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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 which is partially funded 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 2008-2009 academic year and beyond. Students who began prior to 2008 are expected to follow the guidelines that were in effect during the year they began.

Revising this Handbook is a continuous process, and so comments are always welcome.
Cami Thompson
2008

OVERVIEW OF THE DEPARTMENT

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 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, while the 1998 Nobel Prize in Physiology or Medicine was awarded to alum Ferid Murad, M.D., Ph.D., recognizing his discovery of the role of nitric oxide 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 Dr. Kris Palczewski 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. Thus, our research focuses on the future. From bioorganic chemistry and molecular biology to signal transduction and the cell biology of cytoskeletal assembly, the Department of Pharmacology provides a scholarly continuum that uses an understanding of molecular interactions 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 is available at the departmental website, http://pharmacology.case.edu

Current Departmental Information:

There are 18 faculty members in the Department of Pharmacology. Currently the faculty are distributed throughout the School of Medicine and the Biomedical Research Building. Important contacts:
Chairperson: Dr. Krzysztof Palczewski
Vice- Chair and Graduate Program Director: Dr. John Mieyal
Graduate Studies Coordinator: Cami Thompson
Executive Assistant to the Chair: Vida Tripodo
Departmental Business Manager: Vicki Grace
Accounts Payable: Ivona Golczak
Information Technology: Barry Lukoff

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 currently undergoing renovations. Some highlights include 90 benches and 14 newly remodeled offices. In addition, there are break rooms and state of the art audiovisuals in meeting and presentation rooms.

The purpose of the renovation has been to provide the faculty and students more bench spaces as well as a modernized working environment. Brighter lights, electronic LCD displays, artwork, and new furniture all contribute to a renewed atmosphere.

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 (150,000 sq. ft.) located immediately 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 and the Center for Membrane Biology and Center for Mitochondrial Diseases associated with the Department of Pharmacology, include facilities for two-photon laser microscopy, Q-TOF mass spectrometry, and high resolution electron microscopy. The Proteomics and Mass Spectrometry Center 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 6190-5/02), staffed and equipped 42,000 sq. ft. Animal Facility is located within the SOM. The staff includes three full-time veterinarians. Complete renovation and expansion of this facility is nearly complete. Animals are housed in a 24 hour dark DCM conventional and Specific Pathogen Free (SPF) rooms equipped with bench space w/hood and thorn rack system. The Wolstein Research Building also houses a state-of -the-art animal facility.. School of Medicine transgenic facilities reside within the Wolstein Animal Resource Center and an Athymic Animal facility resides within the Ireland Cancer Center adjacent to the SOM.

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 is provided by Barry Lukoff, a dedicated IT specialist within the Department.

Office: The Pharmacology Office is located in the School of Medicine – Wood building. The newly constructed office in W321 is furnished with copy, fax, and scanner facilities, and features a departmental mail center. It's also the location of 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 Centers for Membrane Biology and Mitochondrial Diseases. The Department has approximately 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 spectrophotometers, and cell culture facilities.

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 several small meeting room available for conferences.

Cleveland Center for Structural Biology: Collaborative venture between The Cleveland Clinic Foundation & CWRU School of Medicine, the Center provides access to sophisticated high-resolution NMR and Raman spectroscopic and X-ray crystallographic facilities at various sites on and near the CWRU campus, including the first 900 MHz NMR Facility in the State of Ohio. These facilities are being complimented by planned acquisitions associated with development of the **Center for Membrane Biology**, affiliated with the Department of Pharmacology.

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. This affiliation provides access to all of the CCC facilities at CWRU SOM, University Hospitals and at the Cleveland Clinic. A full list of 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.

Cancer Pharmacology Core Facility (*Director: Yan Xu, Professor 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 Veiql, 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 and Histology (*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 microdissection of tumor tissue. Expert consultation is also available.

