

Phar 6702: Integrated Biochemical Sciences

Course Instructional Team

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Course Schedule

MM	1:25-3:20	TC Room: WDH 7-135	Duluth Room: L 410 [Zoom Sync/Remote]
WW	1:25-3:20	TC Room: WDH 7-135	Duluth Room: L 410 [Zoom Sync/Remote]
F	11:15-12:05	TC Room: WDH 7-135	Duluth Room: L 410 [Zoom Sync/Remote]

Recitation Sessions: TTh 6:30-7:30 TC Room: 7-135 Duluth Room: TBA

Overview of the course

Course content:

This course is designed to provide students with a strong foundation in the structure and function of medicinals which is a prerequisite for advanced studies in pharmacy. The basic goals are to familiarize the students to the structural and physical properties of proteins, nucleic acids, lipids and carbohydrates, as well as ligands/drugs that bind to these

macromolecules in an effort to understand the functional role each plays in the biochemistry of medicinals and the normal and abnormal functioning of a cell. A particular emphasis is placed on the basic concepts that are central to structure-function relationships of therapeutics. Macromolecular classes are presented progressively from basic monomeric structural composition and structural diversity to macromolecular assemblies and associated intrinsic function to macromolecular involvement in cellular architecture and cellular processes to molecular pathology with specific examples.

Course format:

The primary method of instruction is lecture-based with use of the textbook as support for class notes and discussions. Use of active learning methods, i.e. collaborative learning groups, class discussion and 10-minute written exercises, will be incorporated by individual instructors. Problem sets, current literature evaluation and case studies will also be assigned to support course objectives and provide practical experience with the material. Five non-cumulative exams will be given during the semester, with the last exam falling on the day assigned by the University for the final examination. Exams are one hour in length and are graded on a percentage basis.

Prerequisites

This is a first semester, PharmD I course and does not rely on prerequisite knowledge from other modules within the COP curriculum. However, to be successful in the course students must have taken Organic Chemistry I and II, General Chemistry, Calculus I, Physics I and have completed the required Biology prerequisites. Students would also benefit from an understanding of the role basic science plays in the profession and the development of lifelong learning skills.

Course Goals & Objectives

Three major long term learning goals:

1. Gain language and foundational definitions of the Pharmaceutical Sciences that are required by the Profession. Specifically, students will be able to understand, apply and/or evaluate the role or function of carbohydrates, lipids, nucleic acids and amino acids/proteins collectively as they form networks of interactions, such as macromolecular assemblies, signal transduction pathways or subcellular compartments within a cell and demonstrate an understanding of these molecules in disease and drug targeting.
2. Understand the structural basis to drug function at the molecular and cellular level, the nature of molecular derangements that lead to cellular malfunction and disease and the rationale of novel targeting in drug development and how these apply to clinical pharmacology.
3. Understand gene regulation and its impact on enzyme activity, signal transduction pathways and tissue specialization and relate genetic differences in protein function or gene regulation to structural and functional changes in cellular processes and their effect in mediating drug efficacy and disease progression.

Learning Objectives:

Students will comprehend the basic biomolecular structure classes below and explain their relationship to normal biological function, molecular pathology and drug intervention. Within each structure class a set of foundational principles is listed, a necessary prerequisite to understanding their context in cell architecture and function as well as disease state.

1. Protein Structure and Function: Demonstrate understanding of chemical and biological nomenclature; acid-base chemistry theory and applications in pharmacy; protein structure and diversity; protein purification and analysis; protein identification; **integrated learning objective with lab, OTC test kits and protein identification**; hemoglobin and myoglobin; clinical implications of iron and bicarbonate administration.
2. Enzymes and Receptors as Drug Targets: Explain drug recognition and enzyme function; kinetics and site directed mutagenesis studies; transition state theory and drug design; case studies using the HIV protease, chymotrypsin, lysozyme, carboxypeptidase; acid base chemistry and enzymes; modern drug discovery and enzyme targets.

