Fall 2011 Medicinal Chemistry Approach to CHEM106 General Chemistry II (Owens) Syllabus

This syllabus is a living document; students must check the syllabus posted on the Department web site http://chem.winthrop.edu/ for any changes prior to every class attendance

- Three lecture hours per week, three credit hours
- Dates reflect T,R lecture days for Fall 2011 semester

Instructor: Pat Owens (owensp@winthrop.edu) Phone: three, two, three, four, nine, two, five
- Office Hours: SIMS312A- MF 2:00-3:00 PM

Required Course Texts:

- *MedChem*: *An Introduction to Medicinal Chemistry 4th Ed*, Graham L. Patrick, 2009
- *GenChem: Chemical Principles: The Quest for Insight, 4th Ed*, Atkins & Jones, 2008

Course Objectives:

- Strengthen thinking skills, improve study habits, and demonstrate ability to learn fundamental principles from large amounts of scientific information.
- Develop a understanding of relevant chemistry in molecular medicine and neuroscience.
- Learn fundamental chemical science principles necessary to understand the scientific basis for molecular medicine

Course Outline: This is the second half of General Chemistry, an introductory chemistry course for science and engineering majors. This course focuses on learning chemistry by examining molecular medicine. Fundamental General Chemistry principles such as molecular structure, solubility, noncovalent interactions, thermodynamics, equilibria, kinetics, and electrochemistry represent the primary reasons for how and why drugs work. Students leave this course with both with a better understanding of relevant chemistry principles and fundamental insights into the scientific basis of modern medicines. This knowledge is useful for future science courses, is very helpful in better understanding human health at the molecular level, and is extremely important in being able to make informed decisions as scientifically literate citizens in a society increasingly engaged with molecular medicine.

Perhaps most importantly, molecules that enter our bodies are of tremendous human interest, whether these substances be medications, nutrients, toxins, or substances of abuse. Learning science by understanding how these molecules interact with and affect us can be a very rewarding and enriching experience. Such knowledge and insight can also lead to discoveries that help to improve the quality and length of human life.

The thematic approach being used in the course is organized in the following manner:

- The first third of this course reviews the fundamental chemical principles needed to be mastered to understand how drugs work.
- The middle third of the course examines anti-inflammatory therapeutics, steroids, cancer treatments, and receptor drug targets. It begins with the mechanisms of action for

medications used to treat inflammation; recent discoveries demonstrate that inflammatory processes are centrally important in cancer, cardiovascular disease and metabolic-syndrome related illnesses. This part of the course covers a broad array of receptor drug targets (nucleic acids, ion channels, GPCRs, kinase-linked receptors) and closely examines receptor-drug interactions and the design of medications to modulate these.

- The final third of the course centers on neuroscience; most drugs work by targeting nerve receptors; a good understanding of neuroscience is essential. The final half of this block covers a broad spectrum of classes of psychoactive drugs. Several classes involve drugs that are most widely abused in modern societies. Most of the other classes are used to treat mental illnesses. According to the National Institute of Mental Health, mental illness is the leading cause of disability for ages 18-44. Mental disorders are common in the United States and internationally. An estimated 26.2 percent of Americans ages 18 and older suffer from a diagnosable mental disorder in a given year. Understanding how these are being treated and the mechanism of action for these medications is an important part of becoming an educated citizen.

Schedule: Lectures are scheduled twice weekly at the appointed hour and location. The course syllabus provides the specific schedule as the semester progresses. All course information is posted on the chemistry department's web page (chem.winthrop.edu).

Final Exam: Students must take the final exam with their section.

- CHEM106 class that meets Tuesday at 12:30 PM will have its final exam at 3:00 PM, Thursday, December 8, 2011

Class Preparation: This is both a very interesting and a very challenging course. Once a principle is covered during a lesson, students will be expected to demonstrate an understanding of that concept throughout the remainder of the semester. Lecture discussions will assume that students understand material from previous lessons. Graded problems throughout the course often cannot be answered without being able to successfully apply previously discussed principles. It is very important for students to continuously review course material. Athletes practice every day, often for years, to master specific skills. Successful students (and faculty) have learned to continuously reexamine those topics and principles that are not completely clear to them. Students are also encouraged to study in groups; teaching peers is perhaps the most effective way to learn chemistry.

Students are responsible for all assigned study material and for all material discussed in lecture. A great deal of important information will be provided during lecture; take excellent notes!! Lectures are not designed to reiterate assigned readings but to focus on conveying important information from various sources to understand the General Chemistry concepts that represent the molecular basis of modern medicine. You are expected to spend whatever time it requires to develop and to demonstrate an understanding of these subjects and lecture materials. You must complete each reading and problem assignments **prior** to class. For each class I recommend that you do the following:

- Study previous lecture notes; you are strongly encouraged to organize and rewrite them immediately after each lecture.
- Study and review course material topics relevant to previous class discussions.
- Read assigned lesson for upcoming lecture, take notes and identify questions
- Work assigned problems

Student Competencies: Assigned chapters, class discussion, homework, problem sets, unannounced quizzes, announced quizzes, tests, and the final exam will all center on development and evaluation of student competencies. Students should expect to face challenging and unfamiliar questions on all graded work; this is done to focus attention on competencies that students have not yet fully mastered. Students can be evaluated five to six separate times on a given competency: homework problems, unannounced quizzes, problem sets, announced quizzes, tests, and the final exam. Students are urged to not fall behind and to master each competency as soon as it is first examined.

