Biochemistry

Degree Offered

Doctor of Philosophy

Program Admission Requirements

*In addition to the general **Graduate School admission requirements**, this program has additional specific requirements.*

Admission to the Biochemistry Graduate Program is through the **Interdisciplinary Program in Biomedical Sciences (IDP), Neuroscience Doctoral Program (NDP), or Medical Scientist Training Program (MSTP)**. After completion of the first-year curriculum of that program, students who choose to complete their dissertation research project with faculty of the Biochemistry Department will have the opportunity to continue their graduate studies by selecting from among a wide range of courses that are offered within the Biochemistry Department as well as other programs at MCW. Courses to be taken are based on the student's interests in consultation with the student's dissertation committee.

Fields of Research

The following areas of research are available in the department:

- The identification and characterization of signalling pathways that prevent cells from completing cytokinesis with unresolved mitotic errors.
- Structure/function studies of kinases and other proteins that ensure faithful progression through cytokinesis.
- Machine learning for drug discovery and personalized diagnosis
- Mass spectrometry-based multi-omics (proteomics, metabolomics, lipidomics)
- Protection of the immature and mature heart during surgery. Cardioplegic components and cyanosis.
- Cancer cell signaling in neurological malignancies.
- Regulation of chromatin structure and accessibility by the conformation and dynamics of nucleosomal histone tails. Additional levels of regulation by histone post-translational modifications (PTMs) and histone variants.
- Post-translational modification of lysine and cysteine residues controls protein function and exploiting these insights in the design of novel chemical probes
- Functional study of the nutrient-dependent O-GlcNAc signaling in pregnancy, early development and metabolism.
- Pre- and Post-natal exposure to non-nutritive sweeteners: impact on development and metabolism

- Diabetes, beta cell biology, inflammation innate immunity, cell signaling, cell fate decisions.
- Molecular mechanisms underlying the functioning of mannose 6-phosphate receptors (MPRs) in mammalian cells.
- Molecular regulation of nutrient utilization in metabolic syndrome, atherosclerosis and inherited diseases of fat metabolism.
- Molecular mechanisms governing G protein-coupled receptor signaling in normal and cancerous cells.
- Structural biochemistry of multi-protein machinery (RNA polymerases and associated factors) involved in gene transcription and RNA processing in the eukaryote.
- Oxidative stress, reactive oxygen/nitrogen species, cell membrane lipids, lipid peroxidation and mechanisms of oxidative apoptosis.
- The role of metabolic modifications such as acetylation. The role of topological stress in DNA. The role of accessory proteins in modulating histone DNA interactions.
- Structure-function relationship of enzymes and receptors using X-ray diffraction methods.
- Characterization of molecular mechanisms of protein dynamics and protein-protein interactions using solution NMR and other biophysical techniques.
- In vivo mechanisms controlling developmental and cardiovascular specific gene expression.
- Druggability of proteins involved in mitochondrial homeostasis in healthy and diseased cells to identify molecular mechanism and novel therapeutic routes.
- Mechanistic differences of Ras/Raf-induced growth inhibition vs. proliferation at molecular levels.
- Protease and protease inhibitors in the cornea. Structure-function of maspin and its effects on carcinoma and corneal cells.
- Structural biology of immunological signaling molecules and the use of NMR spectroscopy in structural proteomics

Overall Course Requirements

A requirement of this program is to fulfill two credits in Bioethics by completing Course (10222) Ethics and Integrity in Science and Course (10444) Research Ethics Discussion Series. For course descriptions of 10222 and 10444 see listing within the **Bioethics Program**.

Courses

02203 Molecules to Cells. *5 credits.*

Molecules to Cells is designed to provide students with integrated concepts of biochemistry, medical genetics, human development and cell and tissue biology. The goal of the curriculum is for students to become aware of the contributions these disciplines bring to future developments in clinical diagnosis and treatment. Molecules to Cells will expose students to the molecular and chemical principles of life from the structure and function of DNA and proteins, to metabolism, membrane transport and cellular recognition. The course provides the basic science foundation in the principles and concepts of genetics that is required for the understanding of the rapidly changing clinical practice of medical and translational research.

