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## PURSUING A PH.D. DEGREE IN PHARMACOLOGY:

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**Preface**

This Handbook provides an overview of the Graduate Program in Pharmacology at Case Western Reserve University under the auspices of the Molecular Therapeutic Training Program (MTTP), which is funded in part by an institutional NRSA training grant from the NIH. The information provided can benefit graduate students, faculty, and anyone else interested in the graduate program. This document describes the special features, requirements, and expectations of the Program. There is also some practical information for beginning students.

The Handbook provides the policies for all graduate students and faculty members involved in graduate education, and these are revised periodically. The current handbook contains revisions that apply to incoming students for the 2011-2012 academic year and beyond. Students who began prior to 2011 follow the guidelines that were in effect during the year they began, except where the recent changes are designated for all students.

Revising this Handbook is a continuous process, and so comments are always welcome.

*John Mieyal, Vice-Chairman and MTTP Director*

*Cami Thompson, Graduate Program Administrator*

2012
The Department of Pharmacology at Case Western Reserve University School of Medicine enjoys a tradition of excellence in basic science research. Our legacy includes the award of the Nobel Prize in Physiology or Medicine in 1971 to Earl W. Sutherland Jr. for his discovery of the now famous "intracellular messenger" cAMP. Several generations of scholars have continued this tradition through their nationally and internationally recognized contributions to the biomedical sciences. In 1994, Alfred Goodman Gilman, an M.D., Ph.D. graduate of the Department, was awarded the Nobel Prize in Physiology or Medicine for his characterization of signal transduction via G-proteins. In 1998, the Nobel Prize in Physiology or Medicine was awarded to another alumnus of the Department, Ferid Murad, M.D., Ph.D., recognizing his discovery of the role of nitric oxide (NO) in intercellular signaling.

The research mission of the Department of Pharmacology builds upon this heritage by seeking to discover specific mechanisms that control physiological processes at cellular and molecular levels. At the forefront of this mission is the Chairman of Pharmacology Kris Palczewski, Ph.D. whose pioneering characterization of the structure of rhodopsin provides a foundation for ever-expanding studies of the structure and function of G-protein coupled receptors (GPCR) that play a central role in modern therapeutics. An understanding of these mechanisms provides the innovation necessary for discovery of new therapeutic interventions. Another major initiative emanating from the Department involves the renovation of the Cleveland Center for Membrane and Structural Biology (CCMSB), spearheaded by Andreas Engel, Ph.D. whose characterization of the aquaporin channels by the advanced techniques of cryo-electron microscopy and atomic force microscopy represents the frontier science of macromolecular structural biology. New Director of the CCSMB, Phoebe Stewart, Ph.D. specializes in developing hybrid structural methods. Her expertise compliments those of several very promising young investigators who are establishing their independent labs and contributing to a critical mass that represents the future of structural pharmacology. Other recently recruited faculty members have joined many long-term members of the Department to create a broad-based research environment and collegial atmosphere that recognizes the special value of students in training and fosters their development. Thus, our research focuses on the future. From bioorganic chemistry and molecular and structural biology to signal transduction and neurobiology, the modern Department of Pharmacology at CWRU provides a scholarly continuum that uses an understanding of molecular interactions along with cutting edge structural biology technologies to unravel clinically relevant drug targets.

Because modern pharmacology is a multifaceted discipline, we have created a rich interdisciplinary training program in pharmacological sciences by joining our primary faculty with affiliated faculty from other departments. This ensures that our research and educational offerings have the necessary breadth and depth for training the newest generation of molecular pharmacologists.

The most up to date information about the Department is available at its website, http://pharmacology.case.edu.

Current Departmental Information:
22 principal investigators lead research programs of the Department of Pharmacology. They are joined by 24 principal investigators who hold joint appointments in Pharmacology; and 42 principal investigators in all are currently available as approved trainers. The training faculty are distributed throughout the School of Medicine, the Biomedical Research Building, the Wolstein Research Building, The VA Medical Research Center, the Cleveland Clinic Lerner Research Institute, and the MetroHealth Medical Center.

Important contacts:
Chairman: Krzysztof Palczewski, Ph.D. (kxp65@case.edu / 368-1300)
Vice- Chairman and Graduate Program Director: John Mieyal, Ph.D. (jjm5@cwru.edu / 368-3383)
Graduate Program Administrator: Cami Thompson (cjt14@case.edu / 368-4617)
Business Manager / Executive Asst. to the Chair: Vida Tripodo (vmt1@case.edu / 368-1300)
Pharmacology Department & Medical School Facilities

Renovations: The Department of Pharmacology has outstanding renovated facilities opened in early 2008, and other portions of the Department are regularly undergoing renovations. Some highlights include 90 benches and 14 newly remodeled offices. The modernized working environment includes brighter lights, electronic LCD displays, artwork, and new furniture, all contributing to a renewed atmosphere. In addition, there are break rooms and state of the art audiovisuals in meeting and presentation rooms.

Laboratories: Three buildings comprising the School of Medicine (SOM) contain approximately 210,000 sq. ft. of space devoted to research laboratories and other research related activities, approximately 30,000 of which is committed to the Department of Pharmacology. Additional research space resides within the Celeste Biomedical Research Building (BRB, 150,000 sq. ft.) adjacent to the School of Medicine, in the nearby Institute of Pathology (18,400 sq. ft.), and in the Wolstein Research Building (180,000 sq. ft.). Several state-of-the-art facilities essential to modern biomedical research are located in these buildings and enhance the operation of individual laboratories. Common core facilities include: tissue culture, monoclonal antibodies, various types of spectral analysis (High resolution NMR, EPR, UV-Vis, HPLC-MS), atomic absorption, fluorescence spectroscopy, protein crystallization and X-ray diffraction, peptide and DNA sequence analysis, peptide and oligodeoxynucleotide synthesis, molecular cytogenetics, confocal microscopy and image analysis, small animal molecular imaging, gene expression and SNP microarray, and complete transgenic facilities that offer microinjection and homologous recombination services. Specialized equipment associated with the Palczewski laboratory in Pharmacology, the Center for Mitochondrial Diseases associated with the Department of Pharmacology, and the Cleveland Center for Membrane and Structural Biology on the West Campus, include facilities for two-photon laser microscopy, Q-TOF mass spectrometry, and high resolution cryo-electron microscopy. The Center for Proteomics and Informatics recently established at the CWRU SOM provides state-of-the-art equipment and expertise for advanced studies in proteomics and protein modifications.

Animals: A fully accredited (AAALAC 6190-6/09), staffed and equipped 42,000 sq. ft. Animal Facility is located within the SOM. Complete renovation and expansion of this facility was completed in 2009. Standard Operating Procedures and reference materials are available from the IACUC Office for animal use. The animal health program for all CWRU owned laboratory animals is directed by the Case Animal Resource Center Director, W. John Durfee, DVM, Diplomate ACLAM, and provided by two full-time veterinarians. Animals in each room are observed daily for signs of illness by the attending veterinarian responsible for providing husbandry. Medical records and documentation of experimental use are maintained individually for non-rodents and individually or by cage group for rodents. Veterinary technicians under the direction of the attending veterinarian provide routine veterinary medical care to all animals. Animal care and use is additionally monitored for training and compliance issues by the Training and Compliance Manager. The Case Assurance number is A-3145-01, valid until 04/30/15.

Computer: CWRU maintains a powerful data communication network. This system was recently upgraded and employs a Fast Ethernet System as well as wireless connections throughout the University. The Department of Pharmacology has its own servers to support the Department Intranet and offers a variety of imaging and printing systems to support scientific and administrative efforts. Computing support within the Department is provided by IT specialists through a dedicated service contract (IT Support for Pharmacology) with the School of Medicine IT Support System (CaseMEDhelp@case.edu).

Office: The Pharmacology Office Suite (Room W321) is located in the School of Medicine – Wood building. The newly constructed office is furnished with copy, fax, and scanner facilities, and features a departmental mail center. The office suite also houses the administrative / support staff.

Individual Laboratories: Laboratories are fully equipped for pursuing the most recent advances in cell and molecular biology and protein chemistry. Representative equipment includes instrumentation for UV-visible spectrophotometry, ultracentrifuges, scintillation counters, HPLC and FPLC systems, PCR thermocyclers, microcomputers, microscopes, spectrometers, ultra-low temperature freezers, a cryostat, fume hoods and laminar flow hoods, etc. Additional specialized equipment (noted above) is associated with the Palczewski Laboratory and the Cleveland Center for Membrane and Structural Biology and the Center for Mitochondrial Diseases. The Department has more than 25,000 sq. ft. of space dedicated specifically to research activities.

Other Facilities:

Common Equipment Rooms: Modern instrumentation for cell and molecular biology and protein chemistry experimentation including preparative high speed centrifuges and ultracentrifuges, liquid scintillation counters and spectrophotome-
tors, cell culture facilities, autoclaves, and dark rooms are distributed in common spaces throughout the Department with easy access from adjacent labs.

Pharmacology Conference and Seminar Rooms: The Department provides a seminar room with state-of-the-art features and seating for over 70 people. The seminar room’s features include a built-in projector, dry erase boards, and a complete electronic system that can be either self-sufficient or can accommodate both PC and Mac computers. In addition to the seminar room, the Department has a classroom and several small meeting rooms available for conferences, also fitted with built-in projectors.

Cleveland Center for Membrane and Structural Biology: The CCSMB is a joint venture between Case Western Reserve University and the Cleveland Clinic Foundation, administratively overseen by the Department of Pharmacology (http://ccmsb.case.edu), and directed by Dr. Phoebe Stewart, Professor of Pharmacology. The Center provides access to sophisticated instrumentation which is housed at various sites in the School of Medicine and in the newly renovated building at the nearby West Campus. The NMR facility is well equipped with state of the art NMR instrumentation, ranging from 600 to 900MHz. Two Bruker 600, an 800 and a 900 MHz are equipped with cryogenic probes for solution NMR work. The 800MHz instrument can also be switched to solid-state operation. The X-ray core facility is equipped with a Rigaku MicroMax-007HF, second-generation microfocusing rotating anode generator, Osmic VariMax optics, a Saturn 944+ CCD detector and X-stream 2000 cooling system. The system is used for crystal screening and data collection. The high beam flux along with the CCD detector speedily collects images by exposing the crystals for a few seconds. The Protein Expression Purification Crystallization Core is a state-of-the-art robotic laboratory that facilitates the crystallization of soluble and membrane proteins for structure determination by X-ray crystallography. The PEPPC is located in the Department of Physiology and Biophysics within the School of Medicine, serving investigators throughout Greater Cleveland (http://pepcc.case.edu). The Electron Microscopy facility features a high-end 200 kV cryo-electron microscope for high-resolution imaging of single complexes and 2D crystals. A 120 kV EM is used for sample screening and conventional imaging of sections and negatively stained samples. The Facility also has sample preparation equipment for single particle cryo-EM, 2D crystallography and tomography.

The Pharmacological Sciences Consortium Instrumentation Core (PSCIC) was funded by a special grant from the State of Ohio to provide a multi-component core of instrumentation for exploration of novel approaches to drug discovery, computer-generated molecular modeling, NMR data refinement, confocal microscopy (Joint Venture with the Department of Neurosciences), image analysis, and construction of transgenic mice. The PSCIC facilities have been distributed within the School of Medicine to provide for their most efficient utilization.

CWRU Comprehensive Cancer Center: Approximately 70% of the MTTP training faculty are members of the CWRU Comprehensive Cancer Center (CCC), including Dr. Stan Gerson who is the Director of the CCC, and Dr. Ruth Keri who is the Associate Director for Basic Research. This affiliation provides access to all of the CCC facilities at CWRU SOM, University Hospitals and at the Cleveland Clinic. A full list of Shared Resources is available at: http://cancer.cwru.edu/sharedresources/. Descriptions of the most pertinent Core Facilities are described below:

**Biostatistics** *(Director: Mark D. Schluchter, PhD)* - The Biostatistics Core Facility provides investigators with capabilities in biostatistics, clinical trials, epidemiology, statistical computing, and database and information management. Collaboration with investigators is provided on biostatistical issues and database management in clinical trials, prevention and cancer control research, genetic and population studies, and translational research. Investigators are encouraged to utilize the Core Facility at the first stages of study design, and to maintain an ongoing collaboration throughout the study. Dr. Schluchter teaches a course on Fundamentals of Biostatistics which is an integral component of the Pharmacology training program (see below).

**Cancer Pharmacology Core Facility** *(Director: Yan Xu, Professor of Chemistry)* - The Cancer Pharmacology Core Facility provides accessible, timely and comprehensive analytical services to early phase clinical studies and basic cancer research. It supports the translational research objectives of the Developmental Therapeutics Program and the interactive multidisciplinary and multi-coordinated Laboratory Correlates Conference.

**Gene Expression and Genotyping** *(Director: Martina Veigl, Ph.D.)* - This facility serves researchers at CWRU/UH, utilizing the oligonucleotide-based Affymetrix platform to assess gene expression levels. The facility contains two Affymetrix GeneChip Processors and readers as well as a high-throughput ABI real-time PCR machine. The core prepares samples and processes samples, acquires data, and provides analytical services. The Department of Genetics & Bioinformatics Core Facility also assists the Custom Array Facility in the development of databases and bioinformatics.

**Tissue Procurement, Histology, & Immunocytochemistry** *(Director: Gregory T. MacLennan, M.D.)* – Besides providing normal, benign, diseased, and malignant tissues, and adjacent tissues, from surgeries and autopsies, this core facility can make available hematoxylin and eosin (H&E) stained sections of paraffin-embedded or methacrylate...
embedded tissues for research on a rapid basis. A laser capture dissecting microscope is available to provide micro-
dissection of tumor tissue. Expert consultation is also available.

**Cytometry & Imaging Microscopy Core Facility** *(Director: James Jacobsberger, Ph.D.)* - The Cytometry core pro-
vides flow and laser scanning cytometry and cell sorting instrumentation, expertise, training, consultation, and ser-
tices to Cancer Center investigators. The Core Facility strives to ensure the quality of the data, assist with experi-
mental design, teach the principles of cytometry, and develop protocols and approaches as a set of tools designed to
assist cancer research.

**General Info – Students Entering the Program**

By establishing a common foundation in both cell and molecular biology and the physiological and molecular bases of
pharmacology all students share a common scientific language. As students diversify into the Advanced Training Tracks
they remain united by many functions, most importantly the Graduate Student Organization (GSO) that fosters education-
al as well as social interactions on a monthly basis, and the Departmental Journal Club which provides the opportunity for
the students to present current research findings to the entire department. In addition, the Annual Departmental Retreat
showcases the scientific accomplishments of the entire program and brings the community of faculty, students and re-
search staff together to enjoy the science as well as recreational activities. These periodic functions are reinforced on a
weekly basis by the universally attended Seminar Series in the Pharmacological Sciences which feature frontier research
pertinent to novel therapeutic developments. Furthermore faculty and students are engaged in the recruiting efforts for
new students and new faculty, again in both a professional and social manner. More details on these activities are pre-
sent below. *New students are encouraged to reach out to advanced students in the Program for guidance and con-
structive criticism of their written assignments and presentations.* The listing of requirements and expectations that are
detailed below may seem daunting at times, but the Pharmacology graduate student community here is an assembly of
caring individuals who are very willing to help by providing notes for classes, tips for preparing for exams, and feedback
on practice oral presentations. Collectively the faculty and students are proud of our program, because it holds everyone
to a high standard of excellence, provides guidance and assistance through tough spots, and celebrates achievement!

**Stipends, Tuition and Taxes**

All registered Molecular Therapeutics Training Program (MTTP) students matriculating on a full-time basis are eligible to
receive tuition and stipend support. The stipend level for the 2011-2012 academic year is $25,000. Stipend levels, which
are reviewed annually, are based on a support year of 12 months. Students in the MTTP are funded by NIH institutional
training grants, NIH individual research service awards, federal and privately funded research grants, and university re-
sources.

As described under the Prelim II guidelines, all students are encouraged to revise and submit their thesis proposals to
granting agencies for fellowship support (e.g., an NRSA from the NIH). Students who earn a fellowship that provides at
least 75% of the current stipend amount will be awarded a stipend bonus of $2,000 per year in addition to the MTTP sti-
pend, pro-rated to cover the period of extramural fellowship support. If the extramural fellowship provides a stipend higher
than $27,000 (MTTP stipend plus $2000), the student will receive the full level of stipend provided by the fellowship
award.

Stipend checks will automatically deposited into student accounts once a month. Arrangements for direct bank deposit of
funds may be made by contacting the Pharmacology Administrator.

Tuition rates are set annually by the CWRU Board of Trustees. The per credit hour rate for tuition during the academic
year 2011-2012 is $1430.00. Tuition for MTTP graduate students is funded by NIH institutional training grants, individual
fellowships, or university resources.

Neither CWRU nor the MTTP may advise students about their tax liability. Students can obtain information and tax forms
and publications at local libraries and post offices. Additional tax concerns include: Individuals must take the initiative to
identify themselves to their residential community to trigger the Regional Income Tax Authority’s awareness of their exist-
ence

If students are on a training grant, they should look into the tax implications of that income and consider making quarterly
Please contact the MTTP Director or Coordinator for any other financial issues regarding tuition and stipends. In addition, students should contact Cami Thompson once they are placed on a non-taxable grant, so payroll can be adjusted accordingly.

**Medical Insurance**

The University requires that all students have medical insurance. **No exceptions are allowed.** The MTTP pays for the primary major medical plan offered to registered students by the University Health Service.

Students with private insurance must sign and file a waiver of coverage with the University Health Service. **If a waiver is not submitted, or if it is submitted past the assigned deadline for the semester, the student will be billed personally for payment of insurance fees and late charges.**

In addition to basic major medical coverage, registered students are also eligible to use the University Health Service Clinic for routine medical services. **During the summer semester,** if you are covered by the student insurance and **register for 0 credit hour or more,** there will be no fee for health service. If, however, you do not register, and/or are not covered by the student insurance, you will be charged a one-time fee of $50 at your first appointment. If you never need service, you'll never need to pay the fee. If you need service multiple times, the initial $50 fee will cover all visits, etc. For more information, check the Health Services web site at www.cwru.edu/staff/UHS/uhss.html. A proof of insurance card is available at Health Services and is highly recommended.

**Registration**

Pre-registration for the fall semester is held in April, and pre-registration for the spring semester in November. There is no pre-registration session for the summer semester. Students register at the time indicated on the summer “Schedule of Classes.” Students who do not pre-register must do so during the registration period just before the beginning of each semester. The dates for registration are available through the Department of Graduate Studies / Important Dates and Deadlines (http://gradstudies.case.edu/current/calendars/calendar.html).

Consult with the MTTP Graduate Program Director and Administrator. Students will meet initially with the Director and Administrator to discuss academic progress, planned program of study, course selection, and the appropriate number of credit hours to be taken. The MTTP Director and the Program Administrator will supply information each semester prior to the registration period. **Prior to registration Cami Thompson will send out student registration recommendations according to the typical program of study (below). All electives, and any variations from the typical plan of study, need to be approved by Dr. John Mieyal.**

Registration. Since fall semester 2008 new registration tools have been implemented university-wide on a rolling basis. The Student Information System (SIS) has replaced the SOLAR pin registration system.

SIS is accessible at http://www.case.edu/erp/sis. On the log-in page there is a warning to all users that the site is available to authorized personnel only under pain of prosecution. Continuation requires a valid case ID and password. For more detailed instructions on registering please visit the following url and scroll to the bottom part of the page under “Students.” http://www.case.edu/projects/erp/learning/sisguides.html.

- **Important Note:** Students appointed to a training grant, or coming off of one, should let Cami Thompson know in order to continuously maintain stipends, payments of tuition from the appropriate accounts, and medical insurance.

**Planned Program of Study:**

All students must submit electronically a formal Planned Program of Study (PPOS) into the new PeopleSoft Student Information System. The SIS also includes an electronic process for PPOS approval and degree audit. Each Student submits the PPOS electronically through the SIS; then the PPOS must be reviewed and approved by the student’s adviser, and by the School of Graduate Studies. **The Planned Program of study should be entered into the system the first time the student registers for a class as a new student.** An example is provided in the appendix.
**Monitoring student progress.**

Besides regular interaction with the thesis mentor, there are two other major mechanisms in place to monitor student progress in the MTTP. At least every 6 months the student meets with his/her individual Thesis Progress Committee (see below); and the MTTP Steering Committee conducts an annual review of all MTTP students. These committees are applicable for Ph.D. students and for plan A (thesis) M.S. students.