The course web site will itemize chapter sets of student competencies to more effectively focus student study and to allow student self-evaluation of progress. Links to quizzes given to date will be added to the syllabus schedule as they are returned. Solutions to problem sets and to quizzes will not be posted since more effective student learning occurs through working through these problems individually. Class time will be used to review the quiz and test questions that challenged students most. Periodically, as time allows, graded problem sets will be reviewed in class.

Graded Exercises

- Quizzes will be routinely be given, each be worth 30 points, and often be given at the beginning of class. These quizzes will include questions to evaluate understanding of material covered during the previous lecture as well as questions to evaluate competency in problem solving skills from sets due that day.
- Assigned problem sets will each be worth 15-30 points; only specific problems will be graded. Problem sets are due at the beginning of class; no credit will be given for sets turned in late.
- The assigned review paper will be weighted 75 points.
- Two tests will be given and be weighted approximately 150 points each.
- The cumulative final exam will be worth at least 300 points. You must score better than 50% on the final exam to pass the course. You must score an A on the final exam to earn an A in the course.

Grades: Percentages will be calculated based upon total earned points divided by total points tested. There will be no makeups for graded exercises. You must score better than 50% on the final exam to pass the course. You must score an A on the final exam to earn an A in the course. The following grade range will be used: A = 93-100%; A- = 88-92%; B+ = 85-87%; B = 80-84%; B- = 76-79%; C+ = 72-75%; C = 66-71%; D = 56-65%; F = <56%

Attendance: You are expected to attend all class meetings for the full scheduled time. A student who is absent for any reason is responsible for obtaining the assignments from the instructor or a classmate. Roll will be taken occasionally and the attendance practices of students will be taken into account when final grades are assigned. Absence from a test or quiz without a written doctor's excuse or similar external agency valid documentation is inexcusable. An unexcused student absence will result in a zero for the missed grade AND a deduction of 20-100 points (determined by the weight of the missed test) from the student's previously earned points in the course. For excused absences, missed exercises will not be included in neither the earned nor total points when calculating overall course grades.

General Education Requirements: CHEM 106 and the co-requisite CHEM 108 together fulfill four hours of general education requirement for natural sciences. Listed below are Winthrop's seven fundamental student learning outcomes for natural science courses as well as examples of how they will be fulfilled in CHEM 106 and 108.

Students should be:

1. *Conversant with a few fundamental concepts from among the three main areas of natural science, including earth, life, and physical sciences.* (e.g., enzyme kinetics, protein structure, mechanism of action for psychoactive substances, dose-response toxicological curves).
2. *Able to apply the scientific methodologies of inquiry.* (e.g., CHEM 108 laboratory exercises and experiments)
3. *Able to discuss the strengths and limitations of science.* (e.g., effectiveness and adverse side effects of medicine, limitations of medication, treating inflammation)
4. *Able to demonstrate an understanding of the history of scientific discovery.* (history of human substance abuse, development of aspirin and heroine by Bayer, initial inclusion of cocaine in Coke)
5. *Able to discuss the social and ethical contexts within which science operates.* (e.g., exposure of humans to known carcinogens; addiction to nicotine, toxicity testing and side effects).
6. *Able to communicate about scientific subjects including (lab courses only) the defense of conclusions based on one's own observations.* (e.g., CHEM 108 laboratory presentations and project reports)
7. *Able to discuss the application of scientific knowledge to the social sciences and to non-scientific disciplines.* (the entire course does this)

Students with Disabilities: Winthrop University is dedicated to providing access to education. If you have a disability and require specific accommodations to complete this course, contact Services for Students with Disabilities, at 323-3290. Once you have your official notice of accommodations from Services for Students with Disabilities, please inform me as early as possible in the semester.

Student Conduct Code: "Responsibility for good conduct rests with students as adult individuals." The policy on student academic misconduct is outlined in the "Student Conduct

Code Academic Misconduct Policy" in the online *Student Handbook* (http://www2.winthrop.edu/studentaffairs/handbook/StudentHandbook.pdf).