3. Carbohydrates and Lipids: Illustrate carbohydrate-based drugs and signals; nomenclature, nucleoside drugs; bioenergy and carbohydrates, cell recognition and diseases, carbohydrates and H1N1; membranes; drug-membrane interactions; lipid nomenclatures; lipids and formulation chemistry of drugs.
4. Nucleic Acid Structure/Function: Outline the flow of genetic information; nucleobases, nucleosides, and nucleotides; DNA and RNA structure; DNA supercoiling; topoisomerases and topoisomerase inhibitors; endonucleases and exonucleases; human genome; DNA replication; DNA polymerases; DNA repair; mutations; nucleoside drugs.
5. Nucleic Acid Transcription/Translation: Summarize pro- and eukaryote gene transcription, regulation of gene transcription, RNA processing, pro- and eukaryotic translation, the molecular basis of action for antibiotics targeting prokaryotic transcription and translation, and the molecular basis of action for drugs targeting eukaryotic gene transcription including nuclear receptor action.

Given these foundational concepts, students will be able to understand, apply and/or evaluate the following information, integrated into logical modules having both foundational and applied material. A progression is expected in most modules; molecules > cell localization > cell function > molecular pathology > clinical application.

1. The role or function of carbohydrates, lipids, nucleic acids and amino acids/proteins collectively as they form networks of interactions, such as signal transduction pathways or subcellular compartments. Also, the forces and subcellular and cellular organization necessary to drive networks or pathways of small molecule and macromolecular interaction and how networks are linked within organelles, across membranes, between cells and between tissues. This builds upon the students' knowledge of the foundational material above.
2. The difference between normal and abnormal functioning cellular pathways, and how this relates to tissue-specific cell function, cell to cell communication, signal transduction (within and between cells and across tissue types) and genetic polymorphisms. Within this context the student will also be able to explain the genetic origin of drug response variability. In addition, where important macromolecules occur and the impact of gain or loss of function change on linked pathways, for example ubiquitin-protein ligase -> mitochondria dysfunction -> neurodegeneration -> Parkinson's disease.
3. The nature of molecular derangements that lead to cellular malfunction and disease. For example, students will make connections between the endoplasmic reticulum unfolded protein response and pancreatic cell death in type 1 and type 2 diabetes. Students will understand the integrated nature of disease, how a molecular derangement can manifest in many critical pathways at the intracellular, cell to cell and tissue levels. This includes a strong knowledge of causative agents or insults and logical points of intervention/drug therapy.
4. The molecular basis of disease and the rationale of novel targets in drug development as presented in current literature.

Attendance Policy

Students are required to attend class. Students are expected to attend classes on the campus where they are enrolled. Instructors may choose to take attendance.

Course Materials

Required Text: Stryer, Biochemistry, 6th edition or higher, Freeman and Co., NY.

Assessments and Grading

Graded Assessments:

To evaluate the understanding of students as material is being delivered, open-ended questions will be posed for discussion and supplemented with specific student response multiple choice questions (Turning Point) and consensus response discussions (ChimeIn or word clouds) to enhance participation. A subset of these in-class student participation opportunities will be graded. Within several modules an open-ended (essay) question will be distributed, applying the course

concepts to a “real” scenario for low stakes grading and discussion. The focus of these essay questions is the evaluation of current literature on the molecular mechanisms of disease and/or the development and application of therapeutics to treat disease states from a molecular point of view. Students will be more comprehensively and formally evaluated using high stakes unit exams comprised of multiple choice, calculations, short answer and more extensive essay questioning to assess their application of course concepts. An authentic case study involving OTC test kits is planned to be performed in collaboration with the lab course. This will be a graded exercise by the lab instructional team.

Assignments and Learning Activities:

Students are assigned weekly problem sets and case studies throughout the semester that are completed independently or in study groups. The assignments also serve as a focal point for weekly, in class, active learning sessions to be led by faculty and teaching assistants. Students will be asked open-ended case based questions during class lecture; a thoughtful response will require the assembly of many course concepts. Following a short response period an instructor lead discussion will ensue to address the logic behind a reasonable solution. Additional support for student learning is accomplished through the use of a course electronic forum. Students are encouraged to post questions from course materials, problem sets, case studies, and prior exams on the forum site which is moderated by faculty and teaching assistants.

Graded Assessments [Include quizzes and exams in this table. Indicate delivery method, etc.]