**Thesis Progress Committee Meetings**

Thesis Progress Committees, chaired by a member of the primary Faculty of Pharmacology who can commit to this responsibility for the duration of the student’s studies, are selected by the student and thesis advisor in consultation with the Director of the MTTP. Each Committee includes two primary members of the Faculty of Pharmacology and two other faculty members with expertise complementary to the thesis project. The first meeting of the Thesis Committee is expected to facilitate the student’s preparation for Prelim II (described below); hence it should occur in advance of the deadline for submission of the student’s thesis proposal for Prelim II. Also, the chair of the Thesis Progress Committee should be selected at this first meeting.

After the student completes Prelim II successfully, the Thesis Committee is required to meet at least every 6 months to monitor student progress, to advise on alternative research approaches, and to approve substantial modifications in specific aims of the project. These meetings are a prerequisite for student registration each semester. Meetings can be held more frequently if requested by the student or thesis committee. The MTTP Administrator maintains the 6 month time frames by alerting students and committee members of meeting due dates and arranging the meetings. Students prepare a written summary of the research that has been accomplished during the 6 month period between committee meetings. These summaries should include: 1) specific research objectives for the 6 month period; 2) research accomplished toward these objectives; and 3) research objectives for the next 6 month period. This information should be sent to the entire committee at least one week prior to the thesis committee meeting. Written summaries and evaluations of the meeting are drafted by the student to identify areas for improvement and any revisions in research objectives for the next 6 months that were agreed upon at the committee meeting. The Report is revised as necessary by the thesis committee chair in consultation with the other committee members and the student, and then the finalized report is forwarded to the student, committee members, Program Administrator, and the MTTP Director. The mentor and student are expected to meet after each committee meeting to ensure consensus about how to proceed with the suggestions of the progress committee. As described under Dissertation Defense (below), it is the responsibility of the Thesis Progress Committee to approve the choice of scientific journals that fulfill the publication requirement, and to decide when it is appropriate for a student to schedule the thesis defense.

**Steering Committee and Student Evaluation**

One of the primary responsibilities of the MTTP Steering Committee (comprised of the MTTP Director and the co-Leaders of each of the Advanced Tracks) is to review, evaluate and recognize student performance and progress throughout their time in the Program. Each student is evaluated annually by the full Steering Committee, and at other times during the year as the need arises. It is the responsibility of the faculty mentors to provide evaluations for their students in a timely manner preceding the annual review of students. Confidential reviews and action plans, shared with the student and mentor, are recorded for each student at the time of the annual review and are maintained by the Program Administrator in consultation with the Program Director. Multiple documents form the basis of this annual review, including academic coursework transcripts, planned programs of study, rotation reports, departmental retreat presentation evaluations, prelim exam evaluations, committee meeting evaluations, and evaluations provided by the research mentor. In addition, self-prepared CVs are collected for each student, documenting publications in print, in press, and in preparation, as well as honors and awards; and service to fellow students, the Training program, the Department, the School, or the University. On the basis of these reviews, students may be recognized for their accomplishments in the form of a letter of commendation from the Committee. One model student is chosen each year to receive the Graduate Student of the Year Award, which is presented at the Annual Pharmacology Retreat. Deficiencies in individual student progress are also identified and action plans are agreed upon to help the student overcome the deficiencies. In some cases, after formal consultation between the graduate student, mentor, and the Steering Committee, a student may be placed on academic probation to reflect the seriousness of the lack of progress (coursework and/or research). In most cases, the students are returned to good standing and complete the MTTP requirements for the Ph.D. In other cases, even with frequent intervention by the Thesis Progress Committee and/or the Steering Committee, the student is not able to fulfill the Ph.D. requirements. In these cases, the Steering Committee may recommend to the full primary Faculty of Pharmacology either that the resignation of the student be accepted, or that the student be dismissed from the Program. A majority vote of the primary faculty is required for these actions. In cases where there are difficulties with a student's progress in research or research environment, the Steering Committee meets with both the student and the mentor pri-
Steering Committee Roster (2011-2012)

John Mieyal, Director of the Molecular Therapeutics Training Program (MTTP)
Ruth Keri, co-Director of the MTTP and co-Leader of the Cancer Therapeutics Track
Bill Schiemann, co-Leader of the Cancer Therapeutics Track
Monica Montano, co-Leader of the Molecular Pharmacology and Cell Regulation Track
George Dubyak, co-Leader of the Molecular Pharmacology and Cell Regulation Track
Marvin Nieman, co-Leader of the Translational Therapeutics Track
Robert Bonomo, co-Leader of the Translational Therapeutics Track
Chris Dealwis, co-Leader of the Membrane and Structural Biology and Pharmacology Track
Derek Taylor, co-Leader of the Membrane and Structural Biology and Pharmacology Track

GSO Representatives: Amar Desai and Michael Mullins

Student Records
The MTTP Administrator maintains a file of the progress of each graduate student. A student may request, in writing, an opportunity to review the contents of their educational file. Certain materials are excluded from review as specified in the Family Educational Rights and Privacy Act of 1974 (FERPA).

The FERPA contains several provisions that are important to students. Specific provisions are printed in the University’s General Bulletin. Students may also obtain from the Office of the Provost a copy of the policy, which the University has adopted to meet the requirements of FERPA. As noted above, students are expected to provide periodically updated curricula vitae for review by the MTTP Steering Committee and for publication on their personal websites linked to the Department website.

The MTTP Graduate Student Organization
The graduate students in the Department of Pharmacology participate in a Graduate Student Organization (GSO), which has business meetings on a monthly basis, and intervening social events. The GSO plays an important role in fostering the development of beginning grad students by providing an avenue for them to get informal advice about choosing a lab, receiving tutoring for coursework, preparing for presentations and exams, etc. This organization offers a forum for discussion of issues relating to MTTP students and a mechanism for bringing these issues to the MTTP faculty. The GSO provides suggestions for curricular and programmatic changes, assumes responsibility for choosing, inviting, and hosting a number of invited speakers for the Pharmacological Sciences Seminar Series each year, represents the MTTP on various medical and graduate school student committees, and participates on a volunteer basis in ad hoc committees to revise the curriculum. Students are also invited to participate in the planning and execution of teaching exercises on pharmacological principles for graduate, dental, or medical school courses. To recognize the importance of dialog between the students and faculty on programmatic issues, the MTTP Steering Committee includes the elected President and Vice-President of the GSO; and students serve on the Curriculum Committee and the Prelim I Exam Committee. The GSO plays an important role in uniting the MTTP students as a unique trainee cohort by fostering educational as well as social interactions on a regular basis, and maintaining direct access to the governance of the Program via the Steering Committee.

GSO Officers, 2011-2012
President: Amar Desai
VP and President-Elect: Michael Mullins
Past President: Chris Ryder
Graduate Student Senate representative(s): Michele Mumaw, Debarshi Mustafi
Biomedical Graduate Student Symposium (BGSS) representative: Charlotte Chung
Social Committee: Andrea Boyd-Tressler, Michele Mumaw
Selection Committee – Student-Invited Seminar Speakers: Amar Desai, Chris Ryder
Weekly Frontiers in the Pharmacological Sciences:
- Seminars are arranged according to faculty recommendations and student recommendations. Student invitees are arranged and hosted by the GSO. Students may invite as many seminar speakers as the seminar schedule will allow. The rationale for student-invited speakers is several-fold. The students are engaged directly, the speakers are especially honored by student-initiated invitations, and the student speaker interactions are an important part of the Training Program, expanding the students’ awareness beyond CWRU. Pharmacology Seminar meets every Tuesday at 12 noon in the Webster conference room, W331. For each invited outside speaker a luncheon is arranged with one of three sub-groups of the graduate students on a rotating basis, providing opportunities for the students to interact in an informal setting with investigators from other academic institutions or industrial companies to gain perspective on career advancement options as well as to initiate potential networking contacts.

Weekly Pharmacology Journal Club:
- Students, postdoctoral fellows, faculty, and other research personnel convene to review frontier topics in the pharmacological sciences on a weekly basis. The schedule is organized according to the Advanced Training Tracks of the MTTP. To encourage discussion, all regular attendees are provided a copy of the published article to read in advance. Formal participation in Journal Club is an integral part of the MTTP curriculum (see PHRM 511 on p. 19). Advanced students and postdocs are encouraged to relate their current research findings in the context of their Journal Club presentations. Students are also encouraged to participate in journal clubs sponsored by their thesis laboratory or by other programs especially pertinent to their research interests. Pharmacology Journal Club meets every Thursday at 3 pm in room W331.

Sternlicht Family Memorial Lectureship in Cancer Biology and Pharmacology:
- This annual lectureship was originally established as a mechanism to honor the memory of Robert Sternlicht, late son of Himan and Mona Sternlicht, by helping to promote scientific interactions and dissemination of knowledge in cancer biology and pharmacology. In 2008 Himan Sternlicht, Ph.D. also died of cancer and in 2009 Mona Sternlicht died. Both Him and Mona were long-term members of the Department of Pharmacology, and the lectureship now honors all three members of the family.

Nathan S. Greenfield Family Lecture:
- Through an endowment, Rosalee Greenfield Weiss, Ph.D. and Raymond A. Weiss, Ph.D. established the Nathan S. Greenfield Family Lecture to honor her father and his family. One speaker is invited each year for this event.

Weekly Seminar Series in BSTP Programs and the School of Medicine:
- MTTP students are strongly encouraged to attend seminars especially pertinent to their research interests that occur in the seminar series conducted by the other basic science departments in the School of Medicine. An up-to-date listing of seminars held in the School of Medicine is posted on the bulletin board directly outside of the Department of Pharmacology administrative office, W321.

Frontiers in the Biological Sciences Lecture Series:
- This long-standing lecture series brings at least eight distinguished scientists to the medical school campus each year. The Pharmacology Department hosts one speaker each year.

SURP Seminar Series:
- The Summer Undergraduate Research Program (SURP) is designed to introduce college students to basic laboratory research and scholarly investigation. Attendance is required only for SURP students. The primary aim of the SURP is to show students what research is about through “hands-on” and “minds-on” participation in ongoing research projects within the Department of Pharmacology. This gives students the information they need to con-
sider a research career in basic science in general, and in pharmacology in particular. Informal presenta-
tion/discussion sessions with the undergraduate researchers are led by a faculty member, graduate student(s), or
postdoc(s) on a weekly basis during the summer. The focus of these sessions is on the early phases of commit-
tment to a career in science, both the excitement and the challenges. At the end of the summer the under-
graduate participants present posters on their summer research projects, and this poster session is open
to the entire department.

Other Departmental Events

Annually

SURP Orientation – Undergraduate research students are welcomed during the last week of May and introduced to the
summer program and the scientific community of the Pharmacology Department.

BSTP Graduate Student Orientation – The MTTP Director and/or MTTP Recruitment and Admissions Director, along
with GSO officers, meets with the first year BSTP students before the Fall Semester to provide an overview of the De-
partment and the Program, and to invite students to visit posters representing the research of MTTP trainers and their
students.

Pharmacology Retreat

All members of the Department are invited and expected to attend the Department of Pharmacology Annual Retreat during
the Fall Semester to discuss research and define departmental goals. Inaugurated in 1998, the Departmental Retreat
is held off-campus and typically is scheduled for two days. The purpose of the retreat is fourfold. First, it provides a train-
ing opportunity for students and post-doctoral fellows to hone their presentation skills. Secondly, it fosters collaborative
interactions and unity among all those affiliated with the Department. Thirdly, it has provided a unique opportunity for the
entire Department to participate in workshops on leadership, mentoring, teaching, and other departmental initiatives.
Fourthly, it showcases the Department to potential benefactors. All Pharmacology graduate students and selected post-
doctoral fellows are invited to make either an oral or poster presentation. The oral presentations are 10 minutes in length
and are followed by 5 minutes of questioning. A separate session is set aside for poster presentations. These scientific
presentations simulate the atmosphere of a national/international professional meeting. Although all faculty members att-
end the retreat, the focus of this event is on the work that the students have accomplished. Therefore, as a general rule,
principal investigators do not give presentations. However, each session is overseen by a session chair who is typically a
faculty member. The job of the session chair is to provide a 10 minute synthetic overview to the audience of all talks that
will be presented in that session. In addition, two to three "provocateurs" are assigned to each session (usually a mixture
of faculty and students). These individuals are responsible for assuring that the presenters receive at least a few ques-
tions following their talks, and for guiding discussion as necessary. This opportunity to present to the entire department
(approximately 150 people in attendance) provides an important training experience for the students and post-docs be-
cause it gives them practice in presenting and fielding questions related to their work. They also receive constructive criti-
cisms from the faculty in the form of written evaluations.

Another integral part of the retreat is the Awards Ceremony whose purpose is to recognize and celebrate outstanding per-
formance at many levels within the Department and to encourage all members to strive for excellence. There are awards
for the Graduate Student of the Year (selected by the MTTP Steering Committee) and Postdoc of the Year (nominated
and selected by the Faculty). These awards recognize combined accomplishments in research and scholarship, as well
as service to the greater community of the Department. A research prize is given for the outstanding publication of the
year, and the winner (selected by an established scientist not affiliated with the Department) is honored by the opportu-
nity to present his/her work as the culmination of the scientific program. There is also the option for awards for a research
assistant or faculty member of the year. As a welcoming gesture all postdoctoral fellows who are new to the department
are recognized with a gift. All new graduate students are officially welcomed via a White Lab Coat Ceremony in which the
Chairman and the MTTP Program Director present the students with lab coats and copies of the latest edition of Good-
man and Gilman's The Pharmacological Basis of Therapeutics.

Pharmacology Winter Holiday Celebration – Usually during mid-December each year all members of the Department
and their families are invited to enjoy food, games, and community interaction.

Leave of Absence from Graduate Study

MTTP students undertaking graduate work are expected to pursue their studies according to a systematic plan each year,
registering for credit according to the guidelines for a typical program of study (as delineated below).
Occasionally a student finds it necessary to interrupt his or her studies before completion of the graduate program. Under such circumstances the student must request, in writing, a leave of absence for a period not to exceed one calendar year, explaining the circumstances. This request, which requires endorsement by the student’s advisor, the MTTP Director, and the Department Chairperson, must be approved the Dean of Graduate studies.

During a leave of absence the student must not avail him or herself of aid from faculty members or use of the facilities of the University. A leave of absence does not extend the maximum time permitted for the completion of degree requirements. At the expiration of the leave the student must resume registration unless formally granted an extension (maximum of one more year). A student returning from an official leave must first report to the office of graduate studies admission for clearance to register. A student who fails to obtain a leave of absence, or who fails to register following an official leave, must petition the Dean of Graduate Studies for reinstatement in order to resume work as a student in good standing.

A doctoral student who is granted a maternity or paternity leave of absence related to infant care will receive an extension of the five year time limit from advancement to candidacy to completion of the doctorate. The length of the extension will correspond to the length of the leave.

**Pursuing a Ph.D. Degree in Pharmacology:**

**Modes of Entry: MTTP directly, or via BSTP or MSTP**

Predoctoral students enter the Department of Pharmacology through one of three routes: direct admission to the MTTP (Molecular Therapeutics Training Program), through the BSTP (Biomedical Sciences Training Program), or through the MSTP (Medical Scientist Training Program). While all students must fulfill a set of core courses, the program of study may be modified according to the student’s previous academic achievements (e.g. master’s degree or transfer from another Ph.D. program). MSTP students attain a foundation in physiology and pharmacology from the medical curriculum, so they are exempt from part II of the pharmacology core course (PHRM 402, Physiological Pharmacology).

Direct admit MTTP students enter graduate school knowing they want to pursue a Ph.D. in Pharmacology. These students join the Pharmacology Department and elect the MTTP immediately. During their first semester MTTP students take comprehensive coursework in cell and molecular biology and also do research rotations specifically with trainers who are affiliated with the MTTP (see list of Training Faculty and their research interests, below). **All laboratory rotations need to be approved by the Director of the Graduate Program.** The research rotations afford students an opportunity to experience several different projects, mentors, and lab environments in the Program. Generally, the rotations are 6-10 weeks rotations, and the student must complete a minimum of three rotations, and submit in a timely fashion for his/her written record a rotation report pre-approved by the rotation mentor. **All reports must be submitted in order to receive a grade for the rotations and to be eligible to match with a thesis advisor.** There will be an exit interview after each rotation during which the rotation report will be discussed and the prospect for joining the lab as a Ph.D. trainee will be considered. **A rotation evaluation form must be completed and signed by both the advisor and the student, and sent to the MTTP Administrator, Cami Thompson for inclusion in the student’s file, along with the rotation progress report submitted by the student.** A Ph.D. thesis advisor must be selected by January of the first year.

Like the direct admit MTTP students, BSTP students spend their first semester taking comprehensive coursework in cell and molecular biology and rotating through research laboratories to identify prospective thesis advisors. The BSTP students who are uncertain about their specific graduate program have the option for a wider selection of faculty mentors collectively associated with the BSTP roster of trainers accepting rotation students. The rotations are arranged by the student with the prospective research mentors with the advice of an assigned graduate program director representing one of the areas of interest indicated by the student on his/her application (e.g., some BSTP students who indicated Pharmacology as one of their interests would be advised by the MTTP Director). By the beginning of the Winter Semester of year one BSTP students will chose a mentor and a Ph.D. granting program. Those choosing Pharmacology will transition formally into the MTTP and begin the pharmacology core course requirements of the MTTP.

MSTP students pursue a combined M.D./Ph.D. degree program and spend their first 20 months fulfilling requirements for the M.D. degree. In addition, during this time they are expected to complete at least two of three required research rotations for the Ph.D. Typically MSTP students affiliate with Pharmacology and the MTTP for their Ph.D. studies during the Spring Semester of their second year. The foundations in cell and molecular biology (equivalent to C3MB core courses) and in the physiological basis of therapeutics (equivalent to PHRM 402) are provided by the medical school core academ-
ic program (IBIS). For those MSTP students who know earlier that they want to pursue the Ph.D in Pharmacology, they may take part I of the pharmacology core course (Molecular Basis of Pharmacology, PHRM 401) during their first year.

**Thesis advisor selection** is coordinated through each program (MTTP, BSTP, or MSTP). It has been the policy of the Pharmacology Department to base Training Faculty status and the opportunity to accept a graduate student for Ph.D. training on the demonstrated or potential training skills of the mentor with emphasis on a training environment that provides opportunities for regular interaction with other students and faculty in the Department as well as access to major research facilities. At the time of selection, the advisor is expected to be conducting an active, independently funded research program. All student-advisor matches are approved by the MTTP Director and the Chairman of Pharmacology to ensure a departmental commitment to the student throughout the training period.

**INTRODUCTION TO THE MTTP**

The global objective of the Molecular Therapeutics Training Program (MTTP) is to provide predoctoral students with the necessary knowledge base and research skills to begin independent investigative and teaching careers in the pharmacological sciences. The MTTP provides the uniform didactic and conceptual framework through which predoctoral students obtain the Ph.D. degree in Pharmacology at Case Western Reserve University (CWRU). The program itself is designed with a three-tiered progression. First, a didactic foundation in cell and molecular biology is established along with three meaningful research rotations to facilitate mentor selection. Secondly a foundation in molecular and physiological pharmacology is achieved via an intensive two-part core course. Thirdly, students acquire advanced understanding in their area of specialization via advanced courses and thesis research. To facilitate this advanced stage, the training faculty and advanced courses are organized according to four tracks, namely *Molecular Pharmacology & Cell Regulation, Membrane Structural Biology & Pharmacology, Cancer Therapeutics, and Translational Therapeutics.* This multifaceted approach provides students with a strong foundation in fundamental pharmacology and the associated sciences, coupled with individualized advanced training in modern pharmacology. The interdisciplinary design of the program fosters productive interactions among students and faculty in basic and clinical departments throughout the School of Medicine around the common theme of therapeutics. *The priority outcome of the program is to develop students with the scientific maturity to address new research questions through hypothesis-driven experimental designs.* In view of the rapid advances in biotechnology and genomics, there is an expanding need in the academic and private sectors for well-trained, highly qualified scientists with core training in the principles of pharmacology. This increased demand is widespread, including educators, researchers, and industry leaders that have the appropriate pharmacological expertise. Thus, the long-term goal of this program is to increase the supply of pharmacology-based skilled scientists and educators by providing a rigorous training program that yields Ph.D. graduates who will pursue more advanced postdoctoral training on their way to productive independent careers in academia or research-based industry.