L1 T 8/23	***Lecture 1. General Chemistry Review*** *Electronegativity, Electron Configuration, Lewis Structures, Molecular Geometry, Hybridization, Double Bond* *Energy Molecular Distribution, and Vapor Pressure*
L2 R 8/25	***Lecture 2. Intermolecular Forces (Noncovalent Interactions)*** *Ionic Interactions, Hydrogen Bonds, Van der Waals Interactions, Dipole-Dipole and Ion-Dipole Interactions, F* *Solvation, and Hydrophobic Interactions* *Text Assignment: MedChem – 1.3 (Intermolecular Bonding Forces); Atkins – 5.1-5.5 (Intermolecular Forces)*
L3 T 8/30 PS1 Due	***Lecture 3. Solubility and Lipids*** *Thermodynamics of Liquid-Liquid Solubility, Octanol-Water Distribution Equilibrium Constants [Partition Coef* *Components and Structure, Cell Membrane Structure and Properties* *Text Assignment: Atkins – 8.9 (The Like-Dissolves-Like Rule); MedChem – 18.2.1 (Hydrophobicity), 1.2.1 (C* *Link: UCSF Membrane Tutorial (Great resource!!)* *Reading: The Components and Properties of Cell Membranes* *Link: Kimball's Biology Pages: Fats (Unsaturated Fats, Trans and Omega Fatty Acids, Phospholipids*
L4 R 9/1 PS2 Due Quiz1	***Lecture 4. Condensation and Hydrolysis Reactions*** *Alcohols and Carboxylic Acids, Triglyceride Formation, Polyphosphate and Phospholipid Formation* *Handout: Condensation and Hydrolysis Reactions*
L5 T 9/6 PS3 Due Quiz 2	***Lecture 5. Amino Acids*** *Structure, Chirality, Side Chain Polarity, Peptide Bond,Peptide Condensation and Hydrolysis, Henderson-Hass* *Solubility and pH* *Text Assignment: MedChem – Chapter 2 and Appendix 1*
L6 R 9/8 PS4 Due Quiz 3	***Lecture 6. Protein Structure*** *Primary Structure, Disulfide Bonds, Secondary Structure - Alpha Helices and Beta Sheets, Tertiary/Quaterna* *Noncovalent Interactions, Prions, PostTranslational Protein Modifications* *Text Assignment: MedChem – Chapter 2*
L7 T 9/13 Quiz 4	***Lecture 7. Enzymes: Structure and Function*** *Enzyme Catalysis, Mechanism of Action, Active Site, Substrate Binding, Catalytic Roles, Michaelis-Menton K* *Km and Vmax Determination, Turnover Numbers, Km and Substrate-Enzyme Affinity* *Text Assignment: MedChem – Chapter 3 (Enzymes: Structure and Function)* *Text Assignment: Kimball's Biology Pages: Enzymes*

	Text Assignment: Kimball's Biology Pages: Enzyme Kinetics
L8 R 9/15 PS5 Due	***Lecture 8. Enzymes as Drug Targets*** *Active Site Inhibitors, Allosteric Inhibition, Competitive / Uncompetitive / Non-Competitive Inhibitors, Suicidal* *Text Assignment: MedChem – Chapter 7 (Enzymes as Drug Targets)*
L9 T 9/20 PS6 Due Quiz 5	***Lecture 9. Medical Approaches to Inflammation I*** *Cyclooxygenase Case Study* *Reading: Protein Function – Section III Cyclooxygenase (COX): An Example of How Enzymes Function* *Reading: Molecular Basis of Inflammation*
L10 R 9/22 PS7 Due	***Lecture 10. Medical Approaches to Inflammation II*** *Steroids - Structure, Intracellular Receptors, Anti-Inflammatory MOA* *Reading: Molecular Basis of Inflammation* *Reading: Protein Function – Section II Nuclear Receptors: An Example of How Proteins Function* *Reading: Kimball's Biology Pages: Steroid Hormone Receptors and their Response Elements*
L11 T 9/27	***Lecture 11. Receptors as Drug Targets I*** *Neurotransmitters & Hormones, Agonists, Antagonists, Partial Agonists, Inverse Agonists, Treatment of Horm Cancers* *Text Assignment: MedChem – Chapter 8, Sections 8.1-8.5*
L12 R 9/29	***Lecture 12. Receptors as Drug Targets II*** *Desensitization & Sensitization; Tolerance & Dependence; Receptor Types & Subtypes; Affinity, Efficacy, & I Dissociation Equilibria, EC50, IC 50, Scatchard Plots* *Text Assignment: MedChem – Chapter 8, Sections 8.6-8.9*
L13 T 10/4 Quiz 6	***Lecture 13. Nucleic Acids as Drug Targets*** *Structure of DNA, Central Dogma, Intercalating Drugs, Alkylating & Metallating Agents, Cisplatin, 5-FU* *Text Assignment: MedChem – Chapter 6, Section 6.1 (Structure of DNA)* *Text Assignment: MedChem – Appendix 2 (The Standard Genetic Code)* *Text Assignment: MedChem – Chapter 9, Sections 9.1, 9.3 (Intercalating Drugs, Alkylating & Metallating Age* *Text Assignment: MedChem – Chapter 21, Section 21.2.3 (Alkylating & Metallating Agents)*
L14 R 10/6	***Lecture 14. Receptor Structure and Signal Transduction I – Overview of Ion Channel Receptors***