The following graded assessments will count toward your final grade for this course in the following amounts:

#	Date	Title Brief description	Assessment Goal (required to link to domain)	Points	% of final grade
1	16, Sept.	Group problem, in-class and written summary	Summarize properties hemoglobin. Interpret the molecular basis of disease, hemoglobin and sickle-cell anemia (Ferguson)	10	1.7%
2	18, Sept	Exam 1, 80 in-class synchronous 20 take-home	Illustrate understanding amino acids and proteins, both physical properties and relationship to biological function and molecular pharmacology. (Ferguson)	100	17%
3	24, Sept.	Lab exercise, OTC test kit, to be run by lab faculty	Demonstrate the application of protein based assays in a pharmaceutical setting. Will be given at a time coincident with lectures on protein methods. (Ferguson)	Graded by Lab	0%
4	1-7, Oct.	Topic discussion board and comments	Interpret graphic related to cellular signaling and drug targeting and comment on group members input (Rumbley)	10	1.7%
5	5, Oct.	In-class and take-home written review of drug transporters	Demonstrate the role of transporters in drug disposition from current literature (Rumbley)	15	2.5%
6	14, Oct.	Exam 2, 80pts in-class synchronous 20pts take-home	Show comprehension of enzyme mechanism and enzyme kinetics (Ferguson)	100	17%
7	28, Oct. to 4, Nov.	Topic discussion board and comments	Interpret graphic related to cellular maintenance and comment on groups members input (Rumbley)	10pts	1.7
8	2, Nov.	In-class and take-home signal transduction literature evaluation	Translate current literature review of signal transduction drug targeting to molecular processes discussed in class (Rumbley)	15	2.5%
9	6, Nov.	Exam 3, written in class exam	Demonstrate the structural and functional role of nucleotides in DNA structure and	100	17%

			outline the methods of DNA repair and drug targeting. (Harki)		
10	13, Nov.	Unit assignment due	Cell architecture, trafficking, receptors and transporters. (Rumbley)	50	8.5%
11	20, Nov.	Exam 4, 70pts in class synchronous, 10pts. take-home	Explain the process/function of cellular signaling, vesicle trafficking, cellular maintenance, cell cycle regulation and integration of cellular processes (Rumbley)	80	13.6%
12	Finals Week TBA	Exam 5, written in class exam.	Explain eukaryotic gene regulation and summarized the relationship of human genetics and polymorphisms to drug efficacy (Oetting)	100	17%

Statement on Penalties for Late Work

Assignments received beyond the suggested due date will subject to a one letter grade deduction for each day late.

Exam Policy

Absence from Exam

Make-up exams will be given at the earliest possible convenience of the student missing the exam and will only be given to students that have missed the regular exam due to an absence that is validated under University policy or a verifiable emergency approved by the course faculty, course director, and the Office of Student Services. Under no circumstances will a student take a makeup exam earlier than the scheduled date and time of the exam. **Attending conferences, conflicts with work or other courses, vacations or other personal matters of choice will not be accepted as an excused absence. There are no exceptions to this course policy.**

Grading Information

Course Letter Grades

Grade	Percentage
A	92.5 - 100
A-	89.5 - 92.4
B+	86.5 - 89.4
B	82.5 - 86.4
B-	79.5 - 82.4
C+	76.5 - 79.4
C	72.5 - 76.4
C-	69.5 - 72.4
D	59.5 - 69.4
F	0 - 59.4

Minimum Passing Level

As per the Academic Standing Committee Policy, students who receive a grade below C- in this course must successfully repeat the course before advancing to 2nd year courses.

Detailed Course Outline & Schedule*

Color Legend: Under the column heading Competency/Learning Objective the brown text describes the basic scientific learning objectives along with some disease state correlations, while the orange text describes specific clinical applications and topics. Under column heading Activities/Assignments/Assessments the pink text indicates an ungraded practice problem set, red indicates topic coordination with another course within the semester, blue denotes major section exams (non-cumulative), and green indicates a graded in-class or take-home assignment.