**Overview of MTTP Design**

The Molecular Therapeutics Training Program is developed in three progressive phases (Figure 1). **Stage 1:** At the outset, all students are enrolled in the Core Curriculum in Cell and Molecular Biology (C3MB) [or the equivalent in the medical curriculum for M.D./Ph.D. students] to provide a common foundation in the principles and practice of cell and molecular biology and biochemistry, including protein chemistry and enzymology. Concurrently the students explore at least three different mentoring opportunities and laboratory environments (research rotations) to gain research experience and select a thesis laboratory. **Stage 2:** Students focus on research and study pertinent to evolving their thesis project, and they immerse themselves in an intensive two-part core course in pharmacology, emphasizing the physiological and molecular bases for understanding the actions of drugs, and then placing the study of particular drug classes in the context of the targeted diseases. Upon selection of a thesis lab, each student is assigned to a particular advanced track according to the interests of the student and the mentor and the anticipated nature of the thesis project. An elective course pertinent to the advanced track is selected each semester to be completed along with one of the components of the Pharmacology Core Course (see Fig. 3, below). Stage 2 culminates in a comprehensive written exam (**Prelim I**) that assesses each student’s ability to demonstrate understanding of the core principles of their coursework by responding to questions that challenge them to apply key concepts in new contexts, including situations derived from assigned literature articles. Success in Stage 2 results in advancement to Ph.D. candidacy. **Stage 3:** Students are now focused on developing their specific thesis project. During the initial period of stage 3, students participate in a Grant Writing workshop and incorporate their pilot data into a specific research plan written in the style of an individual NRSA proposal which they defend orally (**Prelim II**) (see Prelim Exam I & II descriptions, below). The benchmarks of success in Stage 3 are research accomplishments and knowledge sufficient to foster at least two first author original research publications and an erudite thesis presentation and defense. Success in Stage 3 results in award of the Ph.D. degree.
Each of the Advanced Training Tracks is well-represented by interactive, collaborative trainers in Pharmacology and other basic and clinical departments throughout the Medical School. The trainers in each track are proposed by the co-leaders of the track and confirmed by the entire Steering Committee which includes the leaders of the Tracks (see Administration, Fig. 2, below). According to research focus, expertise, and collaborative interactions each trainer may be included in one or two of the Advanced Training Tracks. Besides the opportunity to serve as primary thesis advisor for students within the Track, each trainer has the responsibility of serving on Prelim II Exam and Thesis Progress committees, as well as teaching in advanced courses and participating in journal clubs associated with the respective tracks. Besides scientific interactions, students and faculty of each track share in social functions at the Track, Program, and Department levels, adding to the cohesiveness and camaraderie of the training environment.

Overview of the administrative structure - The basic components of the Training Program Administration include the Program Director, co-Director, and Administrative Assistant; the Steering Committee, and the Recruitment and Admissions Committee, all of whom coordinate interactions with the training faculty and the students (Figure 2). Notably, the Program Director and co-Director are the Vice-Chair and Chair of Pharmacology, respectively; and the Vice-Chair heads the Steering Committee. Thus, policies set by the Steering Committee are ensured of coherency with those of the Department of Pharmacology. In addition inclusion of the President and Vice-President of the Graduate Student Organization (GSO) provides first-hand input by and communication with the students.
Graduation Requirements for a Ph.D.

Overview
The degree of Doctor of Philosophy is awarded in recognition of in-depth knowledge in a major field and comprehensive understanding of related subjects. The Ph.D. recipient must also demonstrate an ability to perform independent investigation and to communicate the results of such investigation in an acceptable dissertation and scientific publications.

Typical Training Program
The objective of the MTTP is to provide students with outstanding training in the cellular, molecular, and physiological basis for therapeutics both in the classroom and in the laboratory, with the ultimate goal of preparing them for independent careers in research and teaching. To accomplish this goal, we have devised an intensive, multi-faceted training experience composed of:

- Laboratory research rotations
- Core coursework in fundamentals of modern pharmacology, including laboratory experience with animal models
- Advanced electives to build on the fundamentals and to focus on specific interests
- Continuous training in the critical evaluation of the scientific literature
- Continuous training in effective presentation of scientific data, both oral and written
- Independent thesis research documented by peer reviewed publications
- Workshop on grant writing
- Short course on biostatistical analysis

Overview of the Curriculum. A typical curriculum for the MTTP student (entering directly or via the Biological Sciences Training Program (BSTP)) is illustrated in Figure 3. Predoctoral students in the program are expected to complete all formal course requirements, except Prelim II, by the end of their second year. The first two years also include research experiences in the form of three laboratory rotations (one 6-8 week full time rotation in summer preceding year 1, and two 6-10 week rotations part time during fall year 1); and other essential training experiences such as seminars on responsible conduct of research (IBMS 500). The goal of the initial 2-year period is to provide a strong knowledge base in the fundamentals of cell and molecular biology, and the physiological and molecular bases of pharmacology, as well as enriched knowledge in electives courses.

The immersion in the rigorous, seminar-style two-part core course in Pharmacology during the spring semester of year one and the fall semester of year two provides a broad based foundation in the principles of pharmacology which is complemented by concurrent elective courses in the chosen area of specialization. The Pharmacology core courses and the elective courses have a common focus on challenging students to develop the scientific insight that is required to meet the demands of independent research. Upon satisfactory performance in the coursework and seminar presentations, all students are eligible to advance to Ph.D. candidacy at the middle of their second year by successfully completing the comprehensive qualifying exam (Prelim I, see below). Remaining formal coursework is completed in spring of year 2, except for Prelim II. Thus, by the beginning of their third year, most students devote essentially 100% of their efforts towards dissertation research. The thesis proposal (Prelim Exam II) is preceded by a special workshop on grant writing and a meeting of each student with their Prelim II/Thesis Committee. Completion of Prelim II should occur no later than September 30 of Year 3. An important goal is for students to complete the Training Program in about 5 years. Specific courses and other training activities for the program are described below, including a special short course on biostatistics.
Planning the Study Program

Graduate study assumes maturity on the part of the student in planning and reaching educational objectives. The students will work closely with the Graduate Program Director Dr. John Mieyal and the Graduate Program Administrator Cami Thompson to aid in the planning and attainment of curricular goals. However, the effectiveness of the overall graduate program also lies with the individual student, the faculty advisor, and the thesis advisory committee to guide the student through the research and dissertation portions of the program. University regulations are intended to maintain uniform minimum standards of performance, to form a basis for planning programs of graduate study, and to provide efficient management and coordination of graduate programs.

The planned program of study (PPOS) is submitted to the graduate school by entering it into the SIS System. Each student needs to submit a PPOS, preferably as they register for their first class. To fill out a program of study, go to “Plan” under the Academics Tab on the SIS Homepage and fill in each required class for each semester.

Coursework and Hour Requirements:

Students entering with a bachelor’s degree must complete a minimum of 36 credit hours of coursework (which may include independent study/research course 601), and seminars. 24 of the 36 credit hours must be graded courses (see Fig. 3, above). A minimum cumulative quality-point average of 3.00 in all courses taken for credit as a graduate student at CWRU (excluding those with the grade “S” or “P”) is required for award of the doctoral degree. Besides the overall GPA of 3.0, Pharmacology students must obtain a grade of B or better in all required courses.

In addition, all students must take a minimum of 18 credit hours of dissertation research (Course 701). The doctoral residency requirement is intended to insure a period of intensive academic interaction with faculty and peers, and sustained independent research. Formal fulfillment of residency requires continuous registration in at least six consecutive academic terms (fall, spring and/or summer) from matriculation to a period not exceeding five years after the first credited hour(s) of dissertation research (701). For students entering with an approved master's degree, completion of 18 total credit hours of new coursework is required (12 credits hours must be graded courses); and 18 credit hours of PHRM 701.

Core course requirements for the Ph.D. in Pharmacology.

The first summer and fall consists of research rotations, the C3MB courses, and independent study (9 credit hours). Year 1 spring includes the molecular therapeutics core course, the responsible conduct of research course, and elective course, seminars and independent study (9 credit hours). In fall of year 2 the physiological therapeutics core course, an elective course, the course in seminar presentation, and independent research are completed (9 credit hours). Coursework is completed in spring year 2 along with Prelim I and admission to candidacy, permitting registration for dissertation research (9 credit hours). Two additional graded credits are assigned to the completion of Prelim II (PHRM 525) by Sept. 30 of year 3. These requirements are presented in the Table below.

<table>
<thead>
<tr>
<th>Course</th>
<th>Credits</th>
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</thead>
<tbody>
<tr>
<td>1) Three Rotations (PHRM 400)</td>
<td>0</td>
</tr>
<tr>
<td>2) C3MB (CBIO 453)</td>
<td>4</td>
</tr>
<tr>
<td>3) C3MB (CBIO 455)</td>
<td>4</td>
</tr>
<tr>
<td>4) IBMS 500: Becoming a Professional Scientist– Responsible Conduct of Research</td>
<td>0</td>
</tr>
<tr>
<td>5) Principles of Pharmacology I: Molecular Basis of Therapeutics (PHRM 401)</td>
<td>3</td>
</tr>
<tr>
<td>6) Principles of Pharmacology II: Physiological Basis of Therapeutics (PHRM 402)</td>
<td>3</td>
</tr>
<tr>
<td>7) Frontiers in Pharmacology, J Club Series (PHRM511)</td>
<td>2</td>
</tr>
<tr>
<td>8) Two advanced electives (from the Advanced Track offerings)</td>
<td>6</td>
</tr>
<tr>
<td>9) Prelim I Comprehensive Examination</td>
<td>0</td>
</tr>
<tr>
<td>10) Independent Research and Study (PHRM 601)</td>
<td>12</td>
</tr>
<tr>
<td>11) Formal Short Course on Biostatistics</td>
<td></td>
</tr>
<tr>
<td>12) Prelim II Dissertation Proposal, including grant-writing workshop (PHRM525)</td>
<td>2</td>
</tr>
</tbody>
</table>

Descriptions of core courses.

Each MTTP or BSTP student spends the first summer doing a research rotation in a particular lab; the direct-admit MTTP students chose among the Training Faculty of the MTTP, while the BSTP students choose among the broader faculty constituency of the BSTP. Generally the start date is July 4th with some flexibility for the incoming student’s schedule. The fall semester is spent taking comprehensive coursework in cell and molecular biology and rotating through second
and third research labs. Before the beginning of the second semester, MTTP and BSTP students choose a Ph.D. mentor, and BSTP students identify a specific Ph.D. program. Each year, several BSTP students choose Pharmacology as their degree-granting program, and then they continue in step with those directly admitted to Pharmacology to fulfill the requirements of the MTTP.

Research Rotations (PHRM 400). The main purpose of research rotations is to allow each student to select a laboratory and mentor for thesis studies. A second objective is to introduce students to a broad scope of research problems and approaches. The rotations are 6-8 weeks (full time summer) or 6-10 weeks (part time academic year), and they are arranged by the students after consulting with a program faculty advisor and available faculty mentors. The Director of the MTTP advises first year students and coordinates rotation experiences. Students are expected to spend at least 20 hours per week in the lab during the academic year. A minimum of three different rotations must be completed by the end of the fall semester of year 1, but additional rotations are permitted if needed. In addition to carrying out a research project, the rotating student participates in research meetings, journal clubs, and departmental seminars. This immersion allows the student to evaluate the research environment of the lab and to choose a thesis advisor that best matches his/her interests. Students are required to submit a progress report before the end of each rotation, presenting the data generated and describing the goals and accomplishments of the project and the proximate future directions. Each rotation mentor evaluates the student’s report and suggests revisions as necessary. The mentor also completes a written summary of the strengths and weaknesses of the rotation and discusses this evaluation with the student, including an indication whether the student will have the opportunity to pursue Ph.D. thesis studies with that mentor. The student’s rotation report and the mentor’s evaluation are submitted to the Director of the BSTP or MTTP, and to the MTTP Administrator as part of the student’s permanent record.

C3MB Courses (CBIO 453/455). All students take the Coordinated Curriculum in Cell and Molecular Biology (C3MB). This fall semester, first-year course consists of two primary components, Cell Biology (CBIO453) and Molecular Biology (CBIO455). Each class meets for 10 hours per week, typically scheduled Monday through Friday from 9-11 am. The objective of these courses is to provide all students with a strong foundation in basic biomedical sciences with a particular emphasis on biochemistry, cell biology, molecular biology, and genetics. The faculty who teach this course represent most of the Departments in the School of Medicine, however Pharmacology Faculty contribute a disproportionate share, almost 20% of total contact hours. General topics include protein chemistry, cell structure, molecular biology of prokaryotes, molecular genetics, molecular biology of eukaryotes, neurobiology, bioenergetics, and intracellular organelles of eukaryotes.

Description of Pharmacology Courses:

The Pharmacology courses are designed to give students a deeper understanding of the principles of pharmacology in several contexts, ranging from the fundamentals of chemistry and biochemistry to the biodisposition and actions of drugs in humans.

Principles of Pharmacology I: The Molecular Basis of Therapeutics (PHRM 401). This core course focuses on the chemical and biochemical properties of therapeutic agents and molecular mechanisms of therapeutic action, including kinetic and thermodynamic principles of enzyme catalysis and drug-receptor interactions. Moreover, emphasis is placed on fundamental principles of pharmacokinetics, including the absorption, distribution, metabolism, and excretion of drugs. Mathematical concepts needed to understand appropriate administration of drugs and maintaining therapeutic concentrations of drugs in the body are discussed. A second broad area of emphasis is on fundamental principles of pharmacodynamics, including drug-receptor theory, log dose-response relationships, therapeutic index, receptor turnover, and signal transduction mechanisms. The primary learning objective is to develop a self-directed, critical approach to the evaluation and design of experimental research in the broad context of receptor interactions with endogenous ligands and therapeutic agents in the context of disease models. This is a team-coordinated course involving sessions organized by faculty to facilitate student-directed learning experiences including discussion of study questions, problem solving applications, and primary literature presentations. A two-part laboratory exercise introduces experimental methodologies widely applied during the study of molecular interactions between therapeutic agents and receptor targets to reinforce fundamental principles of drug action. This 3-credit hour course meets 3 hr per week during the spring semester of year 1. Course Director: Johannes von Lintig, Ph.D.

Principles of Pharmacology II: The Physiological Basis of Therapeutics (PHRM 402). This course focuses on human physiology of organ systems including the central nervous system, cardiovascular system, and those systems (gastrointestinal, hepatic, and renal) that are involved in determining the pharmacokinetics or time course of drug action in vivo. A second major emphasis is placed on disease-based sessions where normal physiology, pathophysiology, and key drug classes to treat pathophysiologies are discussed. The students learn key concepts in endocrine pathologies, inflammatory disorders, pulmonary diseases, infectious diseases, and cancer. The main learning
Frontiers in Pharmacology - Student Journal Club Series (PHRM 511)

This course is designed to provide students with practical experience in delivering effective oral scientific presentations, and expanding their knowledge base. These objectives are accomplished by requiring students to present primary research articles to the full assembly of the Department of Pharmacology, specifically on topics outside of their research focus. In this way students learn to make effective Powerpoint slides, to organize a concise and coherent scientific presentation, to broaden their knowledge base, and to present the information in an understandable, insightful and engaging manner to a general scientific audience. The primary focus of the course is on developing effective presentation skills. However, important emphasis is placed on learning new areas, systems, and methodologies; and critically analyzing published scientific data related to modern pharmacological research. Students also obtain practical experience in the peer-review process by providing insightful critical analyses of all presentations by other students, and by receiving peer feedback on their own talks. Before each student presentation forms for the critiques are provided which list the key elements of an effective presentation with spaces for comments. In addition to student feedback, student presentations are evaluated by a panel of four faculty members that assigns a score for each performance. Students are also evaluated on their participation in the question/answer portion of each presentation, on their thoughtful critique of the presentation, and on written critical evaluations of two of the presented articles. Evidence for the successful impact of this course is the fact that a disproportionately higher number of MTTP students are awarded presentation prizes at the annual Graduate Student Symposium of the School of Medicine, and several students each year win presentation awards in other contexts as well, including national meetings.

Bioethics - On Being a Professional Scientist (IBMS 500) Semester two (spring) of year 1 is concluded with a focus on responsible conduct of research. All trainees are required to participate in the course entitled “Being a Professional Scientist: Ethics and Biomedical Research,” offered annually at the CWRU School of Medicine. This course is directed currently by Nicole Deming, J.D., M.A., Assistant Professor of Bioethics. The course was revised recently so that it meets each week for 3 hr throughout the semester. Each session is initiated by a lecture/case presentation to the entire class, and then the class is subdivided into discussion groups led by the training faculty affiliated with the various Ph.D. programs throughout the School. The goal of this course is to provide graduate students with a foundation in bioethics and an opportunity to think through their professional ethical commitments.

Responsible Conduct of Research seminars – It is important that the foundation in bioethics that is provided to all students during year 1 (IBMS 500) be reinforced throughout their years of training in research. Accordingly, as an integral component of the weekly Frontiers in Pharmacology Journal Club, two sessions per year are devoted to issues of responsible conduct of research. Each of these sessions is focused on one or more cases where ambiguities in research conduct have been documented. All faculty, staff and students are invited to these sessions; however students in training are required to sign in. All graduate students are required to document participation in at least six of these sessions during their matriculation in the MTTP. The focal cases are distributed at the beginning of the session, and the participants are divided into groups of 6-10 individuals, with at least one primary member of the Faculty of Pharmacology and one other Faculty Trainer participating in each small group discussion. Text: F.L. Macrina, Scientific Integrity 3rd Edition, Text and Cases in Responsible Conduct of Research, ASM Press, 2005.

Advanced Training Tracks, Associated Courses

As mentioned previously, the Tracks have been designed to offer students the ability to form a cohesive group with their peers and to specialize in a specific area of expertise. There are four tracks, Molecular Pharmacology and Cell Regulation, Membrane & Structural Biology and Pharmacology, Cancer Therapeutics, and Translational Therapeutics. The faculty members associated with each of the advanced tracks are shown in Figure 4. Below is the listing of the advanced graduate students in each of the tracks, along with their Ph.D. mentors.
The main objective of the advanced training track in Molecular Pharmacology and Cellular Regulation (MPCR) is to promote scientific and training interactions among faculty and students who share common research interests in the broad area of molecular pharmacology and signaling. The thematic focus is on molecular mechanisms involved in the therapeutic actions of drugs and on identification of cellular regulatory processes that may serve as rational targets for drug development. Presentations of the MPCR students at the annual departmental retreat, as well as ongoing collaborations among MPCR faculty reflect the diversity of cellular targets that are being studied and corresponding regulatory agents with therapeutic potential. Besides the opportunity to serve as thesis mentors, training faculty in this track serve on the Prelim II Exam / Thesis Progress Committees for MPCR students specializing in the pharmacology of cell regulation. Also, in partnership with the students, the training faculty identify topical seminars and journal clubs for MPCR students that supplement the regular Pharmacology events. As noted, the MPCR Faculty are highly interactive, many with productive on-going collaborations. For example, Drs. Keri and Montano have reported on the Role of FOXA1 in mammary gland development; Drs. Manor and Danielpour have studied sensitization of prostate cancer cells to vitamin E by tocopherol transfer protein; Drs. Manor and Kelley have described perturbations of vitamin E status in Niemann-Pick type C disease; Drs. Montano and Berdis have investigated the role of a novel bifunctional exonuclease in the response to breast cancer therapeutics; Drs. von Lintig and Noy have identified a diet-responsive regulatory network that controls beta-carotene absorption and vitamin A production; Drs. MacDonald and Keri have characterized analogs of activated vitamin D3 as potential chemopreventive or chemotherapeutic agents for breast cancer; and Drs. Dubyak and Distelhorst have co-authored a number of manuscripts in the area of calcium-regulated cell signaling and gene expression. Graduate students in this track focus on advanced elective courses that emphasize objectives of the Track and research interests of the associated laboratories. Examples are listed below.