	Ion Concentration Gradients, Ion Channel Structure and Mechanisms of Action, Ligand-Gated and Voltage-G *Membrane Potentials, Nernst Equation and Membrane Equilibrium Potentials, Ion Movements and Resulting* *Changes,* *Text Assignment: MedChem – Chapter 4, Section 4.6 (Ion Channel Receptors)* *Text Assignment: MedChem – Appendix 4 (The Action of Nerves)* *UCSF Reading: "Diffusion and Transport Across Membranes" Section on Ion Channels (pages 80-86)*
T1 T 10/11 Midterm	***Mid-Term Examination on Material from Lectures 1-13*** A Few Practice Problems....
L15 R 10/13	***Lecture 15. Receptor Structure and Signal Transduction II – Thermodynamics of Ion Channels*** *Sodium-Potassium-ATP Pump Mechanism, Cell Membrane Potentials, Nernst Equation and Membrane Equilibrium Pote* *Movement across Voltage and Concentration Gradients, Ion Movements and Resulting Inhibitory/Excitatory Potential Ch* *Text Assignment: MedChem – Chapter 4, Section 4.6 (Ion Channel Receptors)* *Text Assignment: MedChem – Appendix 4 (The Action of Nerves)* *UCSF Reading: "Diffusion and Transport Across Membranes" Section on ATP-Driven Ion Pumps (pages 73-*
L16 R 10/20	***Lecture 16. Receptor Structure and Signal Transduction III – G-Protein Coupled Receptors (GPCRs)*** *G-Protein Coupled Receptor Structure, Evolutionary Tree of GPCRs, GPCR Signaling Mechanism of Action* *Text Assignment: MedChem – Section 4.7 (G-Protein Coupled Receptors)* *Text Assignment: MedChem – Section 5.1 (Signal Transduction Pathways for G-Protein Coupled Receptors)* *Text Assignment: MedChem – Section 5.2 (Signal Transduction Involving G-Proteins and Adenylate Cyclase*
L17 T 10/25	***Lecture 17. Cholinergics I*** *Nervous System, Cholinergic System, Acetylcholine Structure & Receptor Binding* *Text Assignment: MedChem – Chapter 19 and Appendix 4 (The action of nerves)*
L18 R 10/27	***Lecture 18. Cholinergics II*** *Cholinergic Antagonists, Acetylcholinesterase Inhibitors* *Text Assignment: MedChem – Chapter 19 and Appendix 4 (The Action of Nerves)*
L19 T 11/1 Quiz 7	***Lecture 19. Adrenergics*** *Geometry of Adrenergic Receptors, Main Types of Norepinephrine Receptors, Interaction of Adrenergic Rec* *MOA of Activated Receptors* *Text Assignment: MedChem – Chapter 20*

C1 R 11/3	***Compensatory Time for Review Paper Preparation***
L20 T 11/8	***Lecture 20. Psychoactive Drugs I: Stimulants and Tranquilizers*** *Handout:*
L21 R 11/10	***Lecture 21. Psychoactive Drugs II: Anti-Depressants*** *Handout:*
L22 T 11/15	***Lecture 22. Psychoactive Drugs III: Anti-Psychotics and Hallucinogens*** *Handout*
L23 T 11/17	***Lecture 23. Psychoactive Drugs IV: Cannabinoids, Opium & Opioid Analgesics*** *Cannabinoids, Source and History of Opiates, Structure of Opioids and Opioid Receptors, Endogenous Opio* *Text Assignment: MedChem – Chapter 21*
L24 T 11/22	***Lecture 24. Chemistry of Local & General Anesthetics*** *MOA for Local Anesthetics, pKa Relevance, History of Cocaine Use by Humans, MOA for General Anestheti Widely Used General Anesthetics* *Handout: Local and General Anesthetics*
T2 T 11/29	***Test 2***
R1 R 12/1 Rev Paper Due	***Review***

Review Paper Requirement

1. For this requirement, you are to write a 5-page review paper that focuses on a current medicinal chemistry topic or on a specific class of psychoactive substances.
2. If applicable to the chosen topic, the paper should provide:
    a. An historical perspective
    b. The relevance and societal impact
    c. A clear and detailed description of the molecular mechanisms of action
    d. A discussion of side effects
    e. An overview of the most significant structures
    f. A description of similar substances that may have antagonistic or agonistic activity
    g. An assessment of future activity, needs, or research
3. You must use citations from a minimum of three references from recent journals and books for this paper. A copy of the most important reference must be attached to your paper. Internet citations must be limited to published reports and articles. Use APA or MLA style documentation. The Winthrop Writing Center has excellent resources for research papers and styles of documentation.
4. The paper must be five full pages, exclusive of the reference list, using 12 point font, double spaced, and one inch margins.

Topic selection: Pick an area you would like to learn more about. Develop two to three ideas, survey the literature to ensure sufficient references are available, and submit a prioritized list of possible topics to me by the mid-term examination.

CHEM106 General Chemistry II Course Competencies

Lsn 1: General Chemistry Review: *Electronegativity, Electron Configuration, Lewis Structures, Molecular Geometry, Hybridization, Double Bonds, Aromatic Structure, Kinetic Energy Molecular Distribution, and Vapor Pressure*

- *Electronegativity, charge distribution, and molecular bonding structure*
  - Demonstrate an understanding of electronegativity; understand and be able to clearly explain the basis for electronegativity periodic trends in terms of fundamental laws of electrostatic interactions (Coulomb's Law).
  - Understand how to use relative electronegativities of atoms to clearly depict charge distribution across chemical bonds. Be able to quickly predict the important partial charges on atoms within given molecules.
- *Electron configuration*
  - For a given atom or ion, use the periodic table to quickly list its specific electron configuration
  - Understand the valence electron configuration of atoms and ions
- *Molecular structure*
  - Draw molecular structures showing all bonds from a given molecular representation
  - Quickly draw complete Lewis structures, to include all nonzero formal charges, for a given molecule or ion
  - Predict electron arrangement, molecular geometry, hybridization, and bond angles around given atoms in molecules
- *Multiple bond structure*
  - Know and discuss double/triple bond geometry and hybridization
  - Outline and diagram cis/trans geometry about carbon-carbon double bonds
  - Outline, discuss, and use aromatic electronic structure and geometry
- *Distribution of molecular kinetic energies*
  - Calculate fractions of molecules having kinetic energies greater than a given energy at a given temperature
  - Graphically represent and be able to clearly explain the distribution of kinetic energies of a collection of molecules at various temperatures
  - Understand the kinetic energy conversions into potential energy necessary to separate molecules, to break bonds, or to react molecules
- *Vapor pressures*
  - Use molecular structures to predict relative vapor pressures of given substances
  - Use the kinetic molecular distributions to explain how vapor pressures change with temperature