Cytometry Core Facility (*Director: James Jacobsberqer, Ph.D.*) - The Cytometry core provides flow and image cytometry and cell sorting instrumentation, expertise, training, consultation, and services to Cancer Center investigators. The Core Facility strives to ensure the quality of the data, assist with experimental 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 educational as well as social interactions on a monthly basis, and the Annual Departmental Retreat that showcases the scientific accomplishments of the entire program and brings the community of faculty, students and research 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 and the Departmental Journal Club, both of 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 presented below. **New students are encouraged to reach out to advanced students in the Program. *The listing of requirements and expectations that are detailed below may seem daunting at times, but the 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 2008-2009 academic year is $23,500. 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 resources.

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 2008-2009 is $1242.00. Tuition for MTTP graduate students is funded by NIH institutional training grants 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 existence

If students are on a training grant, they should look into the tax implications of that income and consider making quarterly tax payments. See link: http://www.irs.gov/individuals/students/index.html

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 at least 1 credit hour, there will be no fee for health service. If, however, you do not register for at least 1 credit hour, 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 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\uhs.html. A proof of insurance card is available at Health Services and is highly recommended.

Registration

Pre-registration for the fall is held in April and for spring 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.

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. ***Cami Thompson*** *will send out student registration recommendations prior to registration. All electives need to be approved by* ***Dr. John Mieyal*****.**

Registration. There is a new way to register for classes beginning with Summer and Fall '08. New registration tools are being implemented university-wide on a rolling basis. **This leading edge technology is replacing the SOLAR pin registration system.**

The Student Information System is accessible at http://www.case.edu/erp/sis. All errors with this system should be directed to erpsis@case.edu and provide details on the nature of the error.

Once students are logged in they will need to agree to the confidentiality agreement by clicking a check box. The Student Center will then appear. For more detailed instructions on registering please visit 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 have a formal Planned Program of Study. At the latest, doctoral students must submit a Planned Program of Study to the Graduate Studies Office, when advancing to candidacy. At the latest, Master's students must submit a Planned Program of Study when applying for graduation. When advancing to candidacy after the Prelim I exam, doctoral students must prepare a Planned Program of Study in consultation with the Graduate Program Administrator Cami Thompson. After the faculty advisor, program director, and the department chairperson have approved the Program of Study, it must be submitted to the dean of graduate studies electronically. Subsequent changes to the Program of Study are submitted according to the same procedure. A program of study should include appropriate courses totaling 24 credit hr. corresponding to graded credits, together with work on the doctoral dissertation (minimum of 18 credit hr). See typical curriculum (below).

The new PeopleSoft Student Information System includes an electronic process for degree audit and PPOS approval. Students submit the PPOS electronically through the system, and advisers and Graduate Studies approve them electronically as well. In addition, there is an internal paper-based PPOS that needs to be filled out for the Department of Pharmacology. This form helps organize graded course credits, and credits for courses that are evaluated on a satisfactory/unsatisfactory basis.

Monitoring student progress.

The two major mechanisms to monitor student progress in the MTTP are the individual Thesis Committees and the MTTP Steering Committee. These committees are applicable for Ph.D. students and for students in the M.S. plan B (thesis).

Thesis Committee Meetings

Thesis Committees comprised as described below and 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 constituted by the student and thesis advisor in consultation with the Director of the MTTP. 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 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, advise on alternative approaches, or approve any 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 month that were agreed upon at the committee meeting. The Report is finalized by the thesis committee chair in consultation with the other committee members, and then it 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 thesis committee.

Steering Committee

One of the primary responsibilities of the MTTP Steering Committee (comprised of the MTTP Director and the Leaders 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 co-Leaders of the Advanced Training Tracks to procure evaluations of students in the Track from the respective faculty mentors. 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, annual 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. On the basis of these reviews, students may be recognized for their accomplishments in the form of a letter from the Committee. One model student is chosen each year to receive the Graduate Student of the Year Award that is presented at the Departmental Retreat. Deficiencies in individual student progress are also identified and action plans are agreed upon to help the student overcome the deficiency. In some cases, after formal consultation between the graduate student and the Steering Committee, a student may be placed on 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. In other cases, even with frequent intervention of the Thesis Committee and/or the Steering Committee, the student is not able of fulfill the requirements of the MTTP. 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 privately to assess the basis and seek a resolution, which may include transfer to another laboratory or discontinuation in the Program.