**Advanced Track in Molecular Pharmacology and Cellular Regulation**

<table>
<thead>
<tr>
<th>Cancer Therapeutics Track</th>
<th>Membrane &amp; Structural Biology and Pharmacology Track</th>
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</thead>
<tbody>
<tr>
<td>Student</td>
<td>Ph.D. Mentor</td>
</tr>
<tr>
<td>Chris Ryder</td>
<td>Clark Distelhorst</td>
</tr>
<tr>
<td>Molly Taylor</td>
<td>Bill Schiemann</td>
</tr>
<tr>
<td>Yan Yan</td>
<td>Stanton Gerson</td>
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<td></td>
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<tr>
<td>Molecular Pharmacology &amp; Cell Regulation Track</td>
<td></td>
</tr>
<tr>
<td>Darwin Babino</td>
<td>Johannes von Lintig</td>
</tr>
<tr>
<td>Andrea Boyd-Tressler</td>
<td>George Dubyak</td>
</tr>
<tr>
<td>Luke Bury</td>
<td>Shasta Sabo</td>
</tr>
<tr>
<td>Casey Charvet</td>
<td>Inna Pikuleva</td>
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</tbody>
</table>

**Membrane & Structural Biology and Pharmacology Track**

<table>
<thead>
<tr>
<th>Student</th>
<th>Ph.D. Mentor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Debarshi Mustafi</td>
<td>Kris Palczewski</td>
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**Translational Therapeutics Track**

<table>
<thead>
<tr>
<th>Student</th>
<th>Ph.D. Mentor</th>
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</thead>
<tbody>
<tr>
<td>Charlotte Chung,</td>
<td>Alan Levine</td>
</tr>
<tr>
<td>Meghana Gupta</td>
<td>Danny Manor</td>
</tr>
<tr>
<td>Wannarasmi (&quot;Nui&quot;) Ketchart</td>
<td>Monica Montano</td>
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<tr>
<td>Sharon Rymut</td>
<td>Tom Kelley</td>
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<tr>
<td>Amanda Vreeland</td>
<td>Noa Noy</td>
</tr>
<tr>
<td>I-Ju Yeh</td>
<td>Monica Montano</td>
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• **Cell Signaling (PHOL/CLBY 466, 3 credits).** This is an advanced lecture/journal/discussion format course that covers cell signaling mechanisms. Includes are discussions of neurotransmitter-gated ion channels, growth factor receptor kinases, cytokine receptors, G protein-coupled receptors, steroid receptors, heterotrimeric G proteins, ras family GTPases, second messenger cascades, protein kinase cascades, second messenger regulation of transcription factors, microtubule-based motility, actin/myosin-based motility, signals for regulation of cell cycle, signals for regulation of apoptosis. *Course Director, George Dubyak.*

• **Cytokines: Function, Structure, and Signaling (PATH/CLBY 417, 3 credits).** Regulation of immune responses and differentiation of leukocytes is modulated by proteins (cytokines) secreted and/or expressed by both immune and non-immune cells. Course examines the function, expression, gene organization, structure, receptors, and intracellular signaling of cytokines. Topic include regulatory and inflammatory cytokines, colony stimulating factors, chemokines, cytokine and cytokine receptor gene families, intracellular signaling through STAT proteins and tyrosine phosphorylation, clinical potential, and genetic defects. Lecture format using texts, scientific reviews and research articles. *Course Director, Alan Levine.*

• **Nuclear Receptors in health and Disease (PHRM 315/415; BIOC 415, 3 credits).** This course focuses on hormone-gene interactions mediated by the ligand-inducible transcription factors termed nuclear hormone receptors. The class will address the mechanisms of action, regulatory features, and biological activities of several nuclear receptors. The usage of nuclear receptors as therapeutic targets in disease states such as cancer, inflammation, and diabetes will also be discussed. The course aims to teach students to critically evaluate primary literature relevant to nuclear hormone receptors biology, and to reinforce presentation/discussion skills. Grades for Undergraduates will be based on midterm, final exam; grades for Graduates will be based on midterm, final exam, and presentation of a recently published research article related to the role of nuclear receptors in health and disease. *Course Directors, Monica Montano & Noa Noy.*

• **Phosphorylation and Cell Regulation (MBIO 522, 3 credits).** This intensive seminar course will emphasize signaling pathways mediated by protein phosphorylation/dephosphorylation. Bacterial signaling mediated by histidine/aspartate phosphorylation and regulation of cellular physiological events will be reviewed. Then eucaryotic cell signaling will be reviewed from the surface of the cell and into the nucleus. This includes receptor-dependent phosphorylation/dephosphorylation reactions, cytoplasmic signaling intermediates, protein translation processes dependent upon phosphorylation, and nuclear regulatory events with emphasis on transcriptional mechanisms. In addition to faculty lectures, students will be reviewing the current literature and will present a research proposal based on the current concepts in the field that they choose to cover. *Course Director, Jonathan Karn.*

**Advanced Track in Cancer Therapeutics** – Many of the Training Faculty for the MTTP are members of the Case Comprehensive Cancer Center, which is one of 40 NCI designated Comprehensive Cancer Centers. The Cancer Center is comprised of faculty from Case Western Reserve University, University Hospitals of Cleveland, The Cleveland Clinic Foundation, MetroHealth Medical Center and the Cleveland Veterans Affairs Medical Center. Dr. Keri is the Associate Director for Basic Research within the Center. To build on this considerable strength in cancer biology and cancer therapeutics, the Cancer Center has recently developed a cancer biology Ph.D. training program. This program serves as a hub for cancer biology training that occurs in two departments: Pharmacology and Pathology. Selection of a specific training track is dependent upon the students’ interests in either the fundamental basis of cancer therapeutics (Pharmacology) or mechanisms underlying the pathogenesis of cancer (Pathology). Following completion of the Pharmacology Core Course in Molecular Therapeutics, trainees in the Cancer Therapeutics Track are required to take two advanced courses, at least one of which must be one of the specialized courses on cancer biology:

• **Cancer Biology and Therapeutics (PHRM 520, 3 credits).** Basic concepts of cancer biology and the various therapeutic strategies used to treat this disease. This cancer biology course is intended to give students a broad and basic overview of Cancer Biology and Clinical Oncology. The course will cover not only fundamental principles of cancer biology, but also it highlights advances in the pathobiology and therapeutics of cancer. Classes are lecture and discussion format, with emphasis on critical reading of original journal articles. The specific topics presented will include carcinogenesis, oncogenes, tumor suppressor genes, genetic epidemiology, DNA repair, growth factor action/signal transduction, apoptosis, cell cycle control, cell adhesion, angiogenesis, tumor cell heterogeneity, metastasis, chemotherapy, photodynamic therapy, gene therapy, signal transduction inhibitor therapy, chemoprevention, and clinical oncology of the breast, prostate, lymphatic tissue, colon and other related malignancies. Course grades will be from participation/discussion, presentation and mid-term/final exams. Additional training in therapeutics occurs through a 1 credit hour enrichment course that involves Cancer Center seminars and written critical evaluation of primary literature. *Course Director, David Danielpour.*

• **Molecular Genetics of Cancer (PHRM / BIOC 420, 3 credits).** The molecular basis of cancer is covered in lectures and discussion of scientific literature. The principal topics are cellular and viral oncogenes and tumor suppressors, including their identification, function, and roles in cellular transformation and malignant progression in
Membrane and Structural Biology, a state-of-the-art facility housing world-class instrumentation designed to probe protein provide atomic detail required for the rational design of drugs. MTTP trainers are members of the Cleveland Center for delineation of molecular mechanisms of disease. Not only do the structures elicit insight into basic protein function, they question, the availability of structural information has an enormous impact on fundamental research in biology and in de-

A central theme of this advanced training track lies in determining how membrane proteins act and how various mechanisms of oncogenesis related to the products of cellular proto-oncogenes or tumor suppressor genes. In the course of these examinations we will explore the genetic and molecular genetic approaches used to identify and study oncogenes and tumor suppressor genes. Students should be prepared to present and discuss experimental design, data and conclusions from assigned publications. There will be no exams or papers but the course will end with a full-day, student-run symposium on topics to be decided jointly by students and instructors. Grades will be based on class participation and symposium presentation. Course Director, Yu-chung Yang

In both of these courses students are required to critically read and review modern literature in the field of cancer biology and therapy and develop the skills necessary to evaluate and present current findings.

Advanced Track in Membrane and Structural Biology and Pharmacology (MSBP)- A core group of MTTP training faculty have primary interests in molecular aspects of protein structure and function. Without question, the availability of structural information has an enormous impact on fundamental research in biology and in delineation of molecular mechanisms of disease. Not only do the structures elicit insight into basic protein function, they provide atomic detail required for the rational design of drugs. MTTP trainers are members of the Cleveland Center for Membrane and Structural Biology, a state-of-the-art facility housing world-class instrumentation designed to probe protein and complex structure and function: http://ccmsb.case.edu

Membrane proteins and their complexes are critical in signal transduction and transport processes, and their functions influence all aspects of cellular regulation. Abnormalities in function, whether due to genetic mutation or abnormal regulation, elicit numerous disease states. Of special importance to the unifying theme of the MTTP, membrane proteins are the target of a very large number of drugs and are responsible in large part for drug uptake, distribution, metabolism and elimination. A central theme of this advanced training track lies in determining how membrane proteins act and how various drugs can modify those actions.

Following completion of the two-part core course in the Physiological and Molecular Bases of Therapeutics, students continuing in the Membrane and Structural Biology and Pharmacology Track will receive specialized training in membrane biology and protein structure and function. Training is conducted through a combination of specialized course work and laboratory research focused on determining the structure and/or delineating the function of individual proteins or macromolecular complexes. Specialized courses include bi-weekly journal clubs devoted to structural biology, as well as electives chosen from a variety of opportunities related to protein structure, mechanism, and regulation. According to the overall MTTP design, each student is required to complete two advanced courses. Possible advanced courses in this track include:

- **Membrane Transport Processes** (PHRM 412, 3 credits). The classification and structure of membrane transport proteins and channels. Examination of the common mechanistic features of all systems and the specific features of different classes of transporter. The goals are to understand the role of transport processes in cell homeostasis and to consider transporters and channels as drug targets. Course Co-Directors, Michael Maguire & Vera Moiseenkova-Bell.

- **Protein Biophysics** (PHRM 475, 3 credits). An in-depth understanding of the molecular biophysics of proteins. Structural, thermodynamic and kinetic aspects of protein function and structure-function relationships are considered at the advanced conceptual level. Course Director, Matthias Buck
Advanced Track in Translational Therapeutics - The Translational Therapeutics Track (TTT) is designed to train students to utilize molecular and cellular approaches to addressing problems related to the interindividual differences in drug responsiveness, including variations in drug effectiveness and toxicity. The goal is to interface and ultimately integrate basic science trainees with physician-scientists and clinicians who share an interest in developing and/or employing therapeutic agents in a rational and individualized manner. The proposed integration is designed to promote both the study and understanding of disease and drug action within the context of disease at the molecular, biochemical, genetic, cellular, tissue and organismal levels. Such stages of sophistication allows for optimal research opportunities and cross-fertilization between basic scientists and clinical investigators. As such, the faculty of the TTT has been chosen to represent two different but complimentary views of molecular medicine. One embraces the “bench-to-bedroom” orientation while the other represents the “bedside-to-bench” approach.

Students enrolled in the TTT formulate a forward-looking vision of pharmacological research as it will be developed and applied over the next several decades. This track endeavors to foster research spanning from “proof-of-concept” approaches to therapeutic principles in model systems through the completion of formal Phase 1 and 2 trials in humans. In conjunction, students are expected to master basic core tenets and principles of pharmacology as well as the application of newer technologies upon the strong background of traditional thought. Throughout this process both faculty and peers mentor students. The goal is a careful blending of the principles of drug action with the language of molecular biology to yield expertise in the personalized therapeutics that will be the hallmark of medical practice for the next several decades. The advanced curriculum of the TTT is designed to stimulate students to use multiple and innovative approaches to solve biologically-based therapeutic problems in a pathophysiological setting. In this context the overall goal is to provide students with a critical approach to performing excellent scientific research, based on their foundation in the core courses (described above for all MTTP students), coupled to specialized advanced courses and continuous education opportunities (described below). Following completion of the Pharmacology core courses, TTT trainees are required to take two advanced courses, at least one of which must be one of the specialized courses on translational pharmacology:

- **Contemporary Approaches to Drug Discovery (PHRM 528, 3 credits):** This course is designed to teach the students how lead compounds are discovered, optimized, and processed through clinical trials for FDA approval. Topics will include: medicinal chemistry, parallel synthesis, drug delivery and devices, drug administration and pharmacokinetics, and clinical trials. A special emphasis will be placed on describing how structural biology is used for in silico screening and lead optimization. This component will include hands-on experience in using sophisticated drug discovery software to conduct in silico screening and the development of drug libraries. Each student will conduct a course project involving in silico screening and lead optimization against known drug targets, followed by the drafting of an inventory disclosure. Another important aspect of this course will be inclusion of guest lectures by industrial leaders who describe examples of success stories of drug development. 
  
**Course Director, Chris Dealwis.**

- **Pathways to Research in Translational Therapeutics (PHRM 527, 3 credits):** Students will spend time in the clinical or community setting that most directly relates to their area of research interest. Based on this “bedside” experience and in collaboration with basic science and clinical mentors, students will identify a significant therapeutic challenge in the treatment of the related patient population and will write a review based on the available literature in this field. The course will culminate with presentation of this review at a symposium for the Translational Therapeutics Track of the MTTP. Students with outstanding review articles will be encouraged to submit them for publication. The goals of this course include 1) to provide the research student with an opportunity to in-
teract with health care professionals and with patients, 2) to enhance graduate student understanding of the challenges that patients face in dealing with imperfect therapeutic options, 3) to immerse students in an area of literature that is relevant to their research interests and will potentially inform the way they think about improving therapeutic strategies, 4) to disseminate their semester-long experience to their graduate student peers through public defense of their review article, 5) to produce a scholarly manuscript on a problem in therapy that conceptually takes the therapeutic challenge from bedside to the bench and back again. Course Directors, Amy Wilson-Delfosse and John Mieyal.

Other recommended advanced courses include:

- **Mechanisms of Drug Resistance** (PHARM / MBIO 434, 3 credits). Molecular, cellular and physiological mechanisms of resistance to antibiotics, anti-viral agents, and cancer therapeutic agents. Resistance to drugs is an important health concern in the new millennium. Over the past century, modern medicine has developed and prescribed drugs for various ailments and diseases with known therapeutic benefit. Since the discovery of antibiotics by Dr. Fleming, we have struggled with a new complication in infectious diseases, development of drug resistance. This course will focus on and compare the drug resistant mechanisms selected by viruses, bacteria, parasites, fungi, and tumor cells. Topics to be covered include antiretroviral resistance (e.g., AZT and protease inhibitors), antibiotic resistance (e.g., β-lactams), resistance to chemotherapeutic agents, and resistance to antimalarial drugs (e.g., chloroquine). Course Directors, Eric Arts and Robert A. Bonomo.

- **Basic Cancer Biology and Therapeutics** (PHRM520, 3 credits): This course will cover not only fundamental principles of cancer biology, but will also highlight advances in the pathobiology and therapeutics of cancer. Classes will be of lecture and discussion format, with emphasis on critically reading original journal articles. The specific topics presented will include carcinogenesis, oncogenes, tumor suppressor genes, genetic epidemiology, DNA repair, growth factor action/signal transduction, apoptosis, cell cycle control, cell adhesion, angiogenesis, tumor cell heterogeneity, metastasis, chemotherapy, photodynamic therapy, gene therapy, signal transduction inhibitor therapy, chemoprevention, and clinical oncology of the breast, prostate, lymphatic tissue, colon and other related malignancies. Course grades will be from participation/discussion, presentation and mid-term/final exams. Seminar on the pathophysiology and therapeutics of cancer. Course Director, David Danielpour.

**TTT Peer Discussion Groups:** In addition to course work the focus of the Translational Therapeutics Track is reinforced by identified topical seminars and by monthly social/scientific gatherings. Thus, students meet monthly to discuss their projects in an informal setting. The students drive the meetings. The goal of the Peer Discussion Groups is to provide a forum in which the students can relate progress and difficulties with their projects to their peers in an informal setting. The students come from a diversity of laboratories. This diversity requires the students to be able to describe and justify the relevance of their project to a diverse audience. A second goal of these meetings is for the students to become proficient at describing their projects in a setting other than a formal research presentation. In addition to individual projects, the students also discuss mentoring strategies, career plans, and opportunities.

**Examinations and Dissertation Research**

**MTTP Preliminary Examination I** – A student must be registered during the semester in which any part of the general or qualifying examination is taken. The qualifier is comprised of a two-part written exam administered simultaneously to all eligible students. It is designed to evaluate their understanding of concepts presented in the various core courses. It also assesses their skills in critical reading of research articles and design of experiments. The division into two parts allows each student to receive feedback on deficient areas and work toward improvement on the second segment. Students may be exempt from part 2 if their performance is exceptionally strong on part 1 (e.g., > 1 S.D. above the mean of the performances of all others). Quality control of the exam questions and their scoring is monitored by a designated Prelim I Exam Committee. The exam is scheduled to be completed by all eligible students during January/February of their second year, and the exam process is designed to be completed in approximately one month.

**Eligibility:** Students may sit for the exam if they fulfill two criteria: (a) Successful completion (grade of B or better) in all of the Core Courses, and an overall GPA of 3.0 or better. (b) Satisfactory performance in all research rotations and consistent research effort in the thesis laboratory. The second criterion must be indicated formally in the mentor’s written evaluation of the student in a report submitted to the MTTP Director. Students who have not fulfilled the eligibility criteria are placed on formal probation for a defined period not to exceed one year. If remedial work for course requirements or research performance is not completed satisfactorily during that period, the student is subject to dismissal from the program. No student on probation may sit for the Prelim I Exam.
Purpose: The exam is designed to assess each student’s comprehension of core principles, ability to critically evaluate data, and to integrate concepts and data sets, including the ability to formulate experimental approaches that would resolve ambiguities in published data and advance a published study in a new direction.

Format: Students are administered a two-part written examination, typically containing 8-9 essay-type questions on each part. Both parts assess understanding of core principles and their application in specific research contexts. To facilitate a focus on applications of principles in research the students are assigned a published article for each part of the Exam, chosen by the Prelim I Exam Committee. The article is assigned two weeks in advance of each installment of the two-part exam, and care is taken to minimize the possibility that any individual student would have a particular advantage based on his/her current research involvement.

Questions are developed in a collaborative fashion by the Primary Faculty of Pharmacology and MTTP Training Faculty. They may be crafted in one of two ways. Type I questions are stand alone challenges to the student’s ability to display understanding of core principles in contexts that they have not previously encountered. Type II questions are inspired by specific aspects of the assigned articles, and they test the student’s ability to recognize core principles in practice. Further, they require the students to extend their thinking to experimental designs not included in the published articles. For uniformity of grading all answers are evaluated by two faculty members, the author of the question and one member of the Exam Committee. Any student whose composite score on the two-part Prelim I Exam is substantially below the average for all participating students shall be reviewed by the MTTP Steering Committee and placed on formal probation, or recommended for dismissal from the program. Final decision for dismissal is considered by the Assembly of Primary Faculty of Pharmacology. If probationary status is assigned, this can be removed by successful remediation and re-examination, as designed by the Prelim I Exam Committee.

Completion of Formal Coursework Requirements and Advancement to Ph.D. Candidacy

At the end of fall semester, Year 2, students will have completed the following courses: C3MB (Cell and Molecular Biology), Principles of Pharmacology I & II, Frontiers in Pharmacology Seminar, 3 research rotations, initial thesis-related research, Prelim I, and two advanced courses. Successful completion of Prelim I in January/February of year 2 and achievement of a GPA ≥ 3.0, constitutes formal advancement to Ph.D. candidacy. The Dean of Graduate Studies must be notified in writing of the decision concerning a student’s advancement to candidacy, and a copy of the notification must be sent to the student concerned. Completion of all of the components listed above by May of year 2 places the student in good standing for continuation into the more flexible part of the training program (see below).

Unsuccessful performance in any one of the required components constitutes probationary status; and appropriate remedial measures must be enacted on an individual basis. More than one unsuccessful performance may lead to dismissal from the program. Decisions on student status at this stage are based on the assessment of the MTTP Steering Committee and its recommendations to the full Faculty of Pharmacology.

Dissertation Research (PHRM 701)

When a doctoral student has been advanced to candidacy after successful completion of Prelim Exam I, he/she may begin formal registration for dissertation research, provided that the Department has identified the faculty member who will serve as the student’s principal research advisor and has so notified the Dean of Graduate Studies formally. Upon such written notification the student will be acknowledged by the Dean as eligible to register for one to nine credit hours of Dissertation Research (PHRM 701) each semester. After accumulation of 18 credits of 701, students must continue to register for PHRM 701 (1 credit per semester constitutes full time enrollment) until all graduation requirements are fulfilled. In exceptional cases (e.g., an advanced transfer student), a student who has not yet been advanced to candidacy may begin registering for up to 6 credit hours of PHRM 701 concurrently with registration for coursework at the discretion of the Department and upon written notification to the Dean of Graduate Studies. Once PHRM 701 registration begins students have five consecutive calendar years from the semester of the first credited 701 registration, including leaves of absence, to complete all requirements for the doctorate. Those who fail to complete the requirements within five years may petition for an extension of a maximum of one academic year upon recommendation of the Research Advisor, approval of the Department Chairperson, and the Dean of Graduate Studies. The minimum acceptable registration during this extended period is three credit hours of 701 in each of the two semesters.