Lsn 2: Intermolecular Forces (Noncovalent Interactions)*: Ionic Interactions, Hydrogen Bonds, Van der Waals Interactions, Dipole-Dipole and Ion-Dipole Interactions, Repulsive Interactions, Water Solvation, and Hydrophobic Interactions*

- *Noncovalent interactions and intermolecular forces*
  - Understand and be able to clearly discuss and diagram the basis for attractions between molecules/ions to include ion hydration, hydrogen bonding, London dispersion, dipole-dipole, ion-dipole, and cation-π electron interactions.
  - Understand and use the relative magnitude (in kJ/mole) of chemical bonds (e.g. ionic, covalent and metallic) vs intermolecular forces (hydrogen bonding, London dispersion, dipole/dipole) interactions.
  - Quickly draw diagrams that clearly show appropriate partial charges and intermolecular interactions among a given set of molecules or ions.
  - Predict points of potential H-bond donors and acceptors for any given molecular structure.
  - Predict and discuss relative boiling points (also vapor pressure, melting points, viscosity, surface

tension) from molecular structure

Lsn 3: <u>Solubility and Lipids</u>: *Thermodynamics of Liquid-Liquid Solubility, Octanol-Water Distribution Equilibrium Constants [Partition Coefficients (P)], Phospholipid Components and Structure, Cell Membrane Structure and Properties*

- *<u>Solubility, thermodynamics, and equilibria</u>*
  - Understand and be able to clearly explain the thermodynamics of solution formation
  - Know what equilibria constants are; be able to relate equilibria constants to changes in Gibbs Free Energy
- *<u>Partition coefficients (P)</u>*
  - Understand what is meant by the octanol-water partition coefficient (P) and clearly describe its significance
  - Solve problems involving P, log P, and drug concentrations or amounts distributed across water and 1-octanol phases
  - Be able to predict relative polarities and solubilities (hydrophilic/hydrophobic, lipophilic/lipophobic) of a given molecular structure
- *<u>Phospholipids</u>*
  - Understand and be able to quickly draw molecular structures of components within phospholipid molecules
  - Relate the structure of phospholipids molecules to solubility
- *<u>Membranes</u>*
  - Understand and draw the molecular structure of membranes
  - Understand and describe the forces that hold membranes together
  - Predict and explain how membrane fluidity changes with temperature, degree of saturation, and fatty acid chain length.
  - Clearly outline the role of cholesterol in cell membranes
  - Predict relative membrane permeability for a variety of types of molecules or ions
- *<u>Fats, oils, and fatty acids</u>*
  - Know the structure of saturated, monounsaturated, polyunsaturated, and trans fats; describe associated health effects
  - Relate the melting points of fats and oils to molecular structure
  - Understand and explain what is meant by omega fatty acids

Lsn 4: <u>Condensation and Hydrolysis Reactions</u>: *Alcohols and Carboxylic Acids, Triglyceride Formation, Polyphosphate and Phospholipid Formation*

- *<u>Molecules: carboxylic acids, fatty acids, amino acids, and alkaloids</u>*
  - Outline the structure of a carboxylic acid functional group and diagram its acid/conjugate base forms
  - Be able to draw the structure for fatty acids, to include those having one or more points of unsaturation
- *<u>Condensation reactions</u>*
  - Use partial charges within molecules to outline the basic mechanism for condensation reactions
  - Outline the chemical reactions and mechanisms for the formation of phospholipids from molecular subcomponents
  - Predict and outline fundamental mechanisms for condensation reactions such as those between
    - Acids and alcohols
    - Phosphates and alcohols
    - Amino acids
- *<u>Hydrolysis reactions</u>*
  - Outline the reactions involved in phospholipid hydrolysis

- Outline peptide hydrolysis chemical equations

Lsn 5: <u>Amino Acids</u>: *Structure, Chirality, Side Chain Polarity, Peptide Bond and Resonance, Peptide Condensation and Hydrolysis, Henderson-Hasselbalch Equation, Charge and pH, Solubility and P*