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.

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. This organization offers a forum for the 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 the teaching of pharmacological principles to dental and medical students, To recognize the importance of dialog between the students and faculty on programmatic issues, the MTTP Steering Committee has been reconstituted to include 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 monthly basis, and maintaining direct access to the governance of the Program via the Steering Committee*.

GSO Officers, 2008-2009

President	Kevin Eng	kte3@case.edu	(216) 368-5116
Vice President, President-Elect	Phillip Keiser	pdk7@case.edu	(216) 368-1284
Social Committee	Tonibelle Gatbonton	tonibelle.gatbonton@case.edu	(216) 368-4617
	Eric Lam	eric.lam@case.edu	(216) 368-5290
Graduate Student Senate	Chris Ryder	Christopher.ryder@cae.edu	(216) 368-1191
	Alex Veenstra	alexander.veenstra@case.edu	
Student Seminar	Shalini Jha	shalini.jha@case.edu	(216) 368-3337
	Wannarasmi Ketchart	wannarasmi.ketchart@case.edu	(216) 368-5126
Faculty Sponsor	Dr. John J Mieyal	john.mieyal@case.edu	(216) 368-3383

GSO Officers, 2007-2008

President	Reema S Wahdan-Alaswad	rsw15@case.edu	(216) 368-5671
Vice President, President-Elect	Kevin Eng	kte3@case.edu	(216) 368-5116
Social Committee	Jen Leising	jennifer.leising@case.edu	(216) 368-5671
	Eric Lam	eric.lam@case.edu	(216) 368-5290

Graduate Student Senate	Tonibelle Gatbonton Alex Veenstra	tonibelle.gatbonton@case.edu alexander.veenstra@case.edu	(216) 368-4617
Student Seminar	Phillip Keiser Vivian Gama	pdk7@case.edu vxg33@case.edu	(216) 368-1284 (216) 368-5845
Biomed Grad Student Symposium (BGSS)	Elizabeth Sabens Gina Bernardo	eas30@case.edu gina.bernardo@case.edu	(216) 368-3384 (216) 368-5924
Faculty Sponsor	Dr. John J Mieyal	john.mieyal@case.edu	(216) 368-3383

Seminar Programs/Lectures

Weekly Seminar Series in MTTP:

- Weekly seminar series of current topics of interest in the pharmacological sciences. All MTTP students are required to attend the weekly seminars offered by the Department.

- Seminars are arranged according to faculty recommendations and student recommendations. Student invites are handled by the GSO. Students may invite as many seminar speakers as the seminar schedule will allow. The rationale for student invited speakers is that it encourages the engagement of the students, the speakers are honored by student-initiated invitations. and these interactions are an important part of the training program, expanding the students' awareness beyond CWRU. Pharmacology Seminar meets every Tuesday at 12 noon in room W331.

Weekly Journal Club*:*

- Students, postdoctoral fellows and faculty 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, attendees are expected to read selected papers in advance of the meeting. Students are also encouraged to participate in journal clubs sponsored by other BSTP programs. Pharmacology Journal Club meets every Thursday at 3pm in room W331.

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.

Robert and Himan Sternlicht Memorial Lectureship in Cancer Biology and Pharmacology:

- This annual lectureship was originally set up 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., long-term member of

the Faculty of Pharmacology, also died of cancer and the family has renamed the lectureship to include him.

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.

SURP Seminar Series:

- The Summer Undergraduate Research Program (SURP) is designed to introduce college students to basic laboratory research and scholarly investigation. Its primary aim 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 consider a research career in basic science in general, and in pharmacology in particular. Informal presentation/discussion sessions between selected graduate students and postdocs and the undergraduate researchers are held weekly during the summer. The focus of these sessions is on the early phases of commitment to a career in science, both the excitement and the challenges. At the end of the summer the undergraduate participants present seminars on their summer research projects.