Once students successfully complete Preliminary Examination I and are advanced to candidacy, they may begin immediately to prepare their thesis proposal, while completing any remaining advanced coursework; and they should also identify their Thesis Progress Committee which also serves initially as the Prelim II Exam Committee. This process takes place
during the spring and throughout the summer of year 2. The composition of the Committee is determined by the Director of the Graduate Program in consultation with the student and the mentor, based on prescribed criteria. Namely, the Thesis Progress Committee shall consist of at least 4 CWRU faculty members. At least 2 must hold primary appointments in the Department of Pharmacology, and at least one must hold a primary faculty appointment outside the Department. The chair of the thesis committee must be someone different from the mentor, and be a primary faculty member of the Department of Pharmacology, thus facilitating consistency among thesis committees. Through interactions with the mentor and other members of the thesis committee, the student develops a set of specific aims that will constitute an original research plan. It is understood that some students may have only limited preliminary data at this point in the program. However, the purpose is to propose a well-conceived research plan in which the hypothetical framework emanates from previously published work and current supporting data and leads naturally to the specific aims. Each student is expected to schedule a meeting of his/her thesis progress committee well in advance of the Prelim II Defense date for the purpose of presenting a preliminary research design and receiving constructive criticism. By September 30 of the third year, each eligible student submits an individual NRSA (NIH)-style research proposal to the Prelim II Exam/Thesis Committee, and the student defends that proposal to the Committee (see below). The student’s written document and oral performance are discussed, and a written evaluation is compiled by the chair of the thesis committee and submitted to the Director of the MTTP. The written proposal is for purposes of the prelim II exam, it is not a contractual arrangement that binds the student and mentor to a prescribed research plan. Thus, it is anticipated that each student’s original research plan may evolve continuously throughout the course of dissertation research, as driven by new data.

Recommended Format for Prelim II Proposals (PHRM 525, 2 credit hr): Proposals should not exceed 10 single-spaced pages in length (excluding references) and should follow the general format for an NIH Individual Fellowship Application (http://grants.nih.gov/grants/guide/pa-files/PA-10-108.html) (see Components of the Prelim II proposal, below). Completed proposals must be submitted to the members of the Prelim II Exam/Thesis Committee at least seven days in advance of the scheduled oral defense of the proposal.

Grant Writing Workshop – Integral to the process of preparing an individual NRSA-type proposal on their thesis research for the prelim II exam, students participate in a one-day grant-writing workshop. As noted, all students completing prelim II will be enrolled for 2 credit hr of PHRM 525, and the grant writing workshop is one of the required components of this exercise. Students are provided with a copy of an actual grant proposal that was reviewed by a national panel and received a written summary statement with critiques, but was not funded (revision required). The students read the proposal (without seeing the critiques), and write their own 1-2 page critique to be turned in to the Mock Review Panel, comprised of several training faculty members who convene the workshop. At the workshop, the Review Panel discuss the proposal and provide critiques to illustrate the key components that are necessary for any grant proposal, and the specific items that enhance the quality of the proposal or detract from it. The students are able to compare what they emphasized in their critiques to what the expert panel focused on. The faculty panel summarizes the key points of the discussion and provides the students with a take home copy of the revised proposal, including the introduction which shows how the PI responded to the specific criticisms.

Components of the Prelim II Proposal
1. Hypotheses and Specific Aims (required) - introductory paragraph clearly summarizing the project and long-term goals. Clearly stated hypotheses and a list of the specific goals to be accomplished with brief rationales and approaches. (generally one page)
2. Background and Significance (required) - background of proposed research including work performed previously by others, including supporting literature and unpublished data from the mentor’s laboratory. (generally 2-3 pages)
3. Preliminary results (recommended) – new data generated by the student directly pertinent to the proposed research plan. (1-2 pages)
4. Experimental Design and Methods - detailed description of proposed studies. Within this section, it is important to clearly state the rationale for each experiment, and map out the overall general design. Present enough information to convince the committee that you know how to do these experiments. Detailed protocols of routine assays (northerns, westerns, etc.) are not necessary. More detail may be required for specialized techniques. For each major experimental design (usually each Specific Aim or sub-Aim), you should interpret expected results and discuss alternative outcomes, discuss potential pitfalls in the experiments and alternative strategies. It is much more important to display thoughtful consideration of the rationale for experimental design and interpretation of the potential results than to list detailed protocols for specific experiments. (Generally 4-6 pages).
5. References - Include titles and full pagination, and follow a standard citation technique such as that used in J. Biol. Chem.
6. After submitting the written proposal, the student then prepares a 30 minute oral presentation of the proposal, high-
lighting the basis for each of the hypotheses and corresponding specific aims, presenting key preliminary data, and interpreting the expected and alternative outcomes. The written proposal and the presentation are open to examination by the Prelim II/Thesis Committee in a question/answer session conducted as part of the oral presentation and defense of the proposal. Typically questions may be asked by committee members throughout, as well as following, the oral presentation of the proposal. This constitutes the oral portion of Prelim II.

**Student-Mentor Interaction in the Prelim II Process** - The written proposal will be developed by the student in close consultation with the thesis mentor. This generally involves a series of discussions between the student and mentor where details of the specific aims page are formulated. The general mechanics of effective grant writing and grant formulation are also discussed early and emphasized throughout the process, thereby reinforcing the Grant Writing Workshop (described above). It is appropriate to use the mentor's own grant applications as useful models. However, the proposal should be written independently by the student, and the mentor should not contribute text to the written document. This should be a student-driven and mentor-guided process, where the mentor asks probing questions and offers suggestions rather than providing explicit direction. For example, the mentor and student might discuss general methods, approaches, and reagents that could be used or developed to accomplish the aims. However, the student should provide the overall plan of attack, the written details, rationales, appropriate controls, potential outcomes and interpretations. General areas of weakness or gaps might be identified by the mentor, but specific approaches to fill these gaps should be the student's responsibility. Following the Prelim II examination, the mentor and student are encouraged to meet and discuss the strengths and weaknesses of the examination and the final written proposal. The intent of this meeting is to emphasize the strong points and identify areas where further development would be useful. **Students and Mentors are strongly encouraged to follow up on the Prelim II experience by applying for Ruth L. Kirstein NRSA Individual predoctoral fellowship awards, or analogous fellowships from other granting agencies (e.g. American Heart Association, Department of Defense, etc.). Receiving such an award is a special honor for the student, and a benefit for the laboratory, the MTTP, and the Department.**

**Grading of Prelim II** — Guidelines for formal, consistent grading of the written and oral components of the Prelim II Exam are delineated below:

1. Each component of the Exam is scored independently and anonymously by each committee member before the Exam Committee discusses the performance of the student.
   a. Each member of the Committee scores the written document, according to specific guidelines (see Components of the Prelim II Proposal, above), and provides the score to the Committee Chair prior to the oral exam. The Committee Chair records these initial scores, but does not share or discuss them with the Committee until the oral exam is completed.
   b. Each member of the Committee scores the oral performance, according to specific criteria, namely: overall organization; breadth and depth of knowledge of published work related to the research plan and pilot data; quality of responses to questions and ability to respond to criticism of the experimental design; quality of visual aids. These scores are provided to the Committee Chair before any discussion ensues. The Chair records these initial scores.

2. The Committee Chair then shares the initial scores for the written and oral segments of the Exam and invites discussion, with the goal of reaching a consensus score on each component of the Exam.

3. The written score contributes a factor of 0.4, and the oral performance a factor of 0.6, to the composite score for the overall exam.

4. A composite score of 80-89% corresponds to a grade of B, a passing grade for the exam. > 90% = A; ≤ 79% = C (failure).

5. **For an Unconditional Pass both component scores must be > 80%**. For example, if the written component received a consensus score of 65% and the oral component was scored 90%, this would represent a Conditional Pass with an identified deficiency in the written component. The Committee would devise a remediation exercise and a time limit for removing the condition. An analogous approach would apply for a deficiency in the oral component.

6. If the composite score for the two components is ≤ 79%, this constitutes a failure of Prelim II and requires an individualized remediation plan and a re-take of the Exam. A student who fails Prelim II twice is subject to dismissal from the Program.

7. Each Committee Chair reports the initial scores and final scores, and a summary statement of student performance to the Director of the MTTP. In cases where wide discrepancies between initial and final scores are evident, there will be follow up by the Director and/or the MTTP Steering Committee.

8. Composite scores corresponding to grades of B or better are reported by the thesis advisor through the SIS system as the grades for the 2 credit hr of PHRM 525.
9. A composite score corresponding to a grade of C (failure) for the first attempt at Prelim II is reported by the thesis advisor as a grade of I (incomplete); and remediation and re-examination must be completed by the end of the next semester to achieve a grade of B. A second failure on Prelim II is recorded as a grade of C, and the student’s progress must be reviewed by the MTTP Steering Committee for consideration of a terminal MS degree.

**Required Foundation in Biostatistics, and Consultation** – Students who have completed their required coursework and Prelims I & II are expected to have a foundation in fundamental biostatistics for appropriate analysis of their data. This is the stage in thesis research when students are expected to have generated sufficient data to develop manuscripts for publication. All of the elements of basic biostatistics that are valuable for our Ph.D. students are contained in a short course that is offered each year by Mark Schluchter, Ph.D., Professor of Epidemiology and Biostatistics, in which our students will enroll. The course is comprised of nine 1.5-hr sessions held each Wednesday afternoon starting in mid January [1] Introduction to biostatistics / Data Summarization; 2) Comparing means of two or more groups – t-test, ANOVA; 3) Analysis of frequency data – chi-square, Fisher’s exact test; 4) Nonparametric methods; 5) Sample size and power; 6) Linear regression and correlation; 7) Multiple linear and logistic regression; 8) Survival analysis; 9) Diagnostic tests and Receiver Operating Characteristic Curves]. In consultation with Dr. Schluchter we have identified seven sessions (i.e., #1-6 and #8) as providing the fundamental principles that are applicable to most data generated by research groups affiliated with the Pharmacology graduate program. *All students in the Molecular Therapeutics Training Program of the Department of Pharmacology are expected to take advantage of this biostatistics course, or to provide documentation for completion of an equivalent experience in another context.* Online registration is open at: [http://cru.case.edu/seminar.html](http://cru.case.edu/seminar.html); for questions about the course, please contact Dr. Schluchter at mds11@case.edu.

In addition, Denise Babineau, Ph.D., Director of the Statistical Sciences Core, has arranged access to private consultation with statisticians for investigators in the School of Medicine. This service is open to our students for questions relating to specific study design, statistical software, and data analysis and interpretation. The office hours for such consultation are from 1-2 pm on Tuesdays and Thursdays in the Center for Clinical Investigation (CCI) offices on the 6th floor of the Wolstein Bldg. Technically, each investigator is allowed only one free hour of consultation for each project, but the statistician (schedule permitting) may provide additional consultation on a project (no more than 4 hours).

**Dissertation Defense**

Students become eligible for their Dissertation Defense based on completing all coursework and preliminary examination requirements, and completing a body of original research work through their independent efforts. This accomplishment is characterized by the student’s intellectual command of the experimental design and data they have generated, and their thorough understanding of how their findings advance knowledge in the area of their specialization. As described below, it is the Thesis Committee’s responsibility to decide when a student is ready to defend. *In particular the thesis committee will review drafts of manuscripts being readied for submission. The student and thesis advisor should propose several journals, with relative priorities, where the manuscript may be considered for publication. It is required that the thesis committee agrees prospectively that publication of a first-authored paper in any of the proposed journals will fulfill the publication requirements described below.*

**Publication Guideline and Dissertation Defense.**

The award of the Ph.D. degree depends on the completion of an original research project and the public defense of that project. The thesis committee ultimately decides when the student has acquired the appropriate skills and benchmarks characteristic of the Ph.D. degree, including completion of original research, research independence, creative thought, and knowledge of the field. For the MTTP, another benchmark is successful publication of the thesis research in peer-reviewed scientific journals. *The MTTP expects that a Ph.D. thesis will consist of a body of work that constitutes a complete study that spawns several published manuscripts. Thus, we expect Ph.D. graduates of the MTTP to have two or more first-authored primary research publications in high quality, peer-reviewed scientific journals.* This requirement provides external validation of the originality and importance of the research that comprises the dissertation since the research has been reviewed by multiple outside reviewers that are experts in the chosen field. *As a minimum*, at least one such paper must be published or accepted for publication and the second should be submitted for publication before a student is given permission to defend the thesis. Clearly this minimum is not meant to be the norm because the greater the productivity the greater the opportunity for career advancement. Any proposal to consider less than this minimum publication requirement requires the approval of the Thesis Committee, The MTTP Steering Committee, and the Primary Faculty of Pharmacology. It is in the best interest of every student to be as productive as possible in establishing the basis for career advancement. Therefore at the outset of thesis studies it is much better to set a goal to exceed the minimum publication requirement, rather than to aim lower and achieve less.
MTTP Specific Guidelines

Composition of the Final Defense Committee - The Dissertation Defense Committee shall be comprised of the Thesis Progress Committee and one more member with expertise in the focal research area added to the Committee at the time of the thesis defense. As described (above) the Thesis Progress Committee typically is comprised of four members, at least two of whom hold primary faculty appointments in the Department of Pharmacology; however some committees may have an additional member – e.g., committees for MSTP students are required to include a clinical scientist. The additional defense committee member shall be named by the Director of the Graduate Program from a list of at least three investigators who have not been former mentors or collaborators of the Ph.D. candidate. The list will be provided by the candidate and/or mentor, and the selection will be made by the Co-Leaders of the MTTP track with which the candidate is affiliated in consultation with the MTTP Director.

Timetable and requirements – One month prior to the proposed date for the presentation of a public seminar on the thesis research the candidate shall provide a copy of the completed dissertation to all members of the expanded Dissertation Defense Committee and to the Chair of Pharmacology. An oral defense of the dissertation conducted by the Committee shall occur within two weeks of distribution of the document. *All faculty members are welcome to participate in this exercise.* As usual the Dissertation Defense Committee will examine the candidate’s command of the data and narrative description contained in the dissertation as well as the candidate’s understanding of the scientific impact of the findings and the fundamental principles upon which they are based. The candidate must pass this oral defense in order to progress to the public presentation of the thesis research which must also be satisfactory in order to culminate in celebration of the accomplishment. Typically the dissertation will require at least minor corrections before it is finally approved by the thesis advisor, the Committee, and the Chair of Pharmacology; and these revisions must be completed within 30 days of the public presentation. In the event that the document and/or the oral defense is found to be unsatisfactory by the Dissertation Defense Committee, the scheduling of the public presentation must be postponed. The Committee will devise a specific plan and set of requirements for correcting the deficiencies in the dissertation with a specific deadline, typically not to exceed 60 days from the original oral defense.

Summary – In order to fulfill the requirements for the Ph.D. degree in Pharmacology, the candidate must have (1) completed all required coursework and preliminary examinations; (2) published at least one first-authored paper in a premier journal and submitted at least one other manuscript for publication; (3) Completed a well written dissertation that integrates the novel research findings with the broad area of research that it represents and provides a thoughtful plan for future development of the research project; (4) Successfully defended the dissertation to the Defense Committee which includes an expert in the research area who has not been involved in monitoring the development of the project; (4) presented a satisfactory public seminar on the thesis research; (5) Completed all revisions to the dissertation as delineated by the Defense Committee.

Celebration – It is customary to celebrate the entry of the new Ph.D. scientist into the scientific community. Hence, at the conclusion of the public presentation of the thesis work the candidate will be inducted into the scientific community by being reminded of the commitments to safeguarding the norms of scientific integrity that are expected of practicing scientists (See suggested proclamation below). Then a reception will follow to congratulate the candidate in the midst of a gathering of members of the Department and family and friends of the candidate.

Proclamation:

“Name of candidate,” congratulations on the successful defense and public presentation of your dissertation research - you have fulfilled the requirements for the award of the Ph.D. degree in Pharmacology to be conferred by Case Western Reserve University.

With this honor comes an important responsibility. We send you forth as an independent scientist with the charge to continue to seek new understanding of scientific truth, never being tempted to compromise scientific integrity. By this symbolic handshake you acknowledge your commitment to uphold this responsibility.”
Steps to Completion [Excerpt from Graduate Studies Website]

http://gradstudies.case.edu/current/graduation/phd.html

1. Complete and submit the Application for Graduation through the Student Information System (SIS) by the established deadline for the term.
2. Working with your advisor and committee members, decide on a date, time and place for your final oral exam (defense), making certain that the defense date occurs before the established deadline for the term. (Note that the advisor has to agree that the dissertation is ready to defend).
3. Submit the Notification of the Final Oral Exam form to the School of Graduate Studies at least three weeks prior to your defense date.
4. Submit copies of your dissertation to the members of your defense committee at least two weeks prior to your defense date.
5. At the conclusion of your successful defense, have all committee members sign the two Final Certification for the PhD Degree forms.
6. If you are required to make corrections to your dissertation, make the corrections and then have your advisor sign the certification forms where indicated. If no corrections are required, have your advisor sign the forms at your defense.
7. After your advisor has signed the certification forms, obtain your department chair’s signature.
8. Submit a completed copy of your dissertation.pdf file to the School of Graduate Studies for a format check.
9. Upload the final, approved copy of the completed dissertation as a PDF file to OhioLink (http://etd.ohiolink.edu/submit/+).

Final Materials
Submit the following to the School of Graduate Studies by the established deadlines:

- Two certification forms with all appropriate signatures (The signature of the Dean of Graduate Studies will be provided after submission)
- ETD Document Approval Form
- Two printed copies of your dissertation's Title Page
- Survey of Earned Doctorates

Dissertations are made public immediately upon acceptance, so they should not contain proprietary or classified material. When the research relates to proprietary material, the student and advisor are responsible for making preliminary disclosures to the sponsor sufficiently in advance to permit timely release of the dissertation.

Graduation
A candidate for a degree awarded by the School of Graduate Studies must make an application for the degree to the Office of Graduate Studies by the deadline established for that semester, which is approximately two months before the commencement date at which the degree is expected to be awarded. The candidate must meet all the deadlines for completion of degree requirements set forth in the calendar. All candidates must be registered and in good standing during the semester in which the degree is awarded. Full payment of tuition, fees and fines is a prerequisite to the award of a degree.

Delayed Graduation
A doctoral or master's thesis applicant who meets all deadlines for commencement in one semester except for the deadline for submission to the Office of Graduate Studies of approved copies of the thesis may request use of the “grace” period in order to graduate in the next commencement. Any student utilizing the delayed graduation option must notify the Office of Graduate Studies in writing of the intention to do so. Permission to use the grace period will be granted only once. Such a student will be permitted a one month period from the date of commencement for which application has been made for the purpose of making revisions to the defended thesis or dissertation in accordance with the recommendations of the defense committee, in order to submit the required approved copies to the Office of Graduate Studies. A student who meets the delayed graduation deadline will be awarded the degree in the next commencement without the need to be registered or to pay a special fee. If a student fails to meet this deadline, she or he will be required to register for the appropriate thesis or dissertation credit hours in the next semester and to reapply that semester as a candidate for graduation. Upon written request to the Office of Graduate Studies, a master’s non-thesis (Plan B) applicant may use the grace period only relative to the scheduling of the required Comprehensive Examination or Completion and Submission of the final project.
Getting a Ph.D./M.D. in Pharmacology

CWRU has offered MD/PhD training since 1956 for students aspiring to careers combining academic medicine and biomedical research. The Medical Scientist Training Program (MSTP) provides an outstanding opportunity for students to obtain combined MD/PhD training and launch careers as physician-scientists. The MSTP option is another mode of entry into the Pharmacology Ph.D. program as described above. A complete description of the Program can be obtained by contacting the MSTP Office (Kathy Schultz, Administrative Director) or by consulting the MSTP website: http://mstp.cwru.edu/

Introduction to MSTP the program (Ph.D./M.D.)