Class	Agenda/Topics	Competency/ Learning Objective	Activities Assignments Assessments
MODULE 1A: Amino Acids and Proteins (8/26-9/9)	<p>Lesson 1: Amino acid structures, nomenclature, and derivatives (e.g. histamine), Physical properties - diversity gives rise to shape, function, and form</p> <p>Lesson 2: Concepts of reactivity, shape complementarity, geometry, steric bulk, solubility, Acid-base chemistry of amino acids, Protonation, charge, polarity</p> <p>Lesson 3: Peptides and Proteins, Primary structure, Concept of conformation and structure/function, Secondary structure - backbone geometry, Small peptides and bioactivity/drug, Acid-base chemistry of peptides</p> <p>Lesson 4: Tertiary Structure - proteins, Concept of protein folding, tertiary contacts, and structural diversity, Protein-protein interactions and Quaternary structure, Fundamental forces of molecular associations (emphasis point)</p> <p>Lesson 5: Protein and Peptide Isolation, Purification, and Characterization, Chromatography (Affinity, HPLC, Ion exchange), Mass Spec, Gel Electrophoresis, Western Blot and ELISA, Sequencing</p>	<p>Nomenclature of amino acids, functional groups and related drugs; acid-base chemistry of amino acids and related biomolecules and drugs. Basic competencies in chemical and biological nomenclature; acid-base chemistry theory and applications in pharmacy; protein structure and diversity; protein purification and analysis; protein identification. Clinical: OTC test kits and protein identification, amino acid supplements (in Lab Oct. 8)</p>	<p>Problem Set 1: Take-home and present solutions in recitation.(not graded)</p>
MODULE 2A: Protein Function Example: Oxygen Transport Proteins (9/11-9/18)	<p>Lesson 1: Myoglobin and Hemoglobin- Case Study, Evaluation of primary seq., secondary and tert. structures, The O₂ binding pocket and CO poisoning, Molecular recognition - a first look at protein ligand interactions</p> <p>Lesson 2: pH, CO₂, and O₂ affinity - the Bohr Effect, Histidine and Aspartate as acid base partners in regulating O₂ affinity, Allosteric effectors and structural cooperativity, Biological regulation of O₂ affinity, Chemical basis to regulation and function, Bicarbonate and O₂ affinity</p> <p>Lesson 3: Sickle Cell Anemia case study</p>	<p>Understand the structure/function of hemoglobin and myoglobin, foundations of molecular recognition and oxygen binding, oxygen transport, and pH dependent oxygen transport, understand function at the molecular level, clinical implications of iron and bicarbonate administration. Clinical: Carbon Monoxide Poisoning, Shock, Blood pH, Phenylketonuria (and other amino acid disorders), Sickle Cell anemia/diagnosis/molecular basis to disease, Thalassemia, OTC test kits and protein identification, OTC amino acid supplements</p>	<p>In class assignment on sickle cell anemia and hemoglobin.</p> <p>Exam 1. Essay-based, written in class. (Ferguson)</p>

<p>MODULE 1B: Lipids and Carbohydrates (8/26-9/9)</p>	<p>Lesson 1: Carbohydrate nomenclature and structures, Di-, oligo-, poly-saccharides, Lactose, Sucrose, Pectins, Glycogen, Lesson 2: Mucopolysaccharides - Chondroitin Sulfate, Hyaluronic Acid, Heparin, Glycosylation of proteins and lipids, Carbohydrate function in Signaling (cell-cell recog., influenza recog., etc...), Carbohydrate Antibiotics</p> <p>Lesson 3: Basic lipid structures, nomenclature, and characteristics, cholesterol and related lipophiles, complex lipids, glycerides, phospholipids, sphingosine-derivatives</p> <p>Lesson 4: Lipid aggregates, micelles, liposomes, bilayers, lipid head group structure/function, membrane fluidity/composition</p>	<p>Nomenclature of common lipids, and lipid-like compounds, identify common substitutions to lipids, apply structural concepts to predict the physical properties of micelles, liposomes, and membranes, relate substitution to solubility of lipids, identify lipid-like molecules and recognize their unique amphiphilic properties in conferring cell-cell signaling and receptor signaling, understand the impact of pH and heat on membrane transport. Students are expected to understand the association of cellular lipid function with cellular localization as it relates to normal and abnormal physiology. <u>Application:</u> Outer membrane functional defects like cystic fibrosis and lysosomal defects like Tay-Sachs disease will be used as examples of dysfunction. Clinical: OTC: vitamins and associated lipid-like compounds, soaps and cosmetics</p> <p>Nomenclature of common carbohydrates, identify common substitutions to carbohydrates, apply structural concepts to predict the physical properties of complex carbohydrates, glycosylation and cell-cell signaling and receptor signaling, Clinical: OTC chondroitin sulfate, glucosamine, sucrose, lactose, pectins</p>	<p>Problem Set 2: Take-home and present solutions in recitation. (not graded)</p>
<p>MODULE 2B: Cellular Application of Basic Biomolecules (9/16-9/23)</p>	<p>Lesson 1: Cellular Architecture: Cell Organelles, Organelle localization, Organelle function. Lesson 2: Cellular Architecture: Cellular skeleton - actin, intermediate filaments, microtubules, Endocytosis, Exocytosis, Muscle contraction Lesson 3: Protein and Membrane Trafficking: Surface receptor trafficking, Virus trafficking, Inflammation, Alzheimer's disease</p>	<p>Apply the basic concepts of amino acid and peptide structure to protein structure classes, e.g. the role of actin and intermediate filaments and microtubules (structural classes of proteins) in endocytosis, exocytosis, cell surface receptor trafficking, virus trafficking, trafficking of biomimetic particles, inflammation and cell division. Recognize the function of lipids and carbohydrates in the context of the cell. <u>Application:</u> pathological impact of these structures to disease states such as Alzheimer's disease. Drug therapies directed toward the cytoskeleton include anticancer agents (e.g. taxol) and novel anti-inflammatories.</p>	
<p>MODULE 3B: Membrane Transporters and Transport Kinetics (9/28-10/5)</p>	<p>Lesson 1: Membrane Transporters - passive transport, active or co- transport, Channels/pores, Solute carriers, Pumps, ABC transporters, Kinetics of membrane transport Lesson 2: Transporters in renal elimination of drugs, etc..., Neurologic and cardiovascular depolarization, Drug uptake and elimination, Tissue specific transport</p>	<p>Articulate the role of important membrane transport proteins, including channels/pores, solute carriers, pumps and ABC transporters. <u>Application:</u> Demonstrate a connection with renal elimination of drugs, toxic compounds and their metabolites; neurologic and cardiovascular depolarization; and drug uptake and elimination will illuminate the tissue specific</p>	<p>Coordination with Found. of SAPH: Drug approval /FDA guidelines on drug transport</p> <p>In-class group assignment -</p>