Other Departmental Events

Annually

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

BSTP Graduate Student Orientation – The Chairman of Pharmacology and/or the MTTP Program Director, along with GSO officers, meets with the first year BSTP students early in the Fall Semester to provide an overview of the Department and the Program, and to invite students to visit posters representing the research of MTTP trainers and their students.

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

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. Since 1998, the Department has held an annual scientific retreat. This event is held off-campus and typically is scheduled for two days. The purpose of the retreat is fourfold. First, it provides a training opportunity for students and post-doctoral fellows. Secondly, it fosters collaborative interactions and unity among departmental members and secondary faculty. Thirdly, it provides a unique opportunity for the entire Department to participate in workshops on leadership, mentoring and other Departmental initiatives. Fourthly, it showcases the Department to potential benefactors. Each year, all Pharmacology graduate students and post-doctoral fellows are invited to present 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. During these scientific presentations, every effort is made to simulate a national/international professional meeting environment. Although all faculty attend the retreat, the focus of this event is on the work that the students have accomplished. Therefore, as a general rule, faculty 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 mix-

ture of faculty and students). These individuals are responsible for assuring that the presenters receive at least a few questions following their talks, and for guiding discussion as necessary. *This opportunity to present to the entire department (approximately 100 people in attendance) provides an important training experience for the students and post-docs because it gives them practice in presenting and fielding questions related to their work. They also receive constructive criticisms from the faculty in the form of written evaluations.*

In addition to the scientific presentations, an awards ceremony is another integral part of the retreat. The purpose of this award ceremony is to recognize and celebrate outstanding performance in many levels within the department and to encourage all members of the department to strive for excellence. During the awards ceremony, several members of the department are recognized. An outstanding graduate student (nominated and elected by the faculty) is also recognized. There is also the option of awards for a research assistant or faculty member of the year award; and all postdoctoral fellows who are new to the department are recognized with a welcome gift. In addition to the special recognition that is provided to these singled out individuals all students who are new to the department are officially welcomed by a white coat ceremony in which the Chairman and MTTP Program Director presents the students with embroidered white lab coats and copies of the latest edition of Goodman and Gilman's "The Pharmacological Basis Of Therapeutics". Additionally, at least one workshop or seminar is included in the annual retreat.

Leave of Absence from Graduate Study

MTTP students undertaking graduate work are expected to pursue their studies according to a systematic plan each year whether registered for full time or part-time study.

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. This request, which requires endorsement by the student's advisor, the MTTP director, and the department chairperson, must be submitted to 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. 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. IN PHARMACOLOGY:

The Entrance Programs: BSTP, MTTP & MSTP

Predoctoral Students enter the Department of Pharmacology through one of three programs: the MTTP (Molecular Therapeutics Training Program), the BSTP (Biomedical Sciences Training Program), or the MSTP (Medical Scientist Training Program). While all students must fulfill a set of core courses, their exact program of study is dependent on the student's background and training program.

MTTP students come in knowing they want to pursue a Ph.D. in Pharmacology. These students enroll directly into the Pharmacology Department and begin the MTTP immediately. During their first year, MTTP students also do research rotations, but all of their experiences are with trainers that are part of 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.** This rotation schedule affords students an opportunity to experience several different

projects and investigators in the Program. Generally, these are 7-12 week rotations, and the student must complete a minimum of three rotations. There will be an exit interview after each rotation, **and both the advisor and the student will complete a rotation report/evaluation, and send it to the MTTP Administrator, Cami Thompson.** As in the BSTP, a thesis advisor and lab must be selected by **January** of the first year.

BSTP students spend their first semester taking comprehensive coursework in cell and molecular biology and rotating through research laboratories to identify prospective thesis advisors. Students have the option for a wider selection of faculty accepting rotation students. The rotations are arranged by the student with the prospective research advisors. By the beginning of the Winter Semester of year one the student will chose a mentor, and formally enter into and begin fulfilling the requirements of the MTTP.