1. Summary of requirements pursuant to the Ph.D. portion of the combined degree:
   - Pharmacology core course,
     Molecular Basis of Therapeutics (PHRM 401). Note: Typically PHRM 402, Physiological Basis of Therapeutics, would be waived because its content is covered in the medical curriculum.
   - 3 Research rotations
   - Preliminary exams I and II
   - Two advanced courses in a selected track of research
   - Independent research/at least two first authored manuscripts completed for publication before thesis defense [see complete publication guideline above]

2. Sample schedule for MSTP students in the MTTP:

   YEAR ONE
   - Medical School Curriculum
   - Three Research Rotations
   - Possibly PHRM 401

   YEAR TWO
   - Medical School Curriculum, NBME Exam: USMLE I
   - Selection of thesis advisor
   - PHRM 401, if not completed in Year 1, or Advanced Elective
   - Seminar and Oral presentation series (PHRM 511).
   - Possibly Prelim I and Advancement to Candidacy

   YEAR THREE
   - Complete Advanced Elective Course(s)
   - Independent Research (PHRM 601)
   - Preliminary Exam I and Advancement to Ph.D. candidacy, if not completed in Year 2
   - Possibly Prelim II (Thesis Proposal)

   YEAR FOUR
   - Independent Research (PHRM 701)
   - Preliminary II (Thesis Proposal), if not completed in year 3

   YEARS FIVE AND SIX
   - Thesis Research (PHRM 701)
   - Complete research, submit and revise manuscripts
   - Thesis Defense / Ph.D. degree awarded

   YEARS SEVEN AND EIGHT (or sooner)
   - Clinical Rotations
   - M.D. degree awarded

Getting a M.S. Degree in Pharmacology:

Although training efforts by the Department of Pharmacology are primarily directed toward the award of the Ph.D. degree, training for the M.S. degree is provided also in a variety of contexts. For example, (1) research assistants in the Department who seek educational advancement may pursue the M.S. degree via Plan A (thesis) or Plan B (coursework only).
(2) Medical students who seek to specialize in pharmacology during the scholarly research component of their preclinical program may pursue the M.S./M.D. dual degree (typically, plan B M.S.). (3) Employees in the biomedical/biotechnology industry may seek advanced training in Pharmacology by pursuing the M.S. degree at CWRU (typically plan B). (4) Certain applicants for Ph.D. training may be advised to pursue a master’s degree as a prerequisite for entry into the Ph.D. program. This approach pertains either to individuals who have demonstrated research acuity but have sub-standard undergraduate academic credentials (plan B); or to individuals who have good academic credentials but little, if any, laboratory research experience (plan A). (5) Finally, a Ph.D. candidate who is unable to complete the Ph.D. requirements for extraordinary reasons may petition to have earned credits transferred to fulfill M.S. degree requirements. The costs of pursuing the M.S. degree usually are the responsibility of the student, with notable exceptions. Research assistants may use their employee tuition benefits, and students in special programs such as the M.D./M.S. program will receive the stipend prescribed by that program along with tuition remission during the time of fulfilling the M.S. requirements.

**Masters Plan B (Course work, M.S. direct admit)**

This program is aimed at students who enter the Department seeking a Master’s Degree but do not intend to specialize in research pursuant to writing a Master’s thesis. To satisfy the requirement for a Comprehensive Exam for the M.S. Degree, students will register for 1 credit of EXAM 600 during their final semester and sit for an integrative essay question-style examination on the content of the required coursework. A total of 27 credit hours are required (see below).

A. Required Courses:

**Required Courses**

**Coordinated Curriculum in Cell and Molecular Biology (C3MB)**

- Cell Biology (CBIO 453) 4 credits
- Molecular Biology (CBIO 455) 4 credits
- The Molecular Basis of Therapeutics (PHRM 401) 3 credits
- The Physiological Basis of Therapeutics (PHRM 402) 3 credits
- Frontiers in Pharmacology Seminar Series (PHRM 511) 2 credits
- Two Advanced Courses in Pharmacology (see list) 6 credits
- Master's Qualifying Examination (EXAM 600) 1 credit / Typically this is equivalent to the Prelim I Exam (described above under the Ph.D. program)

B. Independent research and study (PHRM 601) 6 credits

The advancement of understanding and practice of therapeutics is based on research. Therefore all students in degree programs in Pharmacology are expected to become involved in independent research and scholarship. Registration for PHRM 601 requires a pre-arrangement with a faculty mentor who will oversee the combination of study and bench research and prescribe the basis for satisfactory performance, including oral and written reports. With pre-approval of the Departmental Director of Graduate Studies, a student’s study plan may substitute additional specific advanced courses to replace PHRM 601 credits.

C. Sample Plan of Study for Plan B

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<tr>
<th>Semester 1:</th>
<th>Semester 2:</th>
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<tbody>
<tr>
<td>CBIO 453 (4)</td>
<td>PHRM 401 (3)</td>
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<td>CBIO 455 (4)</td>
<td>PHRM 601 (3)</td>
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<th>Semester 3:</th>
<th>Semester 4:</th>
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<td>PHRM 511 (1)</td>
<td>PHRM 511 (1)</td>
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<tr>
<td>PHRM 402 (3)</td>
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<tr>
<td>PHRM Elective (3)</td>
<td>PHRM 601 (3)</td>
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<td>EXAM 600 (1)</td>
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**Course work M.S. degree (Plan B) for students entering as former Ph.D. candidates** - This program is aimed at students who have taken most or all of the courses required for the Ph.D. but have not accomplished sufficient research to write a Ph.D. or Master’s thesis. Passing the qualifying exam (Prelim Exam I) required for admittance to candidacy in the Ph.D. program in Pharmacology and registering for 1 credit of EXAM 600 satisfies the requirements for a Comprehensive Exam for the M.S. degree. A total of 27 credit hours (18 credit hr graded) are required, fashioned analogously to Plan B for students admitted directly to the M.S. program (above).
Masters Plan A (Research, direct admit)

This program is aimed at students who enter the Department seeking a Master’s degree and intend to conduct independent research pursuant to writing and defending a Master’s Thesis. For these students, passing the final exams in PHRM 401 and PHRM 402 satisfies the requirement for a Comprehensive Exam for the M.S. Degree. As above, a minimum of 27 credit hours are required. In addition to the course requirements, candidates for this degree are required to submit an acceptable written thesis based on their original research, and register for at least 9 credit hours of PHRM 651 (master’s dissertation research). The acceptability of the thesis will be determined by an oral examination administered by the student’s Thesis Advisory Committee. This committee must be chaired by a member of the primary Faculty of Pharmacology, and it should include the research mentor and two other faculty members (total of four faculty members, two from the Department of Pharmacology).

Sample Plan of Study for Plan A

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<tr>
<th>Semester 1</th>
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<tr>
<td>CBIO 455 (4)</td>
<td>PHRM Elective (3)</td>
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<tr>
<td>PHRM 651 (1)</td>
<td>PHRM 651 (1)</td>
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Semester 3:

| PHRM 511 (1) |
| PHRM 402 (3) |
| PHRM 651 (2) |
| PHRM Elective (3) |

Semester 4:

| PHRM 511 (1) |
| PHRM 651 (6) |

Research M.S. degree (Plan A) for students entering as former Ph.D. candidates - This program is aimed at students who have taken most or all of the courses required for the Ph.D. and have also made sufficient progress to write and defend an acceptable Master’s Thesis. Passing the qualifying exam required for admittance to candidacy in the Ph.D. Program in Pharmacology (Prelim Exam I) satisfies the requirement for a Comprehensive Exam for the degree. In addition to the course requirements, candidates for this degree are required to submit an acceptable written thesis based on their original research, and satisfy the requirement for 9 credit hours of PHRM 651. The acceptability of the thesis will be determined by an oral examination administered by the student’s advisory committee. A minimum of 27 credit hours are required.

M.D./M.S. Program in Biomedical Investigation – Specialization in Pharmacology

1. Academic Rationale and Purpose. The goal of the joint M.D. / Masters of Science in Biomedical Investigation program at CWRU School of Medicine is to train medical students in basic or clinical research approaches so that the physician graduate may conduct research to advance health. This program is designed for students pursuing a joint, five-year MD/MS at CWRU School of Medicine and is intended for students who wish to prepare for future independent research careers. This joint program is based on existing MS programs in the School of Medicine, now joined with medicine into a dual degree, and thus the program itself does not represent a new discipline. Students will earn a plan B type MS from Graduate Studies, and the name of the joint degree will reflect the particular track pursued by the student (e.g., MD/MS Pharmacology). The core of this degree is 3-6 graduate courses in specific tracks, limited medical school graded credit, a common seminar series, and a full year research project that must culminate in a written report and examination by faculty. The program draws upon the well established educational and research resources at CWRU School of Medicine and affiliated University Hospitals of Cleveland, The Cleveland Clinic Foundation, MetroHealth Medical Center, and the Louis Stokes Department of Veteran Affairs Medical Center, and complements the strengths of its research mentors. Various tracks within the program may be pursued, depending on the research interest of the student. Graduates of the program will be poised to actively engage in research teams and contribute to academic medicine.

CWRU School of Medicine offers several independent MS degrees and a number of combined MD/MS or MD/MA degrees, but none with this emphasis on research and medicine. CWRU oversees a special program at the Lerner College of Medicine that requires a fifth year of research within its medical training; and an increased emphasis on research training is incorporated into the revised University medical curriculum (WR2). These developments spawn an interest by medical students in obtaining advanced degrees in addition to the MD during their usual course of study. This combined MD/MS program is designed to create a single, standardized and rigorous MD/MS curriculum with multiple research and coursework “tracks” at CWRU, rather than fostering a series of individual MD/MS programs with various requirements, standards and expectations of students.
2. Description of the curriculum.

The M. D. Curriculum. Both the University curriculum and Lerner College curriculum cover the fundamentals of normal organ systems and the pathophysiology of diseased organ systems, either in sequence or in an integrated and iterative fashion. Both Programs have an extensive commitment to clinical training. The Lerner College Program incorporates within its five-year curriculum a requirement for active research of at least one year duration, including the preparation of a research thesis. Students in the University Program have always had the option to pursue a year of research after their preclinical coursework. Some components of the medical curriculum are considered equivalent to basic science material taught in graduate Ph.D. programs (for example, Biochemistry, Cell and Molecular Biology Courses) and 6 credits of the medical curriculum will be used as graded credit toward the Master’s portion of the combined MD/MS. The medical curriculum will not change as part of this joint program.

b. The M. S. Curriculum. The individual will earn the type B MS from the Graduate School. The template of the proposed degree includes (1) a requirement for a special problems project that reflects a full year of research (18 hours of 601 non-graded credits) culminating in a written report; (2) 6 graded credits of medical coursework; (3) participation in a common seminar series; (4) scientific integrity training; (5) Qualifying Examination; and (6) successful completion of 9-18 additional graded graduate credits in specific “tracks.” Thus, this program will require 5 years overall to complete the requirements for both degrees. In most tracks, students are anticipated to complete all graduate courses before entering the research year, allowing full focus on the research experience.

c. Admissions and Sample student program. All students will begin the University or the Lerner College Medical Programs, and their admission to the medical school will be determined by the medical admissions committees. Students who wish to join the MD/MS program may apply to the Program after arriving at the University any time prior to their second year of medical school. For acceptance into the Program Oversight Committee (described below), the applicant should present a letter from the Dean of Student Affairs of CWRU SOM that documents good standing as a medical student. The MD/MS Program Oversight committee described below reviews the application and forwards its decision to the Dean of Graduate Studies of CWRU. Acceptance by the Graduate School classifies the applicant as a student in the Joint Degree Program in Biomedical Investigation, but does not guarantee the availability of a specific mentor or track to the student. After acceptance, participation in the Program occurs through documentation of continuous success in the medical core curriculum.

During the first year, the student will begin graduate courses and identify a mentor and a research project leading to the MS degree, with assistance from the Program Oversight Committee (described below). Students are expected to complete at least six graduate course credits (and optimally 9) before beginning the extended laboratory research period, in addition to the six credits obtained from the medical curriculum. Portions of the medical curriculum will earn graded credit toward the joint MD/MS degree as Integrated Biological Science (IBIS) coursework, as in existing IBIS 401-405 courses for the Medical Scientist Training Program. Normal rules, as established by faculties, for advanced standing shall also apply such that only 6 IBIS credits total will be applied toward the joint MD/MS. For students to receive graduate credit for medical coursework, they must register for IBIS credit at the beginning of the semester. Further, it is strongly recommended that students pursue rotation research between the first and second year of medical school, or during the first year as an elective in preparation for the full year of laboratory research, and 1-3 non-graded (601) elective credits may be earned for this activity. Students in the MD/MS joint degree program must attain a cumulative GPA of 3.0 in their graduate courses.

Students are likely to complete the required two semesters of research 601 after the pre-clinical years in medical school, although the research could occur in other years. Before initiating full time research, the trainee must submit a final research proposal to the Program Oversight Committee. This will summarize the courses taken, the proposed thesis topic, and the names and credentials of the MS Research Progress Committee. During the research period, the student is expected to participate in track-specific graduate activities including retreats, student talks, journal clubs and other program functions, as well as the common monthly seminar series for MD/MS students described below. Only under unusual circumstances will the student be allowed to satisfy the research requirement in non-contiguous semesters.

Each track within the joint MD/MS Program has specific course requirements. The requirements for the Pharmacology Track are delineated in the Sample Program (below). As a minimum, graduation requires successful completion of 9 graded credits of graduate courses, 6 graded credits of IBIS medical curriculum, 18 non graded credits of research, and 2 additional non graded credits for departmental seminar and the exam and zero credits for scientific integrity training (IBMS 400) in the program. Students are required to pass a qualifying examination (EXAM 600) established for each student, generally reflecting the preparation and oral defense of a written report on the project.

A unique feature of the MD/MS program is the planned monthly seminar series in which all students throughout the joint program meet monthly to present their work and interact with speakers. MD/MS students will also participate in a year-end retreat, and are required to present their work in a research forum such as the annual SOM Lepow Day competition.
These activities are intended to integrate the medical and research experiences, and to support group identity among these students.

Sample Program (Pharmacology Track)

Year 1  
Two-Semester Medical School Curriculum (IBIS 401/2) / Fall & Spring (3 cr each) 6 credits
Summer  
PHRM 601 (optional, encouraged) 3 credits
Year 2  
Medical curriculum (IBIS 403) 3 credits
Molecular Basis of Therapeutics (PHRM 401) / Spring 3 credits
Physiological Basis of Therapeutics (PHRM 402) / Fall 3 credits
Advanced Elective Course complimentary to research focus / Fall 3 credits
Year 3  
Independent Research (PHRM 601) / Fall & Spring (9 cr each) 18 credits
Frontiers in Pharmacology Seminar Series (PHRM 511) Fall & Spring (1 cr each) 2 credits
Scientific Integrity Training (IBMS 400) / Spring 0 credit
Qualifying Examination (EXAM 600) 1 credit
Year 4  
Two-Semester Medical School Curriculum
Year 5  
Two-Semester Medical School Curriculum

Appendix

Computer Policy

The computer policy for graduate students in the Department of Pharmacology is that all students receive a new personal notebook computer for their exclusive use throughout the training program at the time that they join their thesis research lab. The Department of Pharmacology subsidizes the purchase of these computers for every Pharmacology student in our training program. The Department provides one-half the purchase price of the computer, up to $750.00. The mentor's laboratory budget provides the remainder of the cost. It is important to note that this computer is the property of the PI's laboratory and stays with the PI when the student graduates. We expect the mentor to initiate this process as soon as the student has chosen a lab. The mentor and student should decide on a computer and then contact Cami (368-4617) or Ivona (368-0701) to initiate this process.

Computing Resources

Getting connected
This is the Link that most will find useful: http://help.case.edu/. This web page provides instructions and assistance on connecting and setting up your computer to the CWRU network. Whether it is secure wireless, or a gigabit on-campus connection, how to setup email, or software downloads... It's all here! In addition, the Department of Pharmacology has arranged for daily on-site personnel from the School of Medicine IT Service to provide advice and repair services for everyone's computers.

Free “useful” downloads
The CASE Software Library gives students free use of many of the latest software packages on their own computers, provided they have network access. Students may also use the software in the library from campus computer labs. https://softwarecenter.case.edu

Software packages include: Microsoft Windows 7, Microsoft Office, Photoshop CS4, Illustrator CS4, Symantec Endpoint Protection antivirus, Labview, Matlab, plus many other useful programs!

E-journals
Almost every journal provides quick and easy access to full-text versions of articles. CWRU libraries has established a listing of all e-journals with links: http://www.cwru.edu/chsl/ejournal.htm. (keep this page open while using PubMed)

CWRU has online subscriptions to most of the journals on the above webpage. However, performing a literature search using a computer with a CWRU IP address doesn't guarantee that the journal website will recognize your computer as a paid subscriber. Many times you will need to go through the above link to access the online full-text versions of articles.
Required Program Forms

Advancement to Candidacy Form: Once Ph.D. students have successfully passed all examinations and met all Departmental requirements, they can be formally advanced to candidacy. Notification needs to be sent to the Office of Graduate Studies via this form when advancement occurs.

Predoctoral Standing Form: Students who have already completed or will complete all their required course work in the next semester, and have not been advanced to candidacy, may begin 701 registration. With this special status, students are limited to registering for up to 6 hours of 701 research credits. It is presumed that students will take their exams and be advanced to candidacy during the semester in which predoctoral standing is granted.

Notification for Scheduling the Final Oral Exam for the Ph.D.: Submit a minimum of 3 weeks prior to defense date

Application for Graduate Degree: Must be filed by the deadline specified for that particular semester

Application Packet for Graduation: This packet contains several forms that must be completed, signed and submitted at least one month in advance of graduation. Failure to complete all forms in this packet will cause a student to become ineligible for graduation.

Bound Copy of Dissertation: MTTP doctoral students are required to submit one bound copy of their dissertation to the MTTP Administrator. As stated previously, this copy and one additional copy for the student will be sponsored by the department. The University Office of Graduate Studies requires students to submit two bound copies of the dissertation. These two copies will be paid for by the university.

Student Policies

Student's Right to Know
The Student's Right to Know and Campus Security Act requires that universities throughout the country produce statistics on the retention and graduation rates for their students, as well as crime statistics, on their campuses. This data is available in the Office of the Provost in Adelbert Hall and in the various undergraduate, graduate and professional schools' admissions office.

Policy on Sexual Harassment
It is the policy of Case Western Reserve University to provide a positive, discrimination-free educational and working environment. Sexual harassment is unacceptable conduct that will not be tolerated. All members of the University community share responsibility for avoiding, discouraging, and reporting any form of sexual harassment.

Members of the University community found in violation of this policy may be disciplined, up to and including being discharged for cause or being expelled from the University. Retaliation against persons raising concerns about sexual harassment is prohibited and will constitute separate grounds for disciplinary action, up to and including discharge or expulsion from the University.

The University has passed and disseminated to all parties on this campus--students, faculty and staff--a detailed statement titled Policies and Procedures Regarding Sexual Harassment and Sexual Assault. Copies are available in the Provost’s Office, all the deans’ offices and at many of the University offices throughout the campus. Consultation and advice are available in the offices of the Provost, Affirmative Action and Student Affairs. See the section, "Student Affairs," for policies and procedures regarding sexual assault. This policy and the accompanying procedures shall serve as the only internal University forum of resolution and appeal of sexual harassment complaints.

Non-Discrimination
Case Western Reserve University admits students of any race, religion, age, sex, color, disability, sexual orientation, and national or ethnic origin to all the rights and privileges, programs, and activities generally accorded or made available to students at the university. It does not discriminate on the basis of race, religion, age, sex, color, disability, sexual orientation, or national or ethnic origin in administering its educational policies, admission policies, employment, promotion and compensation policies, scholarship and loan programs, and athletic or other university-administered programs.

Student Resources
University Counseling Services Counseling Service: 368-5872 - 201 Sears Hall Mental Health Service: 368-2510
University Health Service, 2nd floor
Students with Mental Health concerns for yourself or a friend, which include depression, anxiety, eating problems, alcohol issues, sleep problems or any other school adjustment situations, can schedule an appointment at the Health Service to be seen by a health care provider. To schedule an appointment at the Health Service call 368-4539. Students may also schedule appointments in the counseling center for the same issues without first seeing someone at the Health Service. Call 368-5872 to schedule an appointment.

http://www.case.edu/stuaff/ucs/index.html

**Housing and Residence Life: 368-3780 - Room 4, Yost Hall**

The Department of Pharmacology can direct students to available housing options in the area. It is also available on-line @ http://studentaffairs.case.edu/living/services/aloha/

**Office of Student Affairs; 368-2020 - 110 Adelbert Hall**

The University Office of Student Affairs provides leadership in the development of services and programs that supplement the classroom experiences of university students and enrich student life. The staff of the Office of Student Affairs attempts to promote an environment that provides positive, developmental experiences for all students.

Additionally, the office serves as an ombudsman, focusing attention on the rights and responsibilities of students within the university community. The Office of Student Affairs is a central source of information about university policies and procedures that affect student life and co-curricular programs and services.

Students should feel free to contact the Office of Student Affairs for resolution of specific problems and for referral to other university offices and campus agencies.