		function of these broad classes of transporter. Clinical Relevance: Membrane transporters are an integral component of understanding ADME and tissue distribution of drugs and well as the FDA recommendations for drug approval.	transporters
MODULE 3A: Enzyme Kinetics and Inhibition (9/21-10/14)	<p>Lesson 1: Substrates, products and inhibitors - big picture, Catalysis and energetics, Activation energy and equilibria, Concept of chemical reactions, transition states, and transition state stabilization, Molecular Recognition - Enzymes are specific (major emphasis point), Case study - SN1 solution phase versus enz. cat reaction, Basic thermodynamics - free energy, substrate and product conc., and equilibrium constants</p> <p>Lesson 2: Michaelis-Menten kinetics - relating substrate conc. to reaction rate, The Michaelis Complex and substrate affinity, Relationship between kinetics and selectivity in practice, Enzyme inhibition - KM, Kcat perturbation and inhibition, Competitive and non-competitive inhibitors - examples from the formulary, Enzyme mutations and kinetics, The power of site directed mutagenesis in understanding enzyme-function (emphasis point)</p> <p>Lesson 3: Exploiting enzyme mechanisms to treat disease, Enzyme classifications - cofactors, coenzymes, Transition State Theory and Drug Design, Transition State Analogs, Fleming's discovery of lysozyme, Specificity and stereochemical control - chirality and enzymes, Acid Base chemistry and catalysis, SN1 versus SN2 - understanding mechanisms</p> <p>Lesson 4: Case Study - Penicillin binding proteins, Targeting the exogenous process of the bacterial cell synthesis, Unique D-ala-D-ala motif and inhibitor design, Beta-lactam ring strain and activity, Mechanism of Resistance- lactamases, Overcoming resistance - chemical mechanism (clavulanic acid)</p> <p>Lesson 5: Chymotrypsin - serine proteases, Nucleophiles and peptide hydrolysis, Charge relay and tautomerism, Polarization of binding pocket - lock and key fit, Irreversible inhibitors</p> <p>Lesson 6: HIV protease substrates and inhibitors, Relationship of natural substrate</p>	<p>Molecular recognition, enzymatic selectivity and specificity, energetics of enzymatic catalysis, enzymatic rate constants as pharmacological tools (eg selectivity ratio), inhibition, enzyme classification, molecular mechanism of catalysis as a drug target, transition state theory, stereochemical control and enzyme catalysis as a key foundation to drug function and selectivity, molecular basis to drug resistance, point mutation and drug function, irreversible versus equilibrium drug binding and inhibition, G protein coupled receptors: structure and function, and ligand recognition. Clinical: Antibacterials and resistance (eg penicillians and clavulonic acid), HIV protease therapy (eg saquinavir), serine/cysteine protease inhibitors, serpins, thrombosis, PSA, digestive enzymes, selectivity constant and drug selection/evaluation, point mutations and relationship to disease/treatment., opioids and selectivity</p>	<p>Problem Set 3 &4: Take-home and present solutions in recitation.(not graded)</p> <p>Exam 2: Essay-based written. (Ferguson)</p> <p><u>Lab Exercise (9/24): Students will also complete a laboratory exercise involving an OTC test kit that applies foundational knowledge to a clinical problem.</u></p> <p>In-class group literature evaluation and take-home written summary of membrane transporters in drug transport literature</p>