MSTP students pursue a combined M.D./Ph.D. degree and spend their first 20 months in the MD program. During this time they are expected to complete at least two of three required research rotations. Typically MSTP students affiliate with Pharmacology and the MTTP for their Ph.D. studies during the Spring Semester of their second year. The foundation in cell and molecular biology is provided by the medical school core academic program (IBIS) in place of the cell and molecular biology (C3MB) core course. .For those MSTP students who know earlier that they want to pursue the Ph.D in Pharmacology, they may take the PHRM 402 core course during the 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.*

INTRODUCTION TO THE MTTP (Direct Admit)

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 physiology and 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 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 as well as research-based industry.

Overview of MTTP Design

As depicted in **Figure 1**, the Molecular Therapeutics Training Program is developed in three specific phases. ***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 their evolving thesis project, and 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. 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 (*see Prelim Exam Descriptions, below*). Success in Stage 2 results in advancement to Ph.D. candidacy. ***Stage 3***: This stage involves focused specialization in one of four *advanced training tracks* defined by the area of research expertise of the thesis advisor and the other training faculty assigned to that track, and by topical coursework and journal club experiences for continued education. The benchmarks of success in Stage 3 are research accomplishments and knowledge sufficient to foster at least two original research publications and an erudite thesis presentation and defense. Success in Stage 3 results in award of the Ph.D. degree.

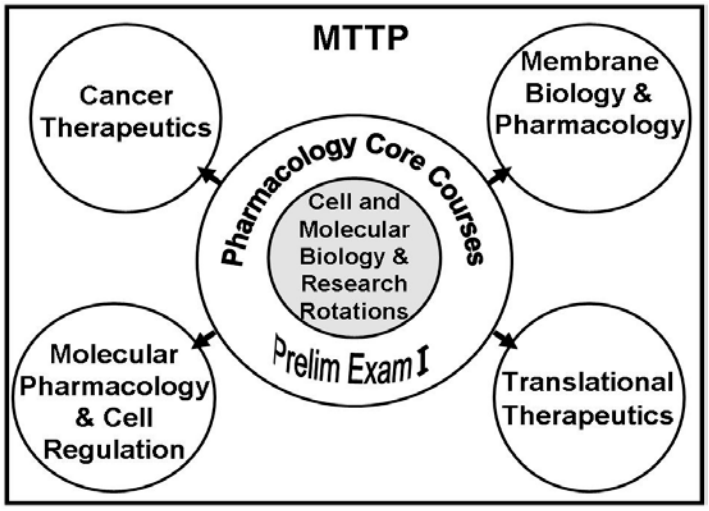


Figure 1. Didactic and research education of students in the Molecular Therapeutics Training Program (MTTP) is developed in **three stages**. **1.** All students complete the core course in Cell & Molecular Biology (or equivalent), and research rotations in three different laboratories. **2.** All students complete the two core courses in Pharmacology (or equivalent) and demonstrate proficiency in *Prelim Exam* I to advance to candidacy. **3.** Ph.D. candidates specialize in one of four advanced tracks according to the expertise of their mentors and their choices of advanced elective courses. *Prelim Exam II* focuses on the thesis project. The Ph.D. degree is awarded for defense of original published research.

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 all of the Tracks (see *Administration*, below). According to research focus and 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 administrative structure of the Training Program is illustrated in Fig. 2. The basic components include the Program Director and Administrative Assistant, the Steering Committee, and the Recruiting and Admissions Committee, all of whom coordinate the interactions with the training faculty and the students. Notably, the Steering Committee includes the Chair and Vice-Chair of Pharmacology, and the Graduate Studies Director of the CWRU SOM. Thus, policies set by the Steering Committee are ensured of coherency with those of the Department and the School. 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 of the MTTP. Overlapping membership between the Steering Committee and the Recruiting and Admissions Committee provides a uniform approach to selecting high quality students and following their progress through the Program. Details of the roles of the Director and the Committees are described below**.**