**Phone Numbers, etc.**

**PHARMACOLOGY**

Director of MTTP Graduate Studies: John J. Mieyal, Ph.D. 368-3383, Room WRT300-9, jjm5@cwru.edu

Educational Program Coordinator: Camala Thompson, 368-4617, Room W 321, cami@case.edu

FAX: 368-1300, Room W357

**BIOMEDICAL SCIENCES TRAINING PROGRAM (BSTP)**

Coordinator: Debbie Noureddine 368.3347, Room WG46 drn2@po.cwru.edu

**THE UNIVERSITY**

CWRU Office of Graduate Studies Nord Hall, 6th Floor General Information 368.4390 Fax 368.4250

Provost & Dean of Graduate Studies: Charles Rozek 368.4390

CWRU Registrar 368.4310 Yost Hall Room 110

CWRUnet 368.2982

CWRU Health Service 368.2450 2145 Adelbert Road

CWRU Security - information 368.4630 **EMERGENCY - 368.3333**

**WEBSITES**

Pharmacology http://pharmacology.case.edu

BSTP (Information regarding the Graduate Student Symposium) http://www.case.edu/med/BSTP/index.html

MSTP http://mediswww.meds.case.edu/mstp/

CASE home page
## Sample Planned Program of Study Form (Year 1-2)

https://sis.case.edu/psp/saprd/

Program: Pharmacology (PhD)

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Current Trainers: MTTP

Robert Bonomo, M.D., Professor of Medicine, Pharmacology, and Molecular Biology and Microbiology, Chief of the VA Medical Service, co-Leader of the Translational Therapeutics Track and Member of the Molecular Pharmacology & Cell Regulation Track.

Research in the Bonomo laboratory investigates the molecular and clinical aspects of bacterial resistance to beta lactams antibiotics and beta-lactamase inhibitors. The main areas involve understanding the structure function relationships of the class A beta-lactamases, SHV-1 and KPC-2. These chromosomai and plasmid encoded beta-lactamase confers high level resistance to cephalosporins and carbapenems, which can render ineffective the most frequently used drugs to treat serious nosocomial infections. Dr. Bonomo also has projects studying OXA carbapenemases found in Acinetobacter baumannii, the cephalosporinase of Pseudomonas aeruginosa, the class A beta-lactamase of Mycobacterium tuberculosis, and metallo-beta-lactamase, NDM-1. The lab also is studying the bacterial membrane proteins, transpeptidases and carboxypeptidases, involved in cell wall synthesis. A major effort also involves rapid molecular diagnostics and typing.
Matthias Buck, Ph.D., Associate Professor of Physiology & Biophysics and Pharmacology, Member of the Membrane Structural Biology & Pharmacology Track.

Dr. Buck's research program characterizes the structures and the dynamics of proteins involved in protein-protein interactions with a concentration on the plexin and the Eph-A1 and Eph-B1 transmembrane receptors. Protein interactions determine the basic mechanisms by which proteins transmit signals in cells and how signaling is disrupted by mutation in diseased states. Knowing at near-atomic resolution which residues interact in protein complex formation will allow them to rationalize their interaction affinity and specificity. Furthermore, it will provide an opportunity for them to alter the proteins for diagnostic or therapeutic purposes. Both plexin and Eph receptor systems play critical roles in development of the cardiovascular as well as the nervous system, but also have direct relevance to the progression of cancers, making them a target for drug design.

Mark Chance, Professor and Director of the Center for Proteomics and Bioinformatics, Interim Chair of the Department of Genetics, Vice-Dean for Research, Member of the Membrane Structural Biology & Pharmacology Track.

The research in Dr. Chance's laboratory is focused high throughput methods to identify the structure and function of large macromolecular complexes in areas relevant to iron transport, DNA mismatch repair, and actin filament assembly and the interaction of cytoskeletal proteins and cell structure. The long term goals of the laboratory are focused on understanding the structure and dynamics of these macromolecular assemblies and how the domain structure of proteins allows and directs protein-protein interactions. Biochemical approaches, mass spectrometry, crystallography, cryo-EM, cross-linking, footprinting, and molecular modeling are used to understand the physiologically relevant functional states. Dr. Chance's laboratory also has a program in examining quantitative protein expression changes in cell and tissues, currently funded projects include examination of protein expression changes in type 1 models of diabetic complications, including drug-receptor targeting.

David Danielpour, Ph.D., Associate Professor of General Medical Sciences/Oncology and Pharmacology, Member of the Cancer Therapeutics and Molecular Pharmacology & Cell Regulation Tracks.

The goals of the Danielpour Laboratory are to define the mechanism by which TGF-β functions as a tumor suppressor of the prostate and how such tumor suppression is lost during carcinogenesis of the prostate and progression of prostate cancer from androgen dependence to androgen independence. Their underlying hypothesis is that changes in androgen receptor and PTEN/PI3K/Akt/mTOR signaling pathways that occur during prostate cancer prostate progression promote loss of tumor suppression by TGF-β largely through intercepting Smad3. A variety of approaches are being used to define mechanisms of cross-talk between the above signaling pathways and how they impact on TGF-β-induced growth arrest, apoptosis, tumor suppression and differentiation. Long-term goals of this laboratory are to develop new therapeutic strategies and diagnostic tools for prostate cancer.

Chris Dealwis, Ph.D., Associate Professor, co-Leader of the Membrane Structural Biology & Pharmacology Track.

Nearly every major process in a cell is carried out by a complex assembly of several proteins. The main focus of the lab involves understanding the structural organization requirements by multiple protein assemblies to facilitate biological function. Their approach is to use a multidisciplinary cycle to study the structure-function relationship of proteins. They also use structure-based drug and protein design to develop novel therapeutics against cancer, Alzheimer's disease and microbial infections. These biophysical studies are facilitated by techniques such as X-ray & neutron crystallography; molecular modeling; CD, MS, and fluorescence spectroscopy; and ultracentrifugation.

Clark Distelhorst, M.D., Professor of Medicine and Pharmacology, Member of the Cancer Therapeutics and Translational Therapeutics Tracks.

Glucocorticosteroid hormones such as prednisone and dexamethasone are used in the treatment of virtually all types of lymphoid malignancies, including acute lymphoblastic leukemia, chronic lymphocytic leukemia, cutaneous T cell lymphoma, and non-Hodgkin lymphoma. The Distelhorst laboratory investigates how glucocorticoids induce apoptosis in order to provide novel insight on fundamentally important mechanisms of apoptosis induction. Understanding the mechanisms accounting for apoptosis will allow for the development of
novel therapies to overcome resistance to glucocorticoid-induced death of cancer cells.

George Dubyak, Ph.D., Professor of Physiology & Biophysics and Pharmacology, co-Leader of the Molecular Pharmacology and Cellular Regulation Track; member of the Membrane Structural Biology and Pharmacology Track.

The Dubyak laboratory investigates multiple aspects of extracellular ATP-based signal transduction in three areas: inflammation, anti-tumor immunity, and cardiovascular disease. A major focus is to understand how the P2X7 receptor, an ATP-gated ion channel, triggers the caspase-1-based inflammasome signaling pathways in macrophages and dendritic cells (DCs) which mediate interleukin-1β-based innate and adaptive immune responses. Because IL-1β lacks a signal sequence it is released/exported from macrophages/DCs via non-classical secretory mechanisms, and the lab is studying released exosomes and shed plasma membrane microvesicles as likely mechanisms for this atypical export. Related projects are analyzing how inflammasome-triggered exosomes provide a pathway for the externalization of antigen-loaded MHC-II vesicles as a novel linkage between innate and adaptive immunity. Most recent research on P2X7 receptor activation and mechanisms of IL-1β secretion is linked to exciting new findings which indicate a key role for extracellular ATP, released from apoptotic tumor cells, in the activation of DC/ T lymphocyte paracrine signaling loops that drive anti-tumor immune responses. Additionally, the lab is studying the role of extracellular pyrophosphate (PPI) – which is derived from the hydrolysis of secreted extracellular ATP – as a critical suppressor of the pathological cardiovascular calcification that occurs in chronic kidney failure, diabetes, and aging. These studies are testing the possible role of the recently identified pannexin-family channels as conduits for the efflux of ATP that is coupled to PPI production.

Andreas Engel, Ph.D., Professor of Pharmacology, Member of the Membrane Structural Biology & Pharmacology Track.

Research concerns the structure and function of membrane proteins of different origin. A major effort is invested in the study of aquaglyceroporins and membrane proteins of the visual system. Electron crystallography and atomic force microscopy are used to analyze two-dimensional crystals assembled from membrane proteins and lipids.

Stanton Gerson, M.D., Professor of Medicine, Director of the Comprehensive Cancer Center, Member of the Cancer Therapeutics and Translational Therapeutics Tracks.

Dr. Gerson plays an active role in development of new therapeutics as the Associate Director for Clinical Research. His laboratory studies the role of the DNA repair protein O6 alkylguanine-DNA alkyltransferase (AGT) in mediating resistance to several chemotherapeutic agents, and they have led in the discovery and development of the AGT modulator O₆-benzylguanine as an adjunctive chemotherapeutic agent that enhances the efficacy of DNA alkylating agents. In addition, Dr. Gerson’s group has evaluated methoxyamine, an inhibitor of base excision repair, as a potentiator of methylating agent chemotherapy. Studies completed through the NCIRAID and a planned IND submission to pursue a clinical trial of methoxyamine and temozolomide for refractory solid tumors are aimed at providing the first agent for inhibition of base excision repair as a therapeutic modality in cancer.

Clifford Harding, M.D., Ph.D., Professor and Chair of Pathology, Member of the Membrane Structural Biology & Pharmacology and Translational Therapeutics Tracks.

Dr. Harding’s research is focused on topics in immunology, particularly functions of antigen presenting cells, including: 1. Antigen presentation by MHC molecules. 2. Phagosomal processing of antigens, including MHC-I cross processing mechanisms that contribute to immune responses to tumors and pathogens. 3. Regulation of antigen presenting cells and T cell responses by signaling by Toll-like receptors, including TLR9 and TLR2. 4. Induction of type I interferon by Toll-like receptors, particularly TLR9, and its role in induction of MHC-I cross presentation. 5. Inhibition of type I interferon induction by TLR2 signaling and by CpG-B agonists of TLR9. 6. Antigen presenting cell dysfunction in infection by Mycobacterium tuberculosis or HIV and the roles of abnormal Toll-like receptor or interferon responses in these mechanisms.

Charles Hoppel, M.D., Professor of Pharmacology and Medicine, Chief of Clinical Pharmacology, Direc-
Yoshikazu Imanishi, Ph.D., Assistant Professor of Pharmacology, Member of the Membrane Structural Biology & Pharmacology Track.

The Imanishi lab is focused on localization of proteins and chemical intermediates involved in phototransduction and the visual cycle using modern imaging techniques, such as two-photon microscopy. They are interested in how these highly specialized neurons are formed and maintained, and how the major component of the outer segment, rhodopsin, can contribute to the formation of the photoreceptor outer segments. The maintenances of photoreceptor outer segments are subject to regulation by circadian rhythm; however the underlying mechanism is currently unknown. The interactions between photoreceptors and adjacent Retinal Pigment Epithelial (RPE) cells are required for normal metabolism and maintenance of photoreceptor cells. RPE cells retain unique biological functions; RPE cells are the most active phagocyte throughout the body, and this activity is responsible for the maintenance of photoreceptor outer segments. Current research addresses how the RPE and the photoreceptor communicate with each other to orchestrate the biogenesis and degradation of photoreceptor outer segment structure.

Thomas Kelley, Ph.D., Associate Professor of Pediatrics and Pharmacology, Member of the Molecular Pharmacology & Cell Regulation Track.

The research focus of the Kelley laboratory centers around three areas. (1) Identifying a mechanistic link between the loss of CFTR function and altered cell-signaling control in CF airway epithelial cells - Currently efforts are devoted to examination of the isoprenoid/cholesterol synthesis pathway. (2) Determining cell signaling consequences of impaired intracellular cholesterol transport. These studies focus primarily on elucidating the consequences of lost NPC1 function in Niemann-Pick type C disease, a pediatric neurological disorder. (3) The impact of beta-arrestin protein expression on airway disease. The Kelley group has observed an increase in arrestin protein expression in airway cells in response to lost CFTR function and as a response to obesity. The goals of this study are to examine the mechanisms leading to increased arrestin expression and to determine the impact this signaling on the development of asthma symptoms and responses to corticosteroids and beta-agonists in asthmatics.

Ruth Keri, Ph.D., Associate Professor and Vice Chair of Pharmacology, co-Director of the MTTP, co-Leader of the Cancer Therapeutics Track, member of the Molecular Pharmacology & Cell Regulation Track.

The Keri laboratory is focused on mechanisms of HER21Neu and hormonal induction of mammary tumor formation and progression. This has involved the combined used of functional genomics with multiple strains of genetically altered mice. Primary goals of the laboratory are to identify key genes that are regulated by HER21Neu and mediate the tumorigenic effects of this orphan receptor tyrosine kinase. The protein products of these target genes may then become candidates for therapeutic intervention. One such target is mTOR. The Keri group has recently found that an inhibitor of mTOR action, rapamycin, induces regression of HER21Neu induced mammary tumors in mice. They are currently evaluating the mechanisms for this tumor response as well as examining the impact of rapamycin on metastatic progression.
**Timothy Kern, Ph.D.**, Professor of Medicine, Director of the Center for Diabetes Research, Member of the Translational Therapeutics Track.

The major focus of research in the Kern laboratory is to learn what causes retinopathy in diabetes, and how it can be prevented. Diabetic retinopathy takes many years to develop in most patients, so studies using research animals have been fundamental to present understanding of this problem. The retinal lesions that develop in streptozotocin-diabetic animals are indistinguishable from those that develop in patients, and include microaneurysms, obliterated capillaries, pericyte loss and hemorrhage. The Kern group has also developed a second model of diabetic retinopathy in which blood hexose levels are elevated in nondiabetic animals by feeding the sugar, galactose. These animals develop a retinopathy identical to that which develops in diabetes, indicating that elevated blood hexose is a major cause of diabetic retinopathy. Efforts currently are directed at identifying how hyperglycemia causes retinopathy, so that new, improved treatment may be devised to inhibit the loss of vision in diabetes.

**Gary Landreth, Ph.D.**, Professor of Neurosciences, Member of the Molecular Pharmacology & Cell Regulation and Translational Therapeutics Tracks.

Dr. Landreth’s research program has two distinct areas of interest that are centered on understanding disorders of the nervous system. Alzheimer's disease is the primary focus of work in the laboratory, aimed at understanding how the beta-amyloid peptides are normally cleared from the brain and the roles of inflammation in AD pathogenesis. The lab is also engaged in identification and validation of new therapeutic agents for the treatment of AD. The lab also has a long standing interest in the roles of the ERK MAP kinases in the nervous system, having developed murine lines in which ERK1 and ERK2 have been knocked out. Analysis of these mice have revealed unexpected roles for these enzymes in neural crest development, patterning of the developing brain and corticogenesis. The ERK knockouts phenocopy neuro-cardiofacial cutaneous, DiGeorge and related syndromes, and a subset of autism spectrum disorders that arise from genetic perturbations of the ERKs or their upstream regulators. The goal is to understand the mechanistic basis of these human disorders.

**Irene Lee, Ph.D.**, Associate Professor of Chemistry, Member of the Translational Therapeutics Track

The goal of the Lee research program is to develop chemical strategies to control cell growth. To this end, they propose to develop a therapeutic cocktail containing agents to inhibit both protein degradation and nucleic acid metabolism. To accomplish this, the Lee laboratory has taken a "rational design" approach to study enzymes involved in stress-related protein degradation and nucleic acid metabolism. At present, studies focus on the enzymology of an ATP-dependent protease, Lon, which functions to remove damaged proteins and certain short-lived regulatory nucleic acid binding proteins in cells. In addition, the Lee laboratory is designing and synthesizing non-natural nucleotides to inhibit damaged DNA synthesis mediated by low fidelity polymerases. The overall strategy is to control the growth of an organism by simultaneously inhibiting pathways involved in protein degradation and DNA synthesis.

**John Letterio, M.D.**, Professor of Pediatric Hematology/Oncology, Member of the Cancer Therapeutics and Translational Therapeutics Tracks.

The major focus of the Letterio laboratory is on the discovery of the critical roles of TGF-β in hematopoietic and immune cell function. The prototype of this family, TGF-β1, is expressed by all hematopoietic cell populations, regulates the proliferation and expansion of their progenitors, and plays an important role in controlling various aspects of their development and differentiated functions. Studies with the TGF-β1−/− mouse allowed the Letterio lab to provide the first direct evidence that a TGF-β1-deficiency state predisposes to multiple pathogenic manifestations of autoimmunity. Furthermore, endogenous TG-β 1 controls developmental expression of both class I and class II MHC antigens, a feature that provide a link between aberrant MHC expression and the inflammation and autoimmunity resulting from TGF-β1-deficiency.

**Alan Levine, Ph.D.**, Professor of Pathology and Pharmacology, Member of the Molecular Pharmacology & Cell Regulation Track.

The intestinal mucosa is the largest lymphoid organ, as assessed by antibodies produced, resident leuko-
cytes, and surface area exposure to the environment. Furthermore, the wall of the intestine is continuously bathed by bacteria, parasites, fungi, amoebae, viruses, mitogens, toxins, and immunogenic food proteins. Therefore, a complex multi-tiered host defense system has evolved in the intestine, involving barrier exclusion by an actively regenerating epithelial cell monolayer, innate inflammatory responses mediated by local synthesis of pro- and anti-inflammatory cytokines, and acquired immune responses regulated by T lymphocytes. The Levine laboratory focuses on the mechanisms that regulate these systems: (1) temporal expression and regulation of pro-inflammatory and anti-inflammatory cytokines and immunoregulatory mediators in response to mucosal inflammation; (2) mechanisms by which co-stimulatory molecules and environmental stimuli direct the development of immune tolerance; (3) biochemical, spatial, temporal, and structural organization of the signal transduction pathway initiating with the anti-specific T cell receptor, and differentially regulated in naive, helper, effector, and mucosal T cells; (4) regulation of integrin affinity/avidity, expression, and activation in both naive and memory T cells by the interstitial extracellular matrix; (5) evaluation of a gene targeted murine model of colitis-associated colorectal cancer; and (6) mechanisms for increased intestinal permeability induced by HIV infection and/or exposure to drugs of abuse, such as opioids, methamphetamine, and cocaine.

**Paul MacDonald, Ph.D.,**Associate Professor of Pharmacology, Member of the Molecular Pharmacology & Cell Regulation and Cancer Therapeutics Tracks

Vitamin D (Vit D) is required for normal calcium and phosphorus homeostasis and it is essential for the proper development and maintenance of bone. Vit D also exerts profound effects on cellular proliferation and differentiation, effectively inhibiting the proliferation of many tumor-derived, malignant cell lines. The vitamin D endocrine system also profoundly influences normal keratinocyte function and is protective against chemically-induced skin tumorigenesis. The mechanisms underlying its tumor protective and antiproliferative roles are currently unknown. The biological effects of vit D are mediated through a nuclear protein termed the vitamin D receptor, or VDR. The VDR is a member of the superfamily of nuclear receptors that function as ligand-activated transcription factors. Thus, vit D and VDR together regulate the expression of specific genes or gene networks in classic target organs such as the intestine, bone, and skin. The global objective of the MacDonald laboratory is to understand the molecular details and signaling mechanisms involved in VDR-mediated gene expression. The current focus is on in vivo and in vitro models of bone and skin to understand the gene networks that are involved in vit D effects on bone development and skin tumorigenesis.

**Danny Manor, Ph.D.,**Associate Professor of Nutrition and Pharmacology, Member of the Molecular Pharmacology & Cell Regulation and Cancer Therapeutics Tracks.

Dr. Manor’s research team aims to gain molecular-level answers to basic questions that surround the etiology, treatment and prevention of cancer. Their research interests can be divided into two areas: (1) understanding the signal transduction pathways that regulate normal cell growth and that are disrupted by oncogenic mutations; and (2) understanding the molecular mechanisms by which some chemo-preventative agents offer protection from cancer (‘molecular prevention’). Specific questions that are currently addressed include the mechanisms that regulate the small GTPases, Rac, Rho and Cdc42, and their exchange factors, the roles of reactive oxygen species in mitogenesis and cancer, and the regulation of antioxidant status.

**Shigemi Matsuyama, Ph.D.,**Assistant Professor of Medicine-Hematology/Oncology, Member of the Cancer Therapeutics Track.