02207 Enzyme Kinetics and Receptor Binding: Theory and Practice. *1 credit.*

This course teaches both the theoretical framework and practical aspects of enzyme kinetics and receptor binding studies. Topics covered include basic steady state kinetics including the determination and meaning of Km and Vmax values for simple and multisubstrate reactions, determination binding properties and kinetic consequences of common reversible inhibitors (competitive, non-competitive, uncompetitive, mixed), slow-on, slow-off inhibitors and irreversible inactivators. Dissociation constants and procedures for determining them will be discussed for both enzymes and macromolecular receptors. Practical methodologies for determining pre-steady state kinetics will be presented. Practical aspects of designing kinetic studies will be discussed and later sessions of the course will involve reading and student-led discussions of studies in the literature that illustrate ways in which studies of enzyme kinetics or receptor binding advanced the study of particular enzymes and other macromolecules. Over the six-week duration of the course each student will prepare a short report in which he or she describes the design and, if possible, execution of a series of kinetic or receptor binding studies that draw on the teachings of the course and are related to the work each proposes to carry out for a dissertation.

022-16268 Protein Chemistry-Principles. *1 credit.*

Protein Chemistry: Principles is a course suitable for all students interested in developing critical thinking skills through literature examples of protein activity and its regulation. In this course, students and instructors will use the primary literature to learn and apply the practical formalisms in protein chemistry – including thermodynamics, kinetics, enzymology, and chemical biology – to the regulation of protein activity. Biology is governed by thermodynamic and kinetic principles, but these principles are often abstract to students. The purpose of this course is for students to develop utility in thermodynamic and kinetic principles and apply them to biological systems. The course will emphasize literature examples and expect students to learn these principles by working through problem sets provided by instructors. Students will be able to differentiate when thermodynamics or kinetics likely govern a given biological system and have a framework by which to analyze new systems. In addition, classroom discussions will include alternative methods and their relative merits. From these analyses, students will hone their critical thinking and communication skills.

022-16267 Protein Chemistry-Applications. *1 credit.*
Protein Chemistry: Applications is a course suitable for all students interested in developing critical thinking skills through literature examples of protein activity and its regulation. Students and instructors will discuss literature that illustrates the in vitro reconstitutions, proteins structure/activity, and methods and logic of experimental design including critical control experiments. In addition, the discussions will include methods learned in the first-year curriculum that might have been applied, but were not. From these analyses, students will hone their critical thinking and communication skills. Grading for this course will be based on 100 total points: 48 pts for classroom participation (metric attached) and 52 pts for a student-directed presentations/discussions (metric attached). At least three instructors will be involved in the grading of final presentations and the final score to be an average of each instructor's total score. The course will be capped at a maximum of 12 students; a minimum of 4 students will be required to offer this course. Instructors for this course will include current faculty members participating in the Biochemistry Graduate Program. The course will be offered every Spring semester. An overarching goal of the course is to prepare students for understanding the methods and logic underlying experimental design in modern biomedical research.

02226 Biophysical Techniques in Biochemistry. *3 credits. Prerequisite:* 022-16268.
This course will introduce the basic theory and practical applications of an array of biophysical techniques commonly used in biochemical research. Optical, fluorescence, and magnetic resonance spectroscopies, x-ray crystallography, mass spectrometry and kinetics techniques are just a sampling of the topics covered in this comprehensive course.