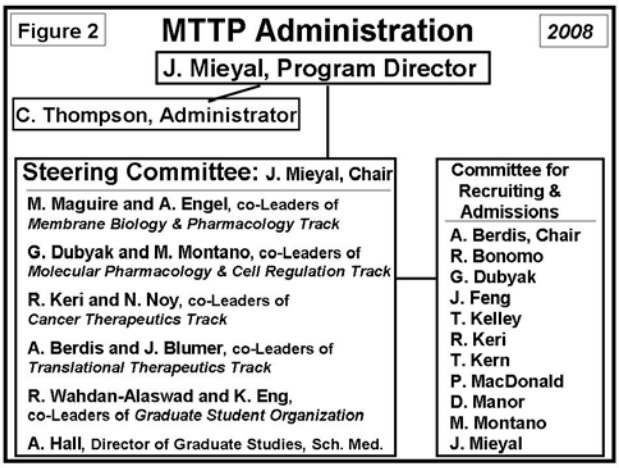


Figure 2. **Administration of the Training Program**. As director, Dr. Mieyal oversees all aspects of the program. Scheduling and clerical responsibilities are accomplished by the Program Administrator who also maintains records of each student's progress and facilitates all meetings of the Steering and Admissions Committees. The Steering Committee, comprised of Program Leaders, is responsible for selection of program faculty, quality control of coursework, student performance, and oversight of admissions. The Recruiting & Admissions Committee coordinates recruiting efforts, evaluates applicant credentials and interview performance, follows up with promising applicants, and makes all admissions decisions.

Graduation Requirements for a Ph.D.

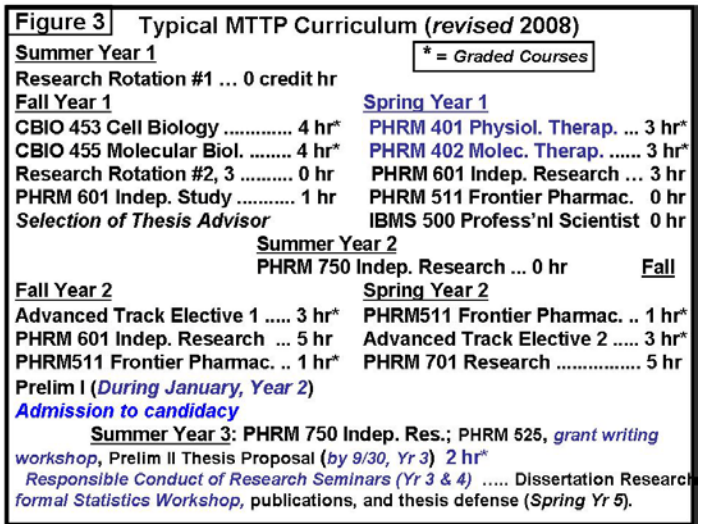
Overview

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, multifaceted training experience composed of:

- laboratory research rotations
- core coursework in fundamentals of modern pharmacology, including animal laboratory experience
- 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 review and publication
- **workshops on statistical analysis of biological data and on grant writing**



Overview of the training program curriculum. A curriculum for the typical 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 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 8-10 week rotations part time during Fall Year 1), and other essential training experiences such as seminars on ethical conduct of research (IBMS 500). The goal of the initial 1.5-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.

The immersion in the rigorous, seminar-style two-part core course in Pharmacology during the second half of year one provides a foundation for advanced courses in the chosen area of specialization during the fall and spring semesters of year 2. The designs of the Pharmacology core courses and the advanced elective courses have a common focus on developing in the students the scientific insight that is required to meet the demands of independent, thesis research. Upon satisfactory performance in the course-work and seminar presentations, all students are eligible to advance to Ph.D. candidacy at the middle of their second year by successfully completing the qualifying exam (Prelim Exam I, *see below*). Remaining formal coursework is completed in spring of year 2, including a special workshop on biostatistics (see below). 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 or less. Indeed the average time to completion of the Ph.D. degree in Pharmacology for graduates over the past **5 years is *5.3 years*. Specific courses and other training activities for the program are described below.