- *<u>Amino acids</u>*
  - Know and be able to quickly draw the general molecular structure of amino acids and be able to clearly diagram the acid/conjugate base forms for both the carboxylic acid and the amine functionalities
  - Be able to quickly draw the complete molecular structure showing all bonds for all of the following amino acids:
    - AA's with nonpolar side chains [Alanine(Ala,A), Valine(Val,V), Leucine(Leu,L), Isoleucine(Ile,I), Phenylalanine(Phe,F)]
    - AA's with polar uncharged side chains [Glycine(Gly,G), Serine(Ser,S), Threonine(Thr,T), Tyrosine(Tyr,Y), Cysteine(Cys,C), Asparagine(Asn,N), Glutamine(Gln,Q)]
    - AA's with carboxylic acid side chains [Aspartic Acid(Asp,D), Glutamic Acid(Glu,E)]
    - AA's with basic side chains [Lysine(Lys,K), Arginine(Arg,R), Histidine(His,H)]
  - Understand and explain amino acid chirality
- *<u>Peptides</u>*
  - Understand how peptide bonds are formed and draw appropriate resonance structures to explain peptide bond geometry
  - Diagram and understand the mechanisms for condensation and hydrolysis reactions of peptides
- *<u>Acid-base systems</u>*
  - Predict reactions of acids with water; predict reaction of bases with water.
  - Write and use equilibria expressions for dissociation of weak acids and bases, K_a and K_b; pKa's
  - Know the Henderson-Hasselbalch equation: be able to understand and use.
  - Predict predominant (and relative amounts) of acid/base forms (e.g. $COOH/COO^-$, $NH_3^+/\text{-}NH_2$) present at a given pH.
  - Know what an alkaloid is and be able to quickly draw acid/conjugate forms of a given alkaloid.
- *<u>Acid-base properties of amino acids</u>*
  - Predict acid-base forms of amino acids present at various pH's
  - Relate pH to amino acid functional group solubility in lipids or water

Lsn 6: <u>Protein Structure</u>*: Primary Structure, Disulfide Bonds, Secondary Structure - Alpha Helices and Beta Sheets, Tertiary/Quaternary Structures and Associated Noncovalent Interactions, Prions, PostTranslational Protein Modifications*

- *<u>Protein structure</u>*
  - Know the primary structure of peptides
  - Understand protein secondary structure; draw diagrams to represent the underlying reason for the formation of alpha helices and beta sheets
  - Understand the various types of interactions that can occur between side chains; draw appropriate diagrams and clearly discuss these
  - Understand protein tertiary and quaternary structures
  - Understand the underlying reasons for the structure of globular proteins

Lsn 7: <u>Enzymes: Structure and Function</u>: *Enzyme Catalysis, Mechanism of Action, Active Site, Substrate Binding, Catalytic Roles, Michaelis-Menton Kinetics, Lineweaver-Burk Plots, Km and Vmax Determination, Turnover Numbers, K_M and Substrate-Enzyme Affinity, Factors Affecting Reaction Rates, Rate Law, Arrhenius Equation, Activation Energy, Kinetic Molecular Distribution*

- *<u>Enzyme-substrate interactions</u>*
  - Be able to draw and to clearly explain reaction energy diagrams for enzyme-substrate interactions

- Understand the effects of inhibitors and what is specifically meant by IC50
- Understand and clearly explain the basis for important types of noncovalent enzyme-substrate interactions
- Clearly describe the enzyme inhibition process

- *Michaelis-Menton kinetics*
  - Write equilibria associated with enzyme-substrate interactions
  - Understand how reaction order changes with substrate concentration
  - Be able to use the Lineweaver-Burke relationship to calculate V_{max}, turnover number, and K_M
  - Understand the significance of K_M; understand the relation of K_M to enzyme-substrate complex stability and to maximum reaction rate
- *Chemical kinetics*
  - Understand the two fundamental requirements for a chemical reaction to occur…
  - Draw reaction coordinate-energy profiles and clearly label activation energies, and heat gained or lost
  - Understand and be able to clearly explain the role of catalysts
  - Understand and be able to use fundamental principles to clearly describe the dependence of reaction rate changes with temperature
- *Arrehenius equation*
  - Know and be able to use the Arrehenius equation for rate constant determination
  - Demonstrated the ability to calculate relative rates of reactions for different activation energies or temperatures
  - Understand and be able to calculate a reaction's activation energy from given rate constants at different temperatures
  - Understand relative impacts of temperature changes on rates for chemical reactions with low and high activation energies
  - Be able to use activation energies to predict rate constants at different temperatures
- *Rate law*
  - Understand what is meant by the rate law and outline the experimental procedures and methodology to determine reaction order
  - Use a given rate law to calculate rate constants and their associated units

Lsn 8: Enzymes as Drug Targets: *Active Site Inhibitors, Allosteric Inhibition, Competitive / Uncompetitive / Non-Competitive*
Inhibitors, Suicidal Substrates

- *Enzyme inhibition*
  - Understand and fully explain the basis for competitive enzyme inhibition
  - Understand and fully explain the basis for noncompetitive enzyme inhibition
  - Illustrate and discuss the effects of various types of inhibition on maximum reaction velocities and on substrate concentrations required to achieve half of the maximum reaction velocities
  - Discuss what is meant by suicidal inhibitors and use your understanding of condensation reactions to predict the specific mechanism of action for a given active site and inhibitor structures.

