GRADUATE STUDIES IN

Biochemistry and Molecular Biophysics

Penn
University of Pennsylvania

Overview

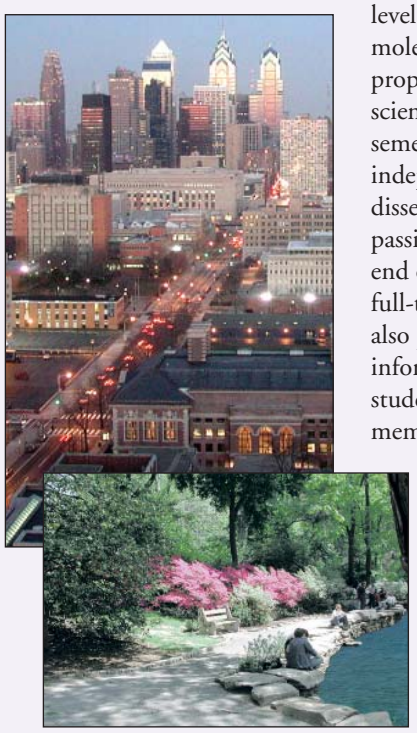
The central focus of the Graduate Group in Biochemistry and Molecular Biophysics is the relationship between form and function. The goal of the program is to provide students with a foundation in the physical and quantitative methods necessary to explore the molecular basis of biological events. The 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."

Front cover: A mitotic cell with a monopolar spindle shows a gradient of Aurora B phosphorylation spreading outward from centromeres (green). Phosphorylation is detected by a FRET-based biosensor targeted to chromatin (green) and displayed using a blue-yellow (high-low) color scale. Ballister (BMB student), Lampson and co-workers (*J. Cell Biol.* **194**:539-549, 2011).

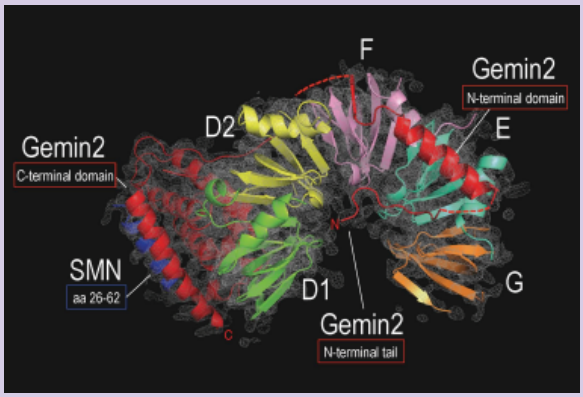
Curriculum

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, students should have achieved a general level of understanding of biochemistry, molecular biology, and cell biology appropriate for a contemporary biomedical scientist, through appropriate courses, semester-long laboratory rotations, and independent study with their intended dissertation advisor. After successfully passing a Candidacy Examination at the end of the second year, the student 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.

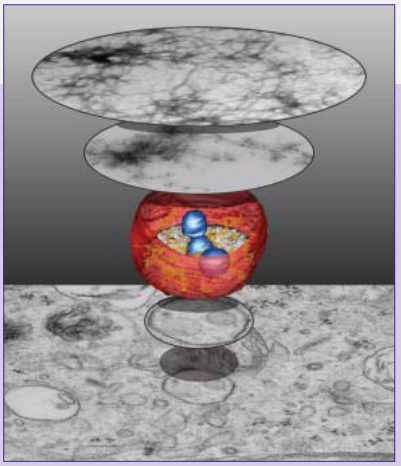


Close to Center City Philadelphia (upper left), Penn offers an historic campus featuring architectural wonders such as the Fisher Fine Arts Library designed by renowned Philadelphia architect Frank Furness in 1890 (above). Amid the noise and clutter of the city, students find respite in the the natural beauty of the Biopond (left).



Much of gene expression regulation in eukaryotes occurs post-transcriptionally and is mediated by RNA-binding proteins and small non-coding RNAs. Small nuclear RNPs (snRNPs) are the major subunits of the splicing machinery that produces mRNAs. Each snRNP contains a small RNA ringed by 7 Sm proteins, a remarkable structure that is assembled by the SMN complex. Dissecting this process, the Dreyfuss laboratory captured a key assembly intermediate containing 5 Sm proteins, gripped by Gemin2 and part of SMN, and determined its crystal structure. Dreyfuss and co-workers (*Cell* **146**:384-395, 2011).