Coursework

Planning the Study Program

Gradate 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.

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. 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, 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. The 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 not fewer than 18 total credit hours is required*.

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

The first year consists of the C3MB courses and research rotations, as well as a scientific ethics course (15 credit hours). This is included with the additional 15 formal course credit hours which are required in Pharmacology as listed and then described below.

1) Three Rotations (PHRM 400)	0 credits
2) C3MB (CBIO 453)	4 credits
3) C3MB (CBIO 455)	4credits
4) Principles of Pharmacology I: Physiological Basis of Therapeutics (PHRM401)	3 credits
5) Principles of Pharmacology II: Molecular Basis of Therapeutics (PHRM402)	3 credits
6) Frontiers in Pharmacology, J Club Series (PHRM511)	2 credits
7) Two advanced electives (*from the Advanced Track offerings*)	6 credits

8) Prelim I Comprehensive Examination 0 credits
9) Formal Workshop on Biostatistics
9) Prelim II Dissertation Proposal, including grant-writing workshop (PHRM525) 2 credits

Description of the first semester 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 1st 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, BSTP students choose mentor labs and identify with a 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 the student to select a laboratory and mentor for the thesis work. 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 8-10 weeks (part time academic year), and they are arranged by the students after consulting the availability of faculty mentors. A minimum of three different rotations must be completed by the end of the fall semester, year 1. Additional rotations are permitted if needed. Students are expected to spend at least 20 hours per week in the lab during the academic year. In addition to carrying out a research project, rotating students participate in research meetings, journal clubs, and department seminars. This 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 evaluated by each rotation mentor, a written summary of the strengths and weaknesses of the rotation is discussed with the student and submitted to the Director of the BSTP or MTTP. The Director of the MTTP advises first year students and coordinates rotation experiences.

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 in the first semester, Cell Biology (CBIO453) and Molecular Biology (CBIO455). Each class meets for 10 hours per week in the first semester, 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 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. In the spring semester of year 1, the intensive Pharmacology I and Pharmacology II coursework gives students the basics and background, along with the research focus of their mentor's lab, to choose a particular Advanced Track in Pharmacology that would be appropriate for them.

Principles of Pharmacology I: The Physiological Basis of Therapeutics (PHRM 401) - This course focuses on human physiology of organ systems that are involved in determining the time course of drug action *in vivo* (pharmacokinetics). Emphasis will be 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 will be discussed. A second broad area of emphasis is on fundamental principles of drug action within the body (pharmacodynamics), including drug-receptor theory, log dose-response relationships, therapeutic index, receptor turnover, and signal transduction mechanisms. This is a highly interactive course in which faculty lectures are minimized and student-directed learning is emphasized. An animal laboratory examines the actions and dose-response relationships for cardiovascular drugs in an *in vivo* setting. Students are evaluated in multiple ways, including formal assessment of oral and written presentations, problem-solving and team interaction in the setting of the animal laboratory where an unknown drug must be identified, and a take-home final exam with questions

addressing both general knowledge and experimental design skills. This 3-credit hour course meets 6 h per week during the first half of the spring semester of year 1 (mid-January through February). *Course Director*: **Paul N. Macdonald, Ph.D.**

Principles of Pharmacology II: The Molecular Basis of Therapeutics (PHRM 402) - This course focuses on the chemical and biochemical properties of therapeutic agents, molecular mechanisms of therapeutic action including kinetic and thermodynamic principles of enzyme catalysis and drug-receptor interactions, signal transduction, the genetic basis of disease states, and interindividual variation in response to drugs. 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 specific diseases. This is a team-taught course involving focal lectures by faculty followed by student-directed learning experiences including discussion, problem solving applications, and primary literature presentations. A laboratory exercise introduces experimental methodologies widely applied during the study of molecular interactions between therapeutic agents and receptor targets to reinforce fundamental principles of molecular drug action. Students are evaluated in multiple ways, including formal assessment of oral presentations, a manuscript that analyzes and interprets the data generated in the laboratory exercise, and a take-home final exam with questions testing both analytical reasoning and experimental design skills. This 3-credit hour course meets 6 h per week during the second half of the spring semester of year 1 (March and April). *Course Director*: **John J. Mieyal, Ph.D.**