Dr. Matsuyama studies (1) the molecular mechanism of programmed cell death, and (2) the development of a drug-delivery system using cell penetrating peptides. His group found that Ku70 keeps Bax (a key protein inducing apoptosis) in an inactive form in non-apoptotic cells, and that the dissociation of Bax from Ku70 is required for Bax-mediated apoptosis. Ku70 is a ubiquitously expressed protein that has been known to play an important role for double strand DNA break repair. Dr. Matsuyama’s laboratory is investigating how apoptotic stress such as DNA damage modifies Ku70’s activity to regulate Bax activity. The understanding of the mechanism of Ku70 modification will contribute to understanding apoptosis-resistance mechanisms of cancer cells. Dr. Matsuyama’s laboratory found a new series of cell permeable pentapeptides and is investigating the mechanism of membrane penetration by these pentapeptides, and the potential application of these peptides for drug delivery into cells.
Within eukaryotic cells, mitochondria continually divide and fuse. Defects in these processes are associated with an increasing number of human diseases, including cancer, neurodegeneration and aging. Research in the Mears lab is focused on understanding of the cellular machinery that regulates mitochondrial dynamics in yeast and mammalian cells. They use cryo-electron microscopy along with biochemical and computational methods to elucidate the structural and mechanistic roles of proteins in the eukaryotic fission machinery.

John Mieyal, Ph.D., Professor and Vice-Chair of Pharmacology, Director of the MTTP, Member of the Molecular Pharmacology & Cell Regulation and Translational Therapeutics Tracks.

Reactive oxygen species (ROS) play an important role as second messengers to transduce intracellular signals from hormones, cytokines and growth factors that interact with membrane-associated cell surface receptors. However, little is understood about how ROS selectively modify signaling molecules and influence their activation or deactivation, inter-protein interactions, and translocation to the nucleus. Integral to these processes is reversible S-glutathionylation of cysteine residues on specific proteins. Many diseases, including cardiovascular and neurodegenerative diseases, cancer, diabetes, and AIDS, involve oxidative stress conditions that likely disrupt normal redox signaling and alter the balance between cell survival and cell death. The Mieyal lab studies the enzymatic mechanisms of reversible glutathionylation, aimed at understanding how these reactions link extracellular stimuli to downstream cellular events in health and disease. Current research is focused on models of Parkinson’s disease to discover alternative therapeutic approaches.

Vera Moiseenkova-Bell, Ph.D., Assistant Professor of Pharmacology, Member of the Membrane Structural Biology & Pharmacology Track.

Pain is a serious public health issue that affects up to 20% of the human population at any time. Ion channels are integral membrane proteins that regulate the flow of ions across cellular plasma membranes in response to a variety of stimuli. The Moiseenkova-Bell laboratory is interested in structural and functional analysis of ion channels which are involved in pain and temperature sensation. The key question in understanding ion channel function is how do the protein domains that respond to stimuli communicate with the pore gates to mediate channel opening. Multiple approaches are used, including biochemistry, electrophysiology, X-ray crystallography and single-particle cryo-electron microscopy (cryo-EM) to elucidate activation and gating mechanism of these channels.

Monica Montano, Ph.D., Associate Professor of Pharmacology, co-Leader of the Molecular Pharmacology & Cell Regulation Track and member of the Cancer Therapeutics Track.

The Montano lab studies the role of estrogens in mammary tumorigenesis and the involvement of estrogen receptor (ER) dependent and ER independent pathways. Breast tumor initiation has been proposed to be due to DNA damage attributable to a combination of estrogen metabolism and preexisting lesions. The lab has found that quinone reductase (QR) and ERₙ inhibit estrogen-induced DNA damage and breast cell transformation. Based on these findings it is proposed that QR plays a role in mediating the prevention of breast cancer by antiestrogens such as tamoxifen. Another focus is a novel tumor suppressor cloned in the Montano laboratory, hexamethylene-bis-acetamide-inducible protein 1 (HEXIM1). Animal models have been generated that support the role of HEXIM1 as a tumor suppressor and anti-angiogenic factor. We have also defined the mechanistic basis for HEXIM1 regulation of mammary gland tumorigenesis/angiogenesis.

Marvin Nieman, Ph.D., Assistant Professor of Pharmacology, co-Leader of the Translational Therapeutics Track.

The underlying research theme of the Nieman lab is that protease activated receptor (PAR) subtypes interact with one another to mediate the full range of thrombin signaling for activation of platelets, endothelial cells and mononuclear cells. Thrombin is the terminal enzyme in the clotting cascade that activates cells by cleaving PARs. PAR1 and PAR4 interact on the platelet surface and PAR1 enhances PAR4 activation ~10-fold by serving as a cofactor. In other tissues and cell types, PAR1 interacts with and transactivates PAR2. Therefore, studies examining thrombin signaling must take into account contributions of other PARs expressed by the cells of interest. The Nieman lab uses a combination of enzyme kinetics, resonance energy transfer, cell
based assays with cell lines and freshly isolated human and mouse platelets as well as animal models to examine the influence of the interaction of PAR subtypes on thrombin signaling with the aim of discovering new therapeutic approaches to controlling blood clotting.

**Noa Noy, Ph.D.**, Professor of Pharmacology, Member of the Molecular Pharmacology & Cell Regulation and Cancer Therapeutics Tracks.

Lipophilic hormones, such as retinoic acids, vitamin D, and derivatives of long chain fatty acids, control multiple biological processes both in the embryo and in the adult. These activities are exerted through the ability of these compounds to regulate gene expression, and are mediated by two classes of proteins: the ligand-inducible transcription factors termed nuclear hormone receptors, and members of the family of intracellular lipid-binding proteins. The Noy laboratory aims to understand the molecular mechanisms by which the transcriptional activities of lipophilic hormones (e.g., retinoic acid) are regulated, to map the gene networks that mediate the biological activities of specific hormones and their cognate receptors; and to link these molecular foundations to the functional consequences of receptor activities in health and in disease states.

**Krzysztof Palczewski, Ph.D.**, Professor and Chair of Pharmacology, Co-Director of the MTTP, and Member of the Membrane Structural Biology & Pharmacology and Translational Therapeutics Tracks.

The light-sensing apparatus of the eye is found within the rods and cones - two types of specialized cells located in the posterior of the retina. Many unresolved issues relevant to phototransduction, light- and dark-adaptation, and the chemical processing of retinoid cycle intermediates remain unanswered, including the enzymology of the retinoid cycle, the mechanisms by which these intermediates diffuse within and between the photoreceptors and the retinal pigment epithelium, and the dependence of phototransduction reactions on the operation of the cycle. The goals of Professor Palczewski's laboratory are to a) understand the biochemical basis underlying the mechanism of rhodopsin inactivation and restoration of the cGMP level; b) delineate the biochemical basis underpinning the similarities and differences between rod and cone cell phototransduction; and c) understand the enzymology of the isomerization of all-trans-retinol to 11-cis-retinol in the retina. Knowledge about phototransduction in the retina, a system with great experimental advantages, will improve further understanding of similar events in hormonal signaling, cellular communication and immune regulation, and provide fundamental information for therapeutic interventions and further studies of retinal disease processes.

**Paul Park, Ph.D.**, Assistant Professor of Ophthalmology and Pharmacology, Member of the Molecular Pharmacology & Cell Regulation and Membrane Structural Biology & Pharmacology Tracks.

The goal of the Park laboratory is to understand the mechanisms of signal transmission at the molecular level in phototransduction and other G protein-coupled receptor-mediated signaling systems. The specific aims of the research include: 1) to test the validity of assumptions in classical schemes of signaling and to explore more recent paradigms of signal transmission; 2) develop and characterize methodologies to detect and monitor molecular interactions involving receptors; 3) develop and characterize tools that will allow for live cell and/or in vivo monitoring of signaling events; 4) to understand at a molecular level how mutations in rhodopsin lead to vision-related disorders. The Park lab uses modern biophysical approaches to tackle these issues, including atomic force microscopy (AFM), single-molecule force spectroscopy (SMFS), and fluorescence-based methods.

**Irina Pikuleva, Ph.D.**, Professor of Ophthalmology and Pharmacology, Member of the Molecular Pharmacology & Cell Regulation and Membrane Structural Biology & Pharmacology Tracks.

Cholesterol is essential for life in mammals. However, if chronically in excess, it becomes a risk factor for cardiovascular and Alzheimer’s diseases, and possibly age-related macular degeneration. The focus of this laboratory is on the four cytochrome P450 enzymes 7A1, 27A1, 46A1, and 11A1 that are necessary for cholesterol elimination from different organs. They are striving to understand how cholesterol-metabolizing P450s function at the molecular level, what roles they play in the development of different diseases, and whether these enzymes could serve as targets for cholesterol lowering medications. One of the current projects is based on previous structural and biochemical studies of CYP46A1, showing that the enzyme active site is conformationally flexible and can accommodate ligands other than sterols. The goal of this project is to identify market-
ed drugs that can either inhibit or stimulate the CYP46A1-mediated cholesterol hydroxylation in vivo. Another project is focused on understanding how deactivation of the CYP27A1 enzyme under oxidative-stress may alter cholesterol metabolism and contribute to age-dependent macular degeneration. In pursuit of these goals, the lab uses in-silico and in vitro screening of drug libraries, X-ray crystallography, mass spectrometry, and tests on animals.

**Shasta Sabo, Ph.D., Assistant Professor of Pharmacology, Member of the Molecular Pharmacology & Cell Regulation Track.**

Formation of synapses between CNS neurons is a complex process that establishes the circuits that govern perception and behavior. Despite the importance of proper synapse formation for brain development and function, fundamental questions about the mechanisms of CNS synaptogenesis remain unanswered. For example, Dr. Sabo's research aims to address the following questions, using sophisticated electrophysiologic and imaging techniques. How are the protein complexes and specialized membrane domains critical for synaptic transmission assembled at the right place and at the right time? Which proteins are essential for synapse development? How are pre- and post-synaptic assembly coordinated? Are the mechanisms of excitatory and inhibitory synapse formation similar? How is the balance of excitatory and inhibitory inputs onto a neuron controlled?

**William Schiemann, Ph.D., Associate Professor of Oncology, Leader of the Breast Cancer Program of the Case Comprehensive Cancer Center, co-Leader of the Cancer Therapeutics Track.**

Tumorigenesis elicits changes in the TGF-beta signaling pathway that engenders resistance to the normally cytostatic activities of TGF-beta, thereby enhancing the development and progression of human malignancies. These genetic and epigenetic events convert TGF-beta from a suppressor of tumor formation to a promoter of their growth, invasion and metastasis. The dichotomous nature of TGF-beta during tumorigenesis is known as the "TGF-beta paradox." Dr. Schiemann's research aims to understand the molecular mechanisms underlying the "TGF-beta Paradox" – likely the most important unanswered question concerning the pathophysiological functions of this multifunctional cytokine in regulating mammary tumorigenesis. Particular focus is on the initiation of metastasis and disease recurrence. The Schiemann group has made numerous and highly significant contributions toward answering this important question, and in doing so, has established new insights into the molecular mechanisms underlying the TGF-beta Paradox and its ability to influence the response of normal and malignant mammary tissues to TGF-beta.

**Phoebe Stewart, Ph.D., Professor of Pharmacology, Director of the Cleveland Center for Membrane and Structural Biology, Member of the Membrane and Structural Biology and Pharmacology Track.**

Cryo-electron microscopy (cryo-EM) plays a central role in hybrid methods to determine structures of membrane proteins and large complexes in multiple conformations without the need for crystals. Docking of atomic resolution structures and computational models into cryo-EM density maps can provide insight at the near-atomic level. The Stewart lab is applying cryo-EM structural methods to a variety of adenovirus/host factor complexes, including defensin and coagulation Factor X. Adenovirus is a common human pathogen, but non-virulent forms have shown great potential for gene delivery and vaccination strategies. When adenovirus is injected intravenously, however, it induces potent innate immune and inflammatory responses, the molecular basis for which remains poorly characterized. Human defensin 5 is a peptide from the innate immune system that blocks viral cell entry. Factor X plays a role in the blood coagulation cascade and leads to highly efficient adenoviral infection of hepatocytes. Thus, elucidating the molecular interactions of these key adenoviral complexes is expected to lead to improved therapeutic approaches with adenoviral vectors. In addition, the Stewart group is studying protein/DNA complexes involved in nonhomologous end joining (NHEJ) and in maintenance of circadian rhythm. DNA damage is a natural occurrence, but if the damage is not repaired correctly, genetic instability may result and lead to cancer or cell death. The human DNA-PKcs enzyme mitigates oncogenesis through NHEJ repair of double strand DNA breaks. Circadian rhythms impact cellular and organismal physiology, regulating sleep cycles, as well as hormone and metabolic activities. In both the DNA repair and circadian rhythm systems, cryo-EM provides a way to study the structure of large and conformationally flexible complexes.
**Derek Taylor, Ph.D.**, Assistant Professor of Pharmacology, Director of MTTP Admissions, Member of the Membrane and Structural Biology and Pharmacology Track

Regulation and deregulation of gene expression are critical events for every process within the cell. Alteration of these intricate processes, for example as consequences of genetic defects or bacterial/viral infections, can readily lead to one of many human ailments. The control of these processes is commonly modulated by multi-protein complexes; in fact, proteins rarely act alone, but interact intimately and precisely with other proteins and nucleic acids to properly perform their cellular functions. The Taylor laboratory studies the structure and molecular mechanisms of macromolecular machines involved in DNA maintenance and RNA maturation and biogenesis. They use cryo-electron microscopy and single particle reconstruction techniques as primary tools for visualizing the macromolecular complexes in order to better understand their functions.

**Gregory Tochtrop, Ph.D.**, Assistant Professor of Chemistry and Pharmacology, Member of the Translational Therapeutics Track.

Most biological events emanate from the inherently chemical process of a small molecule being recognized by a large biological polymer. Research projects in the lab are designed to push back the boundaries of the tools used to monitor protein small molecule interactions. This work spans from pure synthetic organic chemistry to quantitative biochemical. For example, the pool of bile acids in the human body is chemically heterogeneous, consisting of at least 100 distinct members. One of the major interactions responsible for bile acid homeostasis (and consequently cholesterol homeostasis) is their recognition by the nuclear receptor FXR. The experimental approach involves synthesis of $^{13}$C and $^{15}$N isotopically enriched bile acids and monitoring recognition, segregation, and competition, using NMR to detect single bile acids in complex mixtures and understand their effects on the transcription of FXR gene products. Also, the Tochtrop group anticipates generating skeletal diversity through chemistries that 'reorganize' the carbon skeletons of complex natural products into novel molecules. Cleavage of the B-C unsaturated ring fusion of lanosterol is a prime example of this strategy. Here, oxidative cleavage of the unsaturated ring fusion followed by transannular addition or full condensation affords diverse skeletons depending partly on the oxidation state of carbons C-7 and C-11. These molecules are used to probe biological systems using a 'chemical genetic' approach.

**Focco van den Akker, Ph.D.**, Associate Professor of Biochemistry, Member of the Membrane Structural Biology & Pharmacology Track.

The overall goal of research in the van den Akker lab is to elucidate the molecular intricacies of mechanisms of enzyme catalysis and receptor activation, and using that knowledge to develop inhibitors and activators for pharmaceutical purposes. Projects range from cell signaling proteins such as guanylyl cyclases (blood pressure, vision, and bone growth) to beta-lactamases (responsible for the current epidemic antibiotic resistance). The lab group employs state of the art multi-disciplinary biophysical, biochemical, crystallographic, molecular biology, and cell biology techniques.

**Johannes von Lintig, Ph.D.**, Associate Professor of Pharmacology, Member of the Molecular Pharmacology & Cell Regulation Track.

Carotenoids affect a rich variety of physiological processes in nature and are beneficial for human health, serving as free radical scavengers and filters of phototoxic blue light. These isoprenoid pigments also serve as precursors for retinoids (vitamin A and its derivatives) that are essential for vision, cell proliferation, and embryonic development. Recently, molecular players in this pathway have been identified and biochemically characterized. Mutations in the corresponding genes induce various pathologies in humans, including blindness and the fatal Matthew Wood syndrome. The von Lintig research group has established homologous animal models to study the mechanistic basis of these diseases. The biological studies are accompanied by in vitro structure/function analyses of key proteins of these pathways. By defining a detailed molecular framework of carotenoid metabolism in health and disease, the research team believes that improved pharmacological agents can be designed and developed to combat and prevent diseases associated with carotenoid metabolism.

**Bingcheng Wang, Ph.D.**, Professor of Medicine-Nephrology and Pharmacology, Member of the Cancer Therapeutics and Translational Therapeutics Tracks.
The Wang laboratory is interested in the molecular mechanisms driving invasive and metastatic tumor progression responsible for most cancer-related mortality. Their research is focused on Eph receptor tyrosine kinases that have been known as essential guidance molecules of cell migration during embryonic development. Studies in the Wang laboratory demonstrate that Eph kinases also critically regulate tumor cell migration and invasion via crosstalk with integrins, Ras/ERK and PI3K/Akt pathways (Nature Cell Biology 3:527, 2001; Cancer Cell 16:9, 2009). The mechanistic insights laid a foundation for the ongoing translational research devoted to the isolation and characterization of small molecules targeting Eph kinases. Multiple lead compounds have been found that could bind Eph kinases and inhibit both Ras/ERK and PI3K/Akt signaling cascades. Preclinical studies are underway to develop the lead compounds into novel therapeutics against tumor dissemination using mouse models of glioma and prostate cancer.

**Sichun Yang, Ph.D.,** Assistant Professor, Center for Proteomics & Informatics and Pharmacology, Member of the Membrane Structural Biology & Pharmacology and Translational Therapeutics Tracks.

The research in Dr. Yang’s lab is focused on the structure and function of nuclear estrogen receptors (ERs), which are therapeutic targets for the treatment of ER-positive breast cancers. They use an integrated approach, combining computer simulations and X-ray scattering for characterizing ER multidomain assembly. The aim is to determine the overall three-dimensional architecture of ERs and use this structural information to predict new binding sites for novel compounds that can be used for hormone replacement therapy. The long-term goals in Dr. Yang’s lab include the development and application of a conformation-based screening technique for selecting ER-specific agents that may serve novel therapeutic approaches to targeting ER-positive breast cancers.

**Vivien Yee, Ph.D.** Associate Professor of Biochemistry, Member of the Membrane Structural Biology & Pharmacology Track.

Dr. Yee’s laboratory uses X-ray crystallographic methods to determine and analyze the structures of medically important proteins and enzymes with interesting mechanistic questions. Her laboratory combines crystallography with modeling and mutagenesis to study several systems. The first of these focuses on serine proteases which are central in blood coagulation, where their interest is in enzyme-peptide substrate structures, to provide insight into the effect of clinically relevant polymorphisms and into substrate recognition. They are also studying the prion protein, which is implicated in an intriguing family of neurological diseases, the spongiform encephalopathies. Prion protein structures may be helpful in understanding the structural transformation of the protein that is believed to be a key event in the disease. The Yee group is also investigating the 1.2 million Dalton transcarboxylase multienzyme complex. Structures of its large 5s and 12s catalytic subunits serve as models for related mammalian metabolic enzymes, and facilitate speculation on catalytic mechanisms and structural consequences of disease mutations. In collaboration with the Maguire laboratory, studies are under way on the structure of the CorA Mg$^{2+}$ channel, specifically to determine the structure of the open form of the channel and the structure of CorA homologs.

**Youwei Zhang, Ph.D.** Assistant Professor of Pharmacology, Member of the Cancer Therapeutics Track.

Eukaryotic cells have evolved an elaborate network of genome surveillance and repair machinery to insure that DNA replication occurs in an accurate and timely fashion. This surveillance mechanism is termed the S-phase replication checkpoint. The replication checkpoint monitors the progress of replication forks, and when the fork stalls, transmits signals that delay S-phase progression, and maintain the stability of stalled forks so that DNA replication can resume after the initial error is corrected. Two key components of the replication checkpoint are the apical protein kinase, ATR, and its downstream target kinase, Chk1. Replicative stress induces activation of ATR, which then induces activation of Chk1 through phosphorylation at Ser317 and Ser345. Activated Chk1 will activate a cascade of downstream effectors, which will eventually induce cell cycle arrest and damage repair to maintain cell survival, or cell death if the damage is too severe to be repaired. Dr. Zhang’s research group is interested in dissecting the detailed molecular mechanisms underlying the activation of the replication checkpoint, and translating that knowledge into potential anticancer treatment.
Department of Pharmacology

School of Medicine
Case Western Reserve University
School of Medicine - W321
10900 Euclid Avenue
Cleveland, OH 44106-4965

216-368-4617
216-368-1300 FAX

On the web: http://pharmacology.cwru.edu