaction
- Chemical synthesis of DNA- Khorana (via phosphates), Letsinger (via phosphites), and Carruthers (via phosphoramidites)

Modifications of DNA

- Biological methylation of DNA
- Alkylative damage of DNA and enzymatic repair
- Oxidative damage of DNA enzymatic repair
- Cleavage and other damage of DNA by natural products and drugs

Mimicry of DNA

- Peptide Nucleic Acids
- Polyamide Mimics of DNA

Overview of RNA Structure

- Chemistry and structure of nucleobases, ribose, and phoshodiester backbone
- Hydrogen-bonding
- RNA secondary Structure
- Nucleobases Modification

Structural Analysis of RNA

- Chemical modification (Hydroxy Radical Probing, CMCT, DMS, and kethoxal)
- SHAPE (Selective 2'Hydroxyl Acylation analyzed by Primer Extension)
- Reverse-transcription PCR
- Transcriptomics via DNA microarrays.
- RNA-Seq

RNA in Biology

- Mechanisms of Gene Transcription (chemical mapping of the transcription)
- Splicing and translation of messenger RNA
- Catalytic RNA in the ribosome
- RNA interference
- Riboswitches

Overview of Proteins

- Amino acid building blocks
- Structure of peptide bonds
- Disulfide Bridges- Chemical reductants and oxidants
- Isoelectric points of DNA
- Secondary, tertiary, and quaternary structures of DNA

Structural Analysis of Proteins

- Sequencing of DNA- Sanger Methods, Edman Degradations
- X-ray Crystallography, NMR Spectroscopy, and cryoelectron microscopy

Names and structures of the 22 proteinogenic amino acids

- three letter and one letter codes
- polar vs. non-polar; aromatic vs. aliphatic
- acidity and basicity of amino acid side chains
- conformational analysis of amino acids

Biosynthesis of Peptides via Ribosome

- Structure and Function of Ribosome
- Aminoacyl-tRNAs
- Non-ribosomal peptide synthesis
- Incorporation of non-proteinogenic amino acids into proteins

Chemical Synthesis of Peptides

- Activation of amino acids for condensation by carbodiimides
- Protecting groups (N-Boc, N-Cbz, and N-FMOC)
- Logic of solid phase peptide synthesis
- Peptides synthesis using “flow methodology”
- Native chemical ligation

Small Molecule Mimics of Proteins

- Vinylogous amino acids
- Foldamers
- Peptoids
- “Stapled” Peptides

Chemistry of Post-translational Modifications (Reversible and Irreversible modifications)

- Phosphorylation
- Protein acylation (acetylation, myristoylation, palmitoylation, ubiquitinylation)
- Protein alkylation (*N*-methylation, *S*-prenylation)
- Cysteine oxidation (*i.e.*, formyl-glycine in sulfate ester hydrolysis)
- Glycosylation
- Phosphopantetheinylation (Coenzyme A)
- Biotinylation (Biotin)
- Lipoylation (Lipoic Acid)
- Cleavage of the peptide backbone (splicing)
- Formation of a chromophore (green fluorescent protein)
- Lantibiotics

Proteomics

- Mass spectrometry
- Selective capture and analysis of proteins with chemical reagents
- iTRAQ for quantitative analyses of proteins
- Site-specific labeling of proteins

Overview of Carbohydrates
- Common monosaccharide building blocks
- Conformation and reactions of sugars
- Chemistry of glycosyl transfer reactions
- Structures of polysaccharides

Chemistry and Biology of Glycoproteins
- Conformational consequences of glycosylation on protein structure
- Metabolic labeling for the study and identification of glycoproteins

Chemical Synthesis of Oligosaccharides
- Stereoselective formation of glycosidic bonds
- Protecting group strategies
- Automated Carbohydrate Synthesis

Chemical Analysis of Metabolism
- Metabolomics
- Detecting metals in biology

Synthetic Chemistry in Biological Research
- Forward and reverse chemical genetics
- Combinatorial Chemistry and diversity-oriented synthesis
- Small molecule microoarrays
- Design and synthesis of enzyme inhibitors
- Design and synthesis of mechanistic probes of enzyme function
- Small Molecule Mimics of Proteins

Synthetic Biology for the Preparation of Small Molecules
- Chemoenzymatic synthesis of small molecules
- Engineered Polyketide Biosynthesis
- Engineered Non-Ribosomal peptide synthesis

Course Meetings

Sept.  3, Sept. 8, Sept. 10, Sept. 15, Sept. 17, Sept. 22, Sept. 24, Sept. 29
Oct. 1, Oct. 6, Oct. 8
Oct. 15
Oct. 20
Oct. 22
Oct. 27
Oct. 29
Nov. 3
Nov. 5
Nov. 10
Nov. 12
Nov. 17
Nov. 19
Nov. 24
Nov. 26
Dec. 1
Dec. 3
Dec. 8