Frontiers in Pharmacology - Student Journal Club Series (PHRM 511)

This course is designed to provide students practical experience in presenting effective oral scientific presentations. This is accomplished by direct "hands-on" presentation of primary research articles by the student to the Department of Pharmacology in the Student Journal Club series. Students learn to make effective slides using Powerpoint, to organize a scientific presentation, and to present it 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, methodologies, and critical analysis of published scientific articles related to modern pharmacological research. Students also obtain practical experience in the peer-review process by providing insightful critical analysis of all student presentations. Student presentations are evaluated by a panel of three faculty members that assign a final grade. Students are also graded on their participation in the discussion of the article, on their thoughtful critique of the presentation, and on a written critical evaluation of the presented article. *An example of 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.*

Bioethics - On Being a Professional Scientist (IBMS 500) Semester two of year 1 is concluded with a focus on ethical conduct of science. All trainees are required to participate in the course entitled "Being a Professional Scientist: Ethics and Biomedical Research," offered annually by the CWRU SOM. This course is directed by Dr. E. Juengst, in the Center for Biomedical Ethics. The class meets for 4 sessions that are 4 hours in length for lectures, discussions, and case studies. 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 will be devoted to issues of responsible conduct of research. Each session will be 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 will be distributed in advance, and the participants will be dived 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. *To receive credit for participation, each student must submit a half-page summary of the key points of the deliberation.* Text: *Seminars in ethical issues in research:* F.L. Macrina, *Scientific Integrity* 3rd Edition, Text and Cases in Responsible Conduct of Research, ASM Press, 2005.

Advanced Training Tracks and 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 & Cell Regulation*, *Membrane Structural Biology & Pharmacology, Cancer Therapeutics, and Translational Therapeutics.*

Advanced Track in Molecular Pharmacology and Cellular Regulation -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 that share common research interests in the broad area of molecular pharmacology and signaling. The central thematic focus is on molecular mechanisms involved in the therapeutic actions of drugs and on the identification of cellular regulatory processes that may potentially serve as rational targets for drug development. Besides the opportunity to serve as direct thesis mentors for Ph.D. students in this track, training faculty 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 attendance by members of the Track that supplement the regular Pharmacology events. The MPCR Faculty are a highly interactive group, many with productive, on-going collaborations. For example, Drs. MacDonald and Keri have published a study together that implicates analogs of activated vitamin D_3 as potential chemopreventive or chemotherapeutic agents for breast cancer. Drs. Dubyak and Distelhorst have co-authored a number of manuscripts in the area of calcium-regulated gene expression and in mechanisms involved in cell signaling by calcium. Graduate students in this track will focus on advanced electives (3 credit hr each) that are selected to emphasize the objectives of the Track and the research interests of the associated laboratories. Particularly pertinent advanced electives are those that are led by faculty aligned with this track. Examples are listed below.

- **Cell Signaling (**PHOL/ CLBY 466). *Course Director*, **George Dubyak**.
- **Cytokine Structure and Function** (PATH/ CLBY 417). *Course Director*, **Alan Levine**.
- **Endocrine Pharmacology** (PHRM 515). *Course Director*, **Monica Montano**.
- **Phosphorylation and Cell Regulation (**MBIO 522). *Course Director*, **Jonathan Karn**.

Advanced Track in Cancer Therapeutics – Many of the Training Faculty for the MTTP are members of the CWRU Comprehensive Cancer Center, which is one of 39 NCI designated Comprehensive Cancer Centers. The CWRU Comprehensive 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. 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). Students within the Cancer Biology Training Program may enter through the BSTP or direct admission to the MTTP, and they participate in the first year of courses while rotating in laboratories. Upon selection of a mentor, BSTP students also select a training program. Students choosing to enter the MTTP would also become participants in the Advanced Track in Cancer Therapