GRADUATE STUDIES IN
Biochemistry and Molecular Biophysics
Penn Medicine
The central focus of the Graduate Group in Biochemistry and Molecular Biophysics is the relationship between form and function. The goal of the program is to provide students with a foundation in the physical and quantitative methods necessary to explore the molecular basis of biological events. The faculty of the Graduate Group have a common theme of seeking to understand biological phenomena using an array of genetic, biochemical and biophysical approaches. Research topics are far-ranging and include the genetic, biochemical and structural basis of signal transduction; membrane biochemistry; biochemical imaging; mechanisms of transcription; replication and recombination; molecular immunology; protein structure, dynamics and folding; enzymology; regulation of metabolism; RNA biochemistry; de novo protein design; and the mechanism of action of large protein “machines.”

The curriculum is designed to provide a superior graduate level education by tailoring the program to each individual student in order to round out his or her knowledge of biochemistry or molecular biophysics. A central goal is to build on the strengths and interests of the student and prepare the student for dissertation research.

By the end of the second year of study, each student should have achieved a general level of understanding of biochemistry, molecular biology, and cell biology appropriate for a contemporary biomedical scientist, through appropriate courses and semester-long laboratory rotations. After successfully passing a Candidacy Examination at the end of the second year, the student chooses a research topic and advisor and begins full-time dissertation research. Students also participate in research seminars and informal interactions with other graduate students, postdoctoral fellows and faculty members, all of which form an important part of graduate education.

Emerging subtypes of influenza A virus hold the potential to initiate a world-wide epidemic, yet many new strains are resistant to amantadine and rimantadine, that form one of only two drug classes used to treat the flu. The structure of the membrane protein M2 shows how these drugs act as “channel blockers,” preventing the flow of protons through the channel that is required to acidify the viral interior in the endosome. The structure provides information on the mechanisms of channel activation and ion conduction, and provides a starting point for the design of new inhibitors.

Theoretical and experimental approaches are combined to understand properties of protein sequences consistent with a chosen three-dimensional structure. Computational design predicts structurally allowable substitutions (yellow) in a small zinc-binding domain. Experimental kinetic measurements test the folding and stability of these altered polypeptides. Saven, Gai and co-workers (*J. Mol. Biol.* 389:90-102, 2009).

Two-photon phosphorescence lifetime microscopy allows visualization of oxygen gradients in 3D with near diffraction-limited resolution. A specially designed nanoprobe (shown) uses a two-photon antenna to harvest infrared radiation that is passed onto the phosphorescent chromophore via intramolecular FRET. The probe enables non-invasive high-resolution oxygen measurements in tissues and individual cells (inset). Vinogradov, Hochstrasser and colleagues (*ChemPhysChem* 9:1673-1679, 2008).

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Two-dimensional infrared spectroscopy is an emerging technique for the determination and characterization of protein structures, particularly those in which ultrafast motions occur. The spectrum was obtained from a sample of the amyloid β protein that accumulates in Alzheimer’s disease and misfolds into neurotoxic fibrils. The position, width, and intensity of peaks, the presence of off-diagonal cross peaks, and the time evolution of these features on the picosecond time scale, provide unique insight into how these proteins fold into fibrils. Axelsen, Hochstrasser and co-workers (PNAS 105:7720-7725, 2008).

Conventional nucleosomes (left) package chromosomal DNA and carry epigenetic marks, mostly in the form of chemical modifications on the histone “tails” that recruit regulatory proteins to particular chromosome locations. Specialized nucleosomes (right) contain a histone variant CENP-A, which epigenetically marks the chromosome location – the centromere – that directs the inheritance of the entire chromosome at cell division. CENP-A incorporation generates conformational rigidity to the nucleosome core that physically marks the centromere, and recruits additional components required for chromosome segregation. Bassett (MBM student), Black and co-workers (Cell 137:472-484, 2009, Nature Cell Biol. 11:793-795, 2009, PNAS 104:5008-5013, 2007).

A number of advanced laboratories support research efforts based on X-ray crystallography, Small Angle X-ray Scattering (SAXS), macromolecular NMR and EPR spectroscopy, medical and biochemical imaging, computational biophysics, mass spectrometry and a variety of preparative and analytical resources.

Faculty members of the Graduate Group oversee many of these resources. The School of Medicine also maintains a wide range of ancillary resources supporting almost any imaginable biomedical research effort. The vast array of research capabilities that are available is a true advantage to the students and faculty of the Graduate Group.

Detailed structural and thermodynamic evidence indicate that the signaling adaptor protein NHERF1 is regulated by autoinhibitory interactions between its domains, including two PDZ domains and a C-terminal ezrin binding (EB) motif. NMR and optical experiments suggest two distinct closed conformations of NHERF1 (left) stabilized by interactions of the second PDZ domain (blue) with either the EB region (red) or a flexible linker (black). Unlike most PDZ domains that recognized an extended conformation, the initially unstructured EB region becomes helical when bound to the NHERF1 PDZ domain. Roder and co-workers (Structure 17:660-669, 2009).
In addition to classes and research, students participate in many activities that enhance their education and development as scientists. These activities help students develop a network of contacts, acquire career skills, and interact with faculty in less formal environments. In addition, social activities provide a support system and, most importantly, foster long-lasting friendships.

**Friday Research Discussions:** Every Friday during the academic year, faculty, students and postdocs gather over refreshments in the Johnson Foundation Library to listen to a faculty member describe his or her research.

**Annual Retreat:** This two-day event is sponsored by the Graduate Group and the Department of Biochemistry and Biophysics. Students, faculty, and postdocs present their work in poster sessions and talks. A highlight of this event is the student-faculty softball game, followed by the annual picnic.

BMB students also participate in many other activities across the University campus, including the Chemistry and Biology Interface Training Program, which holds student-organized mini-symposia in chemical biophysics, discussion groups, and an annual retreat.

Finally, another unique aspect of the Graduate Group in Biochemistry and Molecular Biophysics is that students play an active role in shaping the program. Student representatives sit on most major committees within the Graduate Group. The faculty seriously considers student input; in fact, many features of the current program are the direct result of student suggestions.

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The Johnson Research Foundation is a significant resource for the Graduate Group. Established in 1929 as the world’s first institute dedicated to biophysical research, this pioneering research foundation motivates and supports investigation of the fundamentals of biological design and function, focusing on protein structure and engineering in three dimensions from angstroms to microns. It continues its tradition of bringing advanced chemistry and physics to biology and medicine.

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Benjamin Franklin exerted a great influence on education in Pennsylvania, having founded the University of Pennsylvania in 1740. Today, casually seated on a bench on the campus reading his newspaper, Franklin seems ready to engage in conversation with a passerby.
ATP, (green), are used to study homologs of genes in muscle cells, stained for actin (red) and myosin (green), to use study homologs of genes linked to inherited forms of muscular dystrophies. Lamittina and co-workers (work in progress).

C. elegans models of disease. Upper: Environmental determinants of protein misfolding. Osmotic stress induces polyglutamine YFP-fusion protein aggregates in C. elegans intestine. Lower: C. elegans muscle cells, stained for actin (red) and myosin (green), are used to study homologs of genes linked to inherited forms of muscular dystrophies. Lamittina and co-workers (work in progress).

The ability to sense molecular tension is crucial for a wide array of cellular processes, including the detection of auditory stimuli, control of cell shape, and internalization and transport of membranes. The motor protein myosin is important in powering key steps in these processes. Optical trap technology can be used to dissect the events of a working stroke of a single myosin I (blue) as it walks along an actin filament (red). The highlighted steps are force sensitive, resulting in a system where motile properties respond to tension. Laakso (BMB graduate, Ph.D. 2009), Ostap and co-workers (Science 321:133-136, 2008).
University of Pennsylvania

Penn is a national leader in higher education and enrolls about 20,000 full time students in its 12 graduate and professional schools. Located across the river from Center City Philadelphia, the Penn campus provides students with easy access via public transportation to a great variety of attractions: numerous museums and art galleries, opera, symphony, ballet, concert and film houses, all major professional sports, renowned gourmet and ethnic restaurants and food markets, the world's largest city park system, and a wealth of historic landmarks and architectural treasures. Students choose among a variety of affordable housing options on campus and throughout the surrounding neighborhoods.

Penn is unique among its Ivy League peers in having all of its schools located on a single campus, facilitating interdisciplinary discourse and research. As home to the nation's first medical school and first teaching hospital, Penn has a strong tradition in biomedical research and training. Penn ranks third in the nation in funding from the National Institutes of Health, and its School of Medicine is ranked second in NIH training grant funding. Additional information is available at http://www.upenn.edu.

Biomedical Graduate Studies

Biomedical Graduate Studies (BGS) serves as the academic home for more than 700 graduate students pursuing a Ph.D. in the basic biomedical sciences. The program is organized into seven graduate groups: Biochemistry and Molecular Biophysics, Cell and Molecular Biology, Epidemiology and Biostatistics, Genomics and Computational Biology, Immunology, Neuroscience, and Pharmacological Sciences. Over 600 faculty members representing more than thirty academic departments and seven schools throughout the University participate in BGS and cooperate in admitting, funding, advising, training, and providing career development information to BGS students. The program's structure provides for exceptionally broad-based, flexible, and interdisciplinary training. Graduate groups in BGS also participate in combined degree programs with the School of Medicine (M.D.), the School of Veterinary Medicine (V.M.D.), and the School of Dental Medicine (D.M.D.). BGS students may also enroll in certificate programs in medicine (HHMI Med into Grad Scholars Program) and in public health. Each program has its own application process. More information about BGS, the combined degree programs, and the certificate programs can be found at www.med.upenn.edu/bgs.

Application and Financial Aid

Admission for Ph.D. study is offered to students having good undergraduate training in biochemistry, physics, organic chemistry, physical chemistry, biology and mathematics. The Graduate Record Examination (GRE) General Test is required; GRE Subject Tests in biology, biochemistry, chemistry, physics, or mathematics are recommended but not required. Completed applications are screened by the Admissions Committee and decisions on admission are based on undergraduate record, GRE scores, letters of recommendation and personal interviews. TOEFL scores are required for international students whose native language is not English.

All students who are admitted receive a fully funded fellowship, including tuition, fees, health insurance, and a competitive stipend. The deadline for applications for entrance in the following fall term is December 8. Applicants are encouraged to apply via the BGS website: www.med.upenn.edu/bgs.

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