Structure of the Rtt109/Vps75 histone acetyltransferase complex provides new insights into chaperone-mediated histone acetylation for maintenance of genomic stability in yeast. Marmorstein and co-workers (*Structure* **19**:221-231, 2011)



Montage of electron micrographs of melanosomes, intracellular organelles of melanocytes that contain intralumenal amyloid fibrils of Pmel17. In increasing magnification from bottom are a thick section from a melanocyte, an early stage melanosome from this section, a three-dimensional electron tomograph, detail from a melanosome and finally an image of recombinant Pmel17 fibrils. Marks and co-workers (*J. Biol. Chem.* **281**: 35543-35555, 2009).

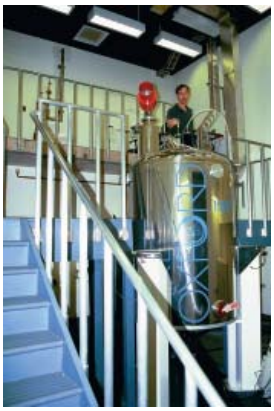
Resources

Research endeavors in biochemistry and molecular biophysics are often technology-intensive. The Department of Biochemistry and Biophysics and the Johnson Research Foundation in conjunction with the Perelman School of Medicine provide an extraordinarily broad set of core resources in the advanced technologies necessary to modern biochemical and biophysical research.

A number of advanced laboratories support research efforts based on X-ray crystallography, Small Angle X-ray Scattering (SAXS), macromolecular NMR and EPR spectroscopy, electron microscopy, 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 Perelman 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.

750 MHz NMR spectrophotometer



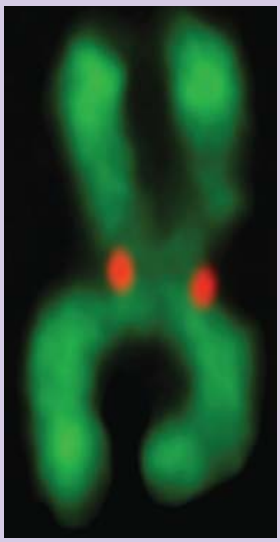
X-ray suite

General spectroscopy lab

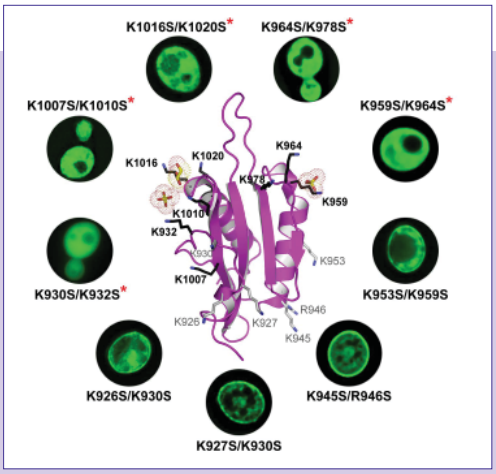
Above and right:
Working in the lab

7 Tesla whole-body MRI

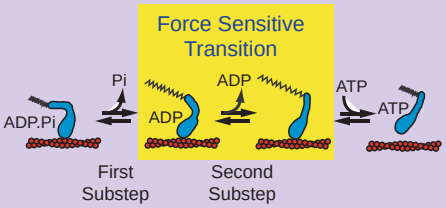
EPR spectroscopy suite



Conventional nucleosomes package chromosomal DNA and carry epigenetic marks. Specialized nucleosomes contain a histone variant, CENP-A, that epigenetically marks the chromosome location – the centromere (red dots) – that directs the inheritance of the entire chromosome (green) at cell division. The physical basis of how CENP-A marks centromere location and the relationship of CENP-A-containing chromatin to the recruitment of key regulatory proteins, such as the Aurora B kinase, are the subject of current investigation. Bassett (BMB student), Salimian (BMB student), Ballister (BMB student), Smoak (BMB student), Lampson, Black and co-workers (*Nature* **467**:347-351, 2010, *Cell* **144**:471-479, 2011, *Curr. Biol.* **21**:1158-1165, 2011).



The KA1 domain found in yeast septin associated kinases and in human MARK kinases is a phospholipid binding domain. Here it is shown that crystallographically identified, conserved binding sites for anionic phospholipids are essential for plasma membrane localization in yeast. Moravcevic (BMB graduate, Ph.D. 2010), Lemmon and co-workers (*Cell* **143**:966-977, 2010).



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 I 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).

Student Activities

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.

The Annual Retreat

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.