	<p>to inhibitors, Transition State theory in practice, From bench to bedside</p> <p>Lesson 7: beta Lactamases, Tamiflu, Aspirin</p>		
<p>MODULE 4B: Cell-to-Cell Interaction, Cell Communication and Signaling Cascades (10/7-11/2)</p>	<p>Lesson 1: Gap junctions and tight junctions, Extracellular Matrix, Cellular communication, tumor invasion, viral recognition</p> <p>Lesson 2: Cellular Signaling, Ligand-gated ion channels, G-protein couple receptors</p> <p>Lesson 3: Cytokine receptors, Integrin receptors, Receptor tyrosine kinases, Nuclear receptors</p> <p>Lesson 4: Signal transduction across the membrane, Agonist and antagonist, Intracellular signal transduction, Signaling cascades in tumorigenesis</p> <p>Lesson 5: G-protein coupled receptors in disease, Morbid obesity, Heart disease, Diabetes</p>	<p>Explain the role of gap junctions and tight junctions in cellular communication and tissue barriers, respectively. Application: Illustrate the function of the extracellular matrix, including the sequestration of growth factors, wound healing, tumor invasion, viral recognition and inflammation. Summarize rationale for drug targeting of direct ligand-gated ion channels, G-protein coupled receptors, cytokine receptors, integrin receptors, receptor tyrosine kinases and nuclear receptors. Understand signaling pathways as well as tissue specific uses of signals, receptors and signaling pathways. Application: specific disease states attributed to G-protein coupled receptors will be presented, including morbid obesity, hypertension, and diabetes. Summarize the molecular mechanism of signal transduction across the membrane and within pathways in the context of agonist and antagonist activity. Clinical: Signal transduction is the target of many common drugs, agonists and antagonists. For example, G protein-coupled receptors are reported to be the target of 50% of drugs.</p>	<p>In-class group assignment – G-protein coupled receptors</p>
<p>MODULE 5B: Membrane and Protein Trafficking, Cell Stress and Cell Death (11/4-11/11)</p>	<p>Lesson 1: Intracellular vesicular transport, Regulation of vesicular transport- Rab GTPases, phosphoinositides, Trafficking in cancer, Alzheimer's and infection</p> <p>Lesson 2: Endocytosis, phagocytosis and pinocytosis, Tissue specific membrane internalization- LDL uptake, receptor down-regulation, Exocytosis - neurotransmitter and insulin release, antigen presentation</p> <p>Lesson 3: Endoplasmic reticulum stress response, Proinsulin production, Pancreatic cell death and diabetes, In-class case discussion</p> <p>Lesson 4: Repression and induction of programmed cell death, Autoimmune</p>	<p>Illustrate the purpose of vesicle budding from the golgi and endoplasmic reticulum and means to regulate vesicle targeting. Application: Demonstrate the role of Rab proteins in cancer, Alzheimer's disease and pathogen infection and survival. Show the role of phagocytosis and pinocytosis in the internalization of extracellular or membrane bound structures, including receptor-mediated Application: uptake of low-density lipoprotein, receptor down-regulation, and drug delivery and the involvement of constitutive and regulated exocytosis in neurotransmitter and insulin release, antigen presentation and protein trafficking. Understand the cycling of endosomes between degradative pathways and molecular recycling pathways. Application:</p>	