Lsn 9: Medical Approaches to Inflammation I: Nonsteroidal Anti-Inflammatory Drugs (NSAID's)

- *Inflammation*
  - Understand the overall molecular basis of inflammation
- *Cyclooxygenase (COX) inhibitors*
  - Understand the mechanism of action of cyclooxygenase (COX) inhibitors
  - Identify key structural features of NSAIDs and understand of specific important interactions with COX enzymes

    - Understand the specific interaction between the NSAID carboxylic group and the COX Arg-120 side chain; describe and effectively explain the effect upon K_M values that occur when neutral glutamine is substituted for Arg-120
    - Understand and clearly discuss aspirin's unique mechanism of action for irreversible COX inhibition
- *COX-2 Inhibitors*
    - Understand key differences between COX-1 and COX-2 enzymes, their physiological roles, and their respective inhibitors
    - Clearly describe the rationale for the development of COX-2 inhibitors
    - Explain the structure differences between nonspecific COX inhibitors and COX-2 specific inhibitors; relate these differences to active site geometries of thee two enzymes
    - Use COX-1 and COX-2 IC50 values for various substances to evaluate their respective potential for therapeutic development

Lsn 10: Medical Approaches to Inflammation II: Steroidal Anti-Inflammatory Drugs

- *Steroid structure and properties*
    - Understand and draw the skeletal structure for steroids
    - Discuss and predict the lipophilic/lipophobic properties of steroids
    - Outline where steroids are produced, what their sources are, and how they work hormones in the human body
- *Inflammation and steroids*
    - Understand the overall molecular basis of inflammation
    - Explain the molecular mechanism of action for steroids as anti-inflammatories
    - Understand the emerging relevance of inflammatory processes in various diseases
- *Central dogma*
    - Understand and clearly describe how genetic information is encoded in DNA
    - Explain what a gene is, what it does, and the two roles of the major regions (promoter and coding) of DNA gene templates
    - Generate a possible DNA sequence for the coding of a given peptide
    - Interpret a DNA or RNA sequence to generate an amino acid sequence that is coded for by this
- *Complex ions*
    - Understand the structure of complex ions and be able to explain the basis for their interaction
    - Relate Lewis acid/base chemistry to complex ion components
    - Clearly explain why complexes are colored and demonstrate an understanding of relevant molecular orbital energies
    - Understand and describe the structure of important biochemical complexes such as iron in hemoglobin.
- *Intracellular Receptors and Zinc fingers*
    - Diagram and discuss the structure of zinc fingers; clearly show the amino acid residues that interact with the zinc ion and how zinc fingers affect protein shape
    - Explain the underlying basis for the zinc finger mechanism of action in steroidal interactions with DNA
    - Discuss a new area of drug research that targets the zinc fingers in estrogen receptors to treat breast cancer

Lsn 11: Receptors as Drug Targets I*: Neurotransmitters and Hormones, Receptor-Ligand Interactions, Agonists, Antagonists, Partial Agonists, Inverse Agonists, Treatment of Hormone-Dependent Breast Cancers, Mechanisms of Actions for active ingredients in Advair*

- *Drug-receptor binding*
    - Understand and clearly discuss the ligand-receptor interactions; know the underlying physical

principles that govern these interactions
    - Understand chirality, enantiomers, racemic mixtures, and the chiral specificity of many drug receptors
    - Know, diagram, and explain the equilibrium constant expression for K_d, the dissociation constant for drug-receptor complex dissociation
- *Receptors*
    - Understand and describe some of the various classes of drug receptors present within the human body
    - Understand the various types of receptor responses
    - Understand receptor response differences to agonists, partial agonists, antagonists, and inverse agonists

Lsn 12: Receptors as Drug Targets II: *Affinity, Efficacy, and Potency; Sensitization, Tolerance, and Dependence, Dissociation Binding Equilibria, EC50, IC 50*

- *Affinity, Efficacy and Potency*
    - Define, illustrate and demonstrate an understanding of affinity, efficacy, and potency
- *Sensitization, Tolerance, and Dependence*
    - Illustrate, describe, and discuss the mechanism of action of the desensitization process that can occur due to prolonged receptor activation by an agonist
    - Illustrate, describe, and discuss the mechanism of action of the sensitization process that can occur due to prolonged receptor binding of antagonists
    - Discuss the molecular basis for tolerance and dependence.
- *Neurotransmitter molecular structures*
    - Acetylcholine
    - Dopamine, norepinephrine, epinephrine, and serotonin [5-Hydroxytryptamine (5-HT)]
    - Glutamate, GABA (gamma-aminobutyric acid)

Lsn 13: Nucleic Acids as Drug Targets

- *Nucleic acid structure*
    - Understand the structure of DNA and RNA to include the major components and specific features
    - Understand the condensation mechanism of action to form phosphate diester polynucleotides
    - Clearly explain the underlying physical basis for the attractions between the two strands of double helix DNA
- *Cancer Chemotherapy Treatments*
    - Outline the mechanism of action for platinum compounds [e.g. cisplatin $PtCl_2(NH_3)_2$] as chemotherapeutic agents for cancer patients
    - Describe the historical development of and outline the mechanism of action for nitrogen mustards as chemotherapeutic agents for cancer patients
    - Describe the mechanism of action for 5-Fluorouracil (5-FU) as a chemotherapeutic agent for cancer patients

Lsns 1-13: Mid-Term Examination

Lsn 14-15: Receptor Structure and Signal Transduction I-II - Overview and Thermodynamics of Ion Channels: *Ion Concentration Gradients, Cell Membrane Potentials, Nernst Equation and Membrane Equilibrium Potentials, Ion Movements and Resulting Inhibitory/Excitatory Potential Changes Ion Channels, Sodium-Potassium-ATP Pump Mechanism, Free Energy Changes of Ion Movement across Voltage and Concentration Gradients*