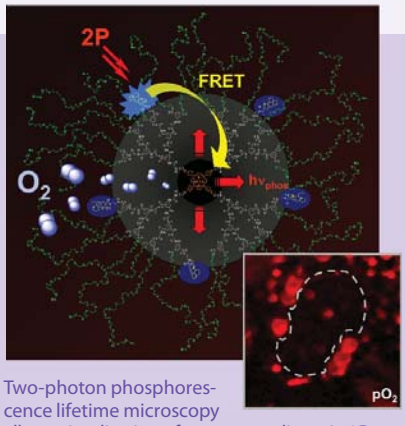
BMB students also participate in many other activities across the University campus, including the Chemistry and Biology Interface Training Program, which holds student-organized mini-symposia in chemical biophysics, discussion groups, and an annual retreat.

The poster session at the Retreat

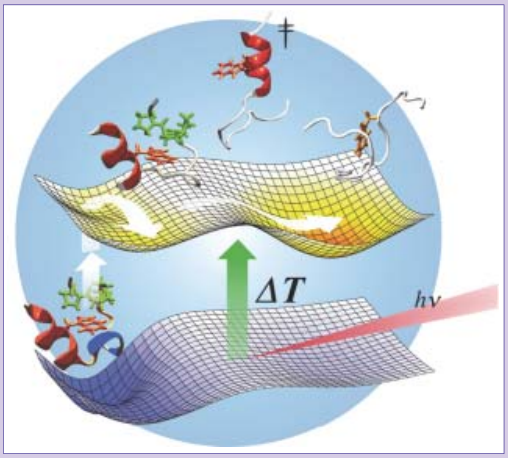
Finally, another unique aspect of the Graduate Group in Biochemistry and Molecular Biophysics is that students play an active role in shaping the program. Student representatives sit on most major committees within the Graduate Group. The faculty seriously considers student input; in fact, many features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

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.

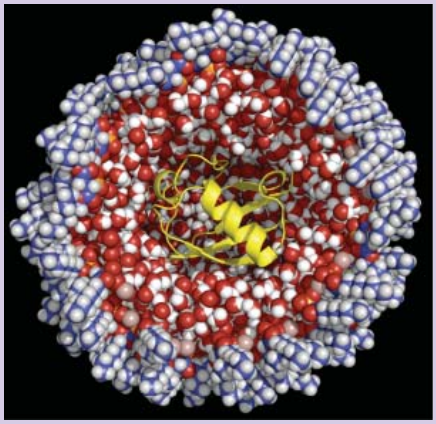
Benjamin Franklin exerted a great influence on education in Pennsylvania, having founded the University of Pennsylvania in 1740. Today, casually seated on a bench on the campus reading his newspaper, Franklin seems ready to engage in conversation with a passerby.



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).



The folding mechanism of a mini-protein, Trp-cage - achieving secondary structural resolution in kinetic measurements of protein folding. Culik (BMB student), Gai and co-workers (*Angewandte Chemie* in press, 2011)



Protein hydration has been difficult to define. Solution NMR spectroscopy is potentially useful but plagued by artifacts. Encapsulation of a protein in the aqueous core of a reverse micelle eliminates these barriers and allows comprehensive characterization of water/protein interactions. Nucci (BMB graduate, Ph.D. 2008), Wand and coworkers (*Nature Struct. & Mol. Biol.* **18**:245-249, 2011 and *J. Am. Chem. Soc.* **133**:12326-12329, 2011)

Faculty

Kathryn M. Ferguson, Ph.D.
Graduate Group Chair – Structural biology, receptor tyrosine kinase, protein-protein interactions

Charles S. Abrams, M.D.
Phospholipid signaling in platelets & lymphocytes

Yair Argon, Ph.D.
Quality control of protein folding by molecular chaperones

Paul H. Axelsen, M.D.
Protein misfolding, protein-lipid interactions & rational drug design

Tobias Baumgart, Ph.D.
Biomembranes: thermodynamics, dynamics & mechanics

Joseph A. Baur, Ph.D.
Molecular mechanisms of aging & caloric restriction

Joel S. Bennett, M.D.
Regulation of integrin function

Shelley L. Berger, Ph.D.
Histone modification & chromatin-mediated regulation

Morris J. Birnbaum, M.D., Ph.D.
Regulation of cellular & organismal metabolism, insulin action

Ben E. Black, Ph.D.
Chromatin structure/epigenetics, chromosome segregation

Kathleen Boesze-Battaglia, Ph.D.
Tetraspanin proteins & role in degenerative disease processes

Ari Borthakur, Ph.D.
MRI techniques for clinical applications

Lawrence F. Brass, M.D., Ph.D.
Molecular basis for intracellular signaling in vascular biology

Theresa M. Busch, Ph.D.
Photodynamic therapy, tumor microenvironment

Sara Cherry, Ph.D.
Systems biology of virus-host interactions

Lewis A. Chodosh, M.D., Ph.D.
Mouse models, breast cancer, genomics

Fevzi Daldal, Ph.D.
Structure, function & biogenesis of cytochrome complexes

Scott L. Diamond, Ph.D.
Mechanobiology, blood systems biology, drug delivery

J. Alan Diehl, Ph.D.
Signal transduction, cell division, metabolism, cancer

Roberto Dominguez, Ph.D.
Actin cytoskeleton, structural biology

Gideon Dreyfuss, Ph.D.
Post-transcriptional gene regulation, high throughput screening

Roland L. Dunbrack, Jr. Ph.D.
Methods & applications of protein structure prediction

P. Leslie Dutton, Ph.D.
Engineering enzyme catalysis-in nature & in the laboratory

S. Walter Englander, Ph.D.
Protein folding, hydrogen exchange

Hua-Ying Fan, Ph.D.
Chromatin structure regulation & transcription memory

Feng Gai, Ph.D.
Spectroscopic study of protein folding/misfolding

Yale E. Goldman, M.D., Ph.D.
Single molecule biophysics of molecular motors & ribosomes

Mark Goulian, Ph.D.
Two-component signaling, bacterial regulatory circuits

Doron Greenbaum, Ph.D.
Protease function, chemical biology, malaria

Ekaterina L. Grishchuk, Ph.D.
Single molecule & laser tweezers studies of cell division

Robin M. Hochstrasser, Ph.D.
Photochemical & photobiological dynamics, nonlinear optical spectroscopy

Harry Ischiropoulos, Ph.D.
Biological chemistry of nitric oxide & neurodegeneration

Paul A. Janmey, Ph.D.
Cytoskeleton, biopolymer mechanics, phosphoinositides

Roland G. Kallen, M.D., Ph.D.
Structure, function & regulation of expression of ion channels

Rahul M. Kohli, M.D., Ph.D.
Molecular evolution, pathogens, DNA modifying enzymes

Todd Lamitina, Ph.D.
Cellular osmoregulation & stress, *C. elegans* genetics

Michael A. Lampson, Ph.D.
Cell division, mitotic kinases, meiosis

Matthew J. Lazzara, Ph.D.
ErbB-mediated cell signaling

Virginia M.-Y. Lee, Ph.D.
Pathobiology of neurodegenerative diseases

Mark A. Lemmon, Ph.D.
Signaling through growth factor receptors & phospholipids

Mitchell Lewis, D.Phil.
Gene regulation, structural basis of recognition

Paul A. Liebman, M.D.
G-protein-GPCR mechanisms, visual transduction

Zhe Lu, M.D., Ph.D.
Mechanisms of ion channels

Kristen W. Lynch, Ph.D.
Regulation of mammalian alternative pre-mRNA splicing

Michael S. Marks, Ph.D.
Intracellular protein transport & organelle biogenesis

Ronen Marmorstein, Ph.D.
Molecular basis for epigenetics & cancer

Hillary C.M. Nelson, Ph.D.
Protein-DNA interactions, heat shock response

Tomoko Ohnishi, Ph.D.
Studies of respiratory components, EPR spectroscopy

E. Michael Ostap, Ph.D.
Molecular motors, cell motility, myosins

Trevor M. Penning, Ph.D.
Aldo-keto reductases in hormone & chemical carcinogenesis

Ravi Radhakrishnan, Ph.D.
Multiscale modeling, physical biology, systems biology

Arjun Raj, Ph.D.
Systems biology of long non-coding RNA, developmental biology

Ravinder Reddy, Ph.D.
Multinuclear & polarization transfer MR techniques

Heinrich Roder, Ph.D.
NMR, protein folding, structure, dynamics & function

Harvey Rubin, M.D., Ph.D.
Genetics & enzymology of bacterial dormancy

Brian M. Salzberg, Ph.D.
Optical recording, excitation-secretion coupling, neural networks

Casim A. Sarkar, Ph.D.
Protein engineering, synthetic biology, cell-fate decisions

Jeffery G. Saven, Ph.D.
Protein engineering, theory, simulation & design of molecular systems

Kim A. Sharp, Ph.D.
Theory of protein & nucleic acid structure & function

James Shorter, Ph.D.
Prionogenesis, protein misfolding, disaggregases

Emmanuel Skordalakes, Ph.D.
X-ray crystallography, telomeres, cancer & aging

David W. Speicher, Ph.D.
Cancer proteomics, membrane proteins, mass spectrometry

Cecilia Tommos, Ph.D.
Protein radicals & electrochemistry, protein forced folding

Phong Tran, Ph.D.
Cytoskeleton organization & cellular pattern formation

Gregory D. Van Duyne, Ph.D.
Structural biology, protein-protein interactions

Sergei A. Vinogradov, Ph.D.
Optical microscopy & imaging of oxygen, imaging probes

A. Joshua Wand, Ph.D.
Protein structure & dynamics, molecular recognition, NMR spectroscopy

Felix W. Wehrli, Ph.D.
MRI, tissue microstructure & function

John W. Weisel, Ph.D.
Molecular/cellular mechanisms in blood clotting & fibrinolysis

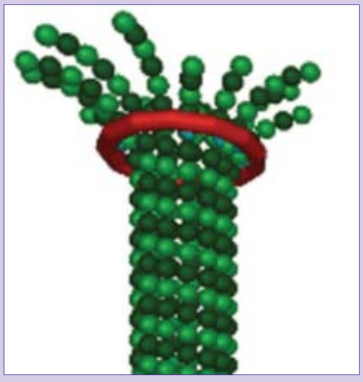
David F. Wilson, Ph.D.
Integration of metabolism, neuroregulation

John H. Wolfe, V.M.D., Ph.D.
Gene vector & stem cell distribution in brain, neuropathology

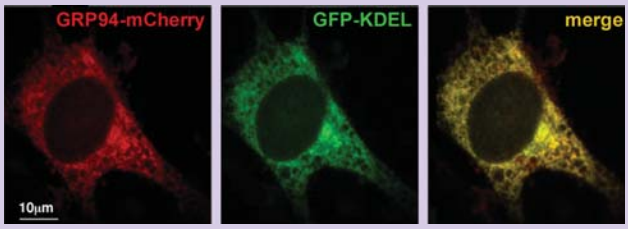
Xiaolu Yang, Ph.D.
Molecular mechanisms of tumor suppression

Takashi Yonetani, Ph.D.
Structure, mechanism & spectroscopy of hemoproteins & heme enzymes

X. Long Zheng, M.D., Ph.D.
ADAMTS13 metalloprotease, microvascular thrombosis

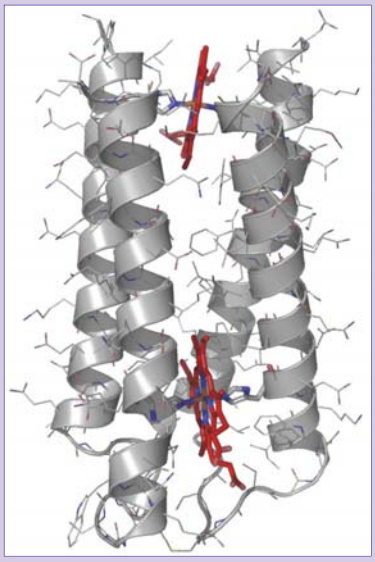


Molecular-mechanical modeling of a Dam1 ring on a depolymerizing microtubule. Grishchuk and co-workers (*PNAS* **104**:19017-19022, 2007; *PNAS* **105**:15423-15428, 2008.)



Above: Molecular chaperones in the endoplasmic reticulum govern proper protein folding and assembly. The ATPase activity of the chaperone GRP94 is required to support the production of the insulin-like growth factor. Shown is live cell imaging of a GRP94 red fluorescence protein fusion that facilitates mechanistic study of GRP94. It is expressed properly in the ER, as shown by co-localization with an ER marker (GFP-KDEL), and is an active chaperone. Argon and co-workers (*PNAS* **106**:11600-11605, 2009).

At right: A designed and engineered artificial oxygen transport protein maquette offers not only a fresh approach to the long sought-after substitute blood, but represents the first critical step in a broad spectrum of enzymatic oxidative transformations; in respiratory energy conversion, metabolism and drug dissimilation. When reproduced in simple maquette protein scaffolds, these activities will on the one hand elucidate the minimal requirements for biological function, and on the other yield working proteins that may one day provide useful technology. Solomon (BMB student), Dutton and co-workers (*Nature* **458**:305-309, 2009).



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 Perelman 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 Perelman 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), public health (PHCP), and environmental health issues (EHS). 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. Applications are accepted online via the BGS website: www.med.upenn.edu/bgs.

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