	<p>disease, Ischemic cardiovascular damage, Necrosis - infection, toxins, and trauma</p>	<p>Demonstrate the role of the ER stress response in proinsulin production and pancreatic cell death associated with diabetes progression. Illustrate the signals involved in repression or induction of programmed cell death (apoptosis) and associate this with common disease states such as autoimmune disease, cancer and ischemic cardiovascular damage and identify insults leading to non-programmed (premature) cell death (necrosis) such as infection, toxins and trauma. Explain the function of degradative machinery in the cell, involved in either protein turnover or cellular component turnover and contribution of protein misfolding and aggregation in multiple disease states. Application: Outline protein folding diseases including Alzheimer's, Parkinson's, Huntington's, Amyotrophic lateral sclerosis, Creutzfeldt-Jacob, and Gaucher's. Clinical relevance: Important molecular targets of drugs have been articulated above (infection, LDL uptake, diabetes, cancer, etc...). The molecular pathology of these states will be presented along with drug target and potential sites of drug targeting.</p>	
<p>MODULE 6B: Cell Cycle, Cellular Recycling, Cell Specialization and Molecular Inflammation (11/11-11/18)</p>	<p>Lesson 1: Cell cycle and cycle progression, Cellular reorganization (cytoskeletal changes)</p> <p>Lesson 2: Cellular specialization/tissue specific expression and function, Transporters in ADME critical tissues</p> <p>Lesson 3: Cytokine/chemokine recruitment and suppression of inflammation, Case Study Discussion - macrophage recruitment to adipose tissue</p> <p>Lesson 4: Molecular mechanism of cell adhesion, Integration of cell surface markers (carbohydrates), cytoskeletal transport and signal transduction in inflammation, Molecular "repair" process - clearing damaged tissue</p>	<p>Interpret the signals necessary to keep inflammation in check or recruit inflammation to a site of insult or injury. Summarize how inflammatory cells reach their targets and the molecular "repair" processes used to clear the insult/signaling tissue. Outline the cellular events within the unique stages of the cell cycle and cellular signaling required to progress through the cell cycle. Explain tissue specific protein/enzyme expression patterns and related cell function outcomes. Clinical relevance: Abnormal cellular functioning of these events lead to a large number of disease states, including asthma, atherosclerotic plaque progression, metabolic syndrome and insulin resistance, inflammatory bowel disease, rheumatoid arthritis, cancer and cardiovascular disease.</p>	<p>Problem Set 5: Take-home and in-class discussion (not graded)</p>
<p>MODULE 4A: Nucleotides, DNA Structure and DNA Replication (10/19-11/6)</p>	<p>Lesson 1: Introduction to DNA, nucleosides and nucleotides, nucleic acids, molecular interactions in DNA</p> <p>Lesson 2: Primary & secondary DNA structure, DNA stabilization/destabilization, molecular recognition of DNA, Tertiary DNA structure</p> <p>Lesson 3: DNA topology, DNA supercoiling, topoisomerase I, topoisomerase 1 inhibitors, Topoisomerase II, topoisomerase II inhibitors, endonucleases, exonucleases, restriction enzymes in biotechnology, DNA ligase</p> <p>Lesson 4: Polymorphisms - defined, E. coli</p>	<p>Nomenclature of nucleic acids, identify differences in DNA and RNA primary, secondary, and tertiary structures, understand the organization of DNA with respect to coiling and histone binding, apply the knowledge of DNA coiling to the mechanisms of action of topoisomerase inhibitors, understand how nucleases cleave DNA strands, understand the fundamental concepts of DNA replication in prokaryotes and eukaryotes, introduce the concept of antimetabolites and discuss how nucleosides have served as platforms for development of anticancer and antiviral drugs, discuss the principles of DNA</p>	<p>Problem Set 6: Take-home and present solutions in class (not graded).</p> <p>Exam 3: Essay-based written in-class.(Harki)</p>