02230 Biomolecular NMR: Structure and Molecular Recognition. *1 credit. Prerequisite:* 022-16268*.*
Nuclear magnetic resonance spectroscopy (NMR) is a powerful tool for the interrogation of biomolecular structure and interactions at atomic

resolution. Structural genomics efforts have produced refinements in the methodology for three-dimensional protein structure determination, such that new structures can be solved in a matter of weeks using increasingly automated processes. This course begins with a description of the quantum mechanical basis for multidimensional NMR using the product operator formalism. This powerful operator algebra rigorously predicts the propagation of the nuclear spin wavefunction under a time-independent Hamiltonian operator governing interactions between nuclear spins and between spins and static or transient magnetic fields, enabling the development of increasingly complex pulse sequences for multidimensional, multinuclear NMR measurements of biomolecules. Simple pulse sequences for magnetization transfer and isotope editing are described using product operators and combined into more complex two- and three-dimensional pulse schemes for triple-resonance correlation of nuclei in proteins. Systematic application of these NMR methods to the sequence-specific assignment of isotopically enriched proteins will then be linked to the interpretation of other of types NMR data (nuclear Overhauser effect; scalar and dipolar couplings) that report directly on tertiary structure. The balance of the course will consist of practical, hands-on training in basics of 2D/3D NMR data acquisition, processing and analysis, as well as interactive computer tutorials on the chemical shift assignment and 3-D structure determination processes.

02235 Biomolecular NMR: Protein Dynamics and Binding. *1 credit. Prerequisites:* 022-16268 *and enrollment in 02230 Biomolecular NMR: Structure and Molecular Recognition.*

NMR spectroscopy is one of the most powerful tools of contemporary structural biology. Multiple NMR applications enable structural, thermodynamic and kinetic analysis of proteins and nucleic acids under physiological conditions with site-specific resolution. The course “Biomolecular NMR: Protein Dynamics and Binding” discusses applications of NMR to protein dynamics, conformational transitions and ligand binding. The topics include NMR line shape analysis and spin relaxation methods that are used to extract structural, thermodynamic and kinetic parameters of conformational transitions and ligand binding in proteins. The course is directed to students who would like to utilize NMR spectroscopy as a part of the dissertation research.

02240 Contemporary X-ray Crystallography. *1 credit. Prerequisite: Completion of IDP course curriculum.*

X-ray crystallography is the main method that is used to elucidate three-dimensional structures of macromolecules and biomolecular complexes, and capable of revealing structural details at high resolutions. Powered by modern synchrotron-based light sources and state-of-the-art computer programs, contemporary crystallographic research has provided mechanistic insights into complex cellular functions such as gene transcription and translation. While crystallographic computer programs are openly available, the use of these packages by biologists who do not have a theoretical comprehension of crystallography can be unproductive. This course is designed to teach non-crystallographers the capability to intelligently use crystallographic programs that are available in the form of bundled software. Attendees will learn systematically the central theory behind the crystallographic tools in use today, and hence grow an appreciation of the physical process that takes place during an experiment to determine the structure of a protein or nucleic acid. A central aim of this is to generate stimulating discussions that will help the students grasp the essence of macromolecular crystallography.

02248 Structural Basis - Macromolecules. *1 credit.*
Prerequisites: Biochemistry of the Cell (course #16201) or equivalent, or consent of the course director.
With the explosion of the number of three-dimensional structures of biological macromolecules that have been determined, it is imperative to learn how to study their structures in detail and learn the molecular basis for their functions. This course discusses the mechanism of action and the relationship between structure and function of selected groups of biological macromolecules. The molecules studied range form enzymes (both soluble and membrane-bound) to proteins involved in signal transduction and in epigenetic gene regulation. At the end of the course, the student will attain the skills to analyze the relationship between structures and functions of proteins.

02776 Special Topics in Biochemistry. *1 credit.*
This is an advanced course that is designed to cover topics of particular relevance to the graduate students within the department. The students provide input regarding the topics to be covered, which vary depending on their current interests. Examples of recent topics are: Enzyme Kinetics and Receptor Binding; Theory and Practice; Structural Basis of Macromolecular Interactions; Oxidative Signaling in Cancer. The format of the course involves lecture as well as student-led discussions of the topics.

02295 Reading and Research. *1-9 credits.*

02301 Seminar. *1 credit.*
Students are given practice in presenting and evaluating their research data. Solutions to research problems encountered are also discussed. Seminar is required beginning in the second semester and continues throughout each student’s program.

02399 Doctoral Dissertation. *9 credits.*