- *Ion Channels*

- Understand the relative intracellular and extracellular concentrations of sodium, potassium, calcium, and chloride ions
- Understand the sodium-potassium pump mechanism to maintain ion concentration gradients and the array of energetics associated with this
- Describe what an ion channel is and the specific properties of the substance that forms the channel
- Outline the difference and define what is meant by voltage-gated and ligand-gated ion channels.
- Describe the structure of voltage gated sodium ion channels and potassium ion channels to explain how they work. Understand the role of these ion channels in moving nerve pulses down an axon
- Understand the role and the basic general mechanism of G-Protein Coupled Receptors (GPCR) in cell signaling processes; explain the importance of these receptors in the pharmaceutical industry
- Understand and be able to clearly explain the physical basis for the selectivity of sodium and potassium ion channels
- Understand how increased permeability can affect voltage-gated ion channels

- *Neurochemistry*
  - Be able to relate concentrations to associated electric potentials (e.g. Nernst Equation) and changes in Free Energy
  - Demonstrate the ability to calculate Free Energy changes, equilibrium constants, and electric potentials associated with given reactions
  - Explain and calculate cell membrane potentials associated with ion concentration gradients
  - Relate resting membrane potential to ion permeability and to intracellular/extracellular concentrations
  - Calculate Free Energy changes necessary to move substances across concentration gradients and to move ions across potential gradients
- *Thermodynamics*
  - Understand and be able to use the Second Law of Thermodynamics to predict reaction spontaneity
  - Clearly explain how spontaneity is related to Free Energy change.
  - *Explain Free Energy changes associated with ATP-ADP interconversion; discuss and effectively use the concept of coupled reaction energetics*

Lsn 16: Receptor Structure and Signal Transduction III – GPCR's: *G-Protein Coupled Receptors Signaling Mechanism of Action*

- Understand the role and the basic general mechanism of G-Protein Coupled Receptors (GPCR) in cell signaling processes; explain the importance of these receptors in the pharmaceutical industry

Lsn 17: Receptor Structure and Signal Transduction IV – Kinase-Linked Receptors: *General Principles, Structure and Activation Mechanism of Tyrosine-Kinase Receptors, Tyrosine Kinase-Linked Receptors, Signal Transduction Involving Kinase-Linked Receptors*

Lsn 18: Cholinergics I: *Nervous System, Cholinergic System, Acetylcholine Structure & Receptor Binding*

- Outline and clearly explain the steps that occur to pass a nerve impulse from one neuron to another
- Know the structure of acetylcholine and explain how it is synthesized and hydrolyzed
- Clearly explain the two major mechanisms used to reduce neurotransmitter concentration levels at nerve synapses
- Understand the two (nicotinic and muscarinic) major classes of cholinergic (acetylcholine) receptors and the mechanism of action for each

Lsn 19: Cholinergics II: *Cholinergic Antagonists, Acetylcholinesterase Inhibitors*

Lsn 20: Adrenergics: *Geometry of adrenergic receptors, main types of norepinephrine receptors, interaction of adrenergic receptors with neurotransmitters, MOA of activated receptors*

- Describe the geometry of adrenergic receptors
- Classify the role of the three main types of norepinephrine receptors (alpha, beta 1, and beta 2)
- Describe the interaction of adrenergic receptors with neurotransmitters
- Discuss the mechanism of action of activated adrenergic receptors
- Be familiar with medications that target adrenergic receptors and discuss their mechanism of action

Lsn 21: <u>Psychoactive Drugs I -- Stimulants and Tranquilizers</u>:

Lsn 22: <u>Psychoactive Drugs II – Anti-Depressants</u>:

- Understand how PCP (angel dust) and Memantine (Namenda) affect the glutamate receptor NMDA (N-Methyl-D-Aspartate)
- Understand the synthesis steps involved in the production of L-DOPA, dopamine, norepinephrine, and epinephrine
- Understand the role of glycine and GABA receptors
  - Be able to explain the electrochemical basis for their inhibitory effects
  - Clearly explain how each of the following substances affects the GABA-ergic system: ethanol, barbiturates, strychnine, diazepam (valium), and caffeine
- Explain the role of monoamine oxidase (MAO) for catecholamine neurotransmitters; identify the role of MAO inhibitors.
- Explain the effect of dopamine levels on brain activity
  - Explain the effects of cocaine and of amphetamines on the dopaminergic system
  - Outline the role of seratonin and identify the substance from which it is produced
    - Explain what SSRI's are and what they are used for

Lsn 23: <u>Psychoactive Drugs III – Anti-Psychotics and Hallucinogens</u>:

Lsn 24: <u>Psychoactive Drugs IV – Cannabinoids, Opium & Opioid Analgesics</u>:

- Relate the structure of opioid receptors to opioid ligand geometry and identify key features of each
- Understand the history of opioid use and development by humans
- Understand the side-effects of opioids
- Describe the structure of natural opioids found in the human body and be familiar with its historical discovery

Lsn 25: <u>Chemistry of Local and General Anesthetics</u>:

- Understand the mechanism of action for local anesthetics
- Relate pK_a's to local pain anesthetics
- Understand the history of cocaine use by humans
- Describe the mechanism of action for general anesthetics
- Be familiar with the molecular structures for the more widely used general anesthetics

Lsns 14-25: Second Half-Term Examination

Lsns 1-25: Comprehensive Final Examination