	<p>DNA polymerases, polymerase fidelity</p> <p>Lesson 5: DNA replication in prokaryotes</p> <p>Lesson 6: DNA replication in eukaryotes</p> <p>Lesson 7: Telomerase and inhibitors, introduction to antiviral & anticancer nucleosides, introduction to HIV replication, inhibition of viral polymerases</p> <p>Lesson 8: DNA damage and DNA mutation</p> <p>Lesson 9: DNA repair</p>	<p>mutation and their implications in carcinogenesis. Clinical: DNA binding drugs (e.g., daunorubicin), topoisomerase I inhibitors (e.g., camptothecin, topotecan, irinotecan), topoisomerase II inhibitors (e.g., ciprofloxacin, novobiocin). Introduction to DNA structure and genetic polymorphisms and how modifications can result in variability in drug metabolism in patients. Anticancer (e.g., cytarabine) and antiviral nucleosides (e.g., acyclovir, AZT). Introduction DNA damage, mutation, and environmental chemicals that promote such processes (e.g., polycyclic aromatic hydrocarbons).</p>	
<p>MODULE 5A: Biotechnology Drugs, RNA Synthesis and RNA Regulation and Eucaryotic Translation (11/13-11/30)</p>	<p>Lesson 1: Cloning vectors; bacterial, insect and mammalian expression vectors; gene cloning; PCR cloning; bacterial, yeast artificial chromosomes.</p> <p>Lesson 2: From gene cloning to biotechnology drug production; industrial production systems.</p> <p>Lesson 3: gene therapy vectors; FDA-approved gene therapy approaches, including CAR-Tcells; DNA and RNA vaccines including vaccines in development for COVID-19.</p> <p>Lesson 4: Eucaryotic RNA synthesis, RNA polymerase, Transcription factors, Regulation of transcription rates</p> <p>Lesson 5: Histone and DNA modification, Epigenetic control over gene expression</p> <p>Lesson 6: Regulatory RNAs, RNA interference, RNA editing</p> <p>Lesson 7: mRNA processing, Eucaryotic translation</p> <p>Lesson 8: Genetic code, Ribosomal structure and assembly</p> <p>Lesson 9: Translation, Translation rate regulation</p> <p>Lesson 10: Drugs targeting translation</p>	<p>Students will understand the biochemical basis of gene transcription and translation, the epigenetic modification of chromatin and the regulation of these processes and apply this knowledge by explaining how these processes are dysregulated in disease and manipulated through specific drugs. Clinical relevance: Many top 200 drugs directly target gene transcription and translation. For example, all natural (e.g. thyroid hormone, steroid hormones, vitamin D) and synthetic (PPAR agonists, SERMS, retinoids etc) nuclear hormone receptor drugs act by regulating gene transcription. Many of these drugs regulate transcription by enzymatically altering chromatin structure. In addition, epigenetic chromatin modification is becoming firmly established as a major contributor to human disease and is a target for drug design. Prokaryotic translation is exceptionally clinically relevant as most antibiotics target translation.</p>	<p>Exam 4: Essay-based written in-class and take-home. (Rumbley)</p> <p>Module 5A assessments: Section of exam 5.</p>
<p>MODULE 6A: Human Genetics, Cancer Genetics and Pharmacogenomics with Applications (12/2-12/9)</p>	<p>Lesson 1: Human Genome and polymorphism, Human genome project, Gene variants, allele frequency and naming</p> <p>Lesson 2: Genetics of common disease, Hazard ratios/penetrance, Clinical example-coronary artery disease</p> <p>Lesson 3: DNA-based diagnostics, including FISH and other DNA-based companion diagnostics; knock out/in mouse production; animal/human cloning; drug production by gene pharming</p> <p>Lesson 4: Cancer Genetics, Defining oncogenes, tumor suppressors, repair</p>	<p>The major learning goal is to understand the different types of genetic variation and its effect on gene function, especially in regards to pharmacological efficacy and adverse outcomes</p> <p>Additionally, it will be important to make sure that foundational information will be presented to support instruction in later courses that are presenting pharmacogenomic ideas. This will be done through close collaboration with other faculty.</p>	

	<p>genes, Multi-stage nature of cancer, Therapy based on gene expression, Clinical example - OncotypeDx</p> <p>Lesson 5: Techniques associated with genotyping, Single allele analysis, GWAS analysis, Sequencing, Next Generation Sequencing, Expression analysis – qPCR, Expression chips, RNA seq</p> <p>Lesson 6: Pharmacogenomics definition/description, Different package inserts, FDA expectations, ADME proteins</p> <p>Lesson 7: Clinical example: CYP2D6 and codeine, SNPs and indels (gene duplication), Clinical example: Drug transporter polymorphism, linkage disequilibrium, HLA, adverse drug reactions</p>	<p>Clinical: Students should be able to understand pharmacogenomic information presented on drug package inserts.</p>	
FINALS WEEK	Exam 5 on Modules 5A and 6A	Oetting, Kim, Shier Exam	Exam 5: Written in-class.

* Subject to change at course instructor's discretion.

[University of Minnesota and College of Pharmacy Policy Reference \(Centralized Syllabus\)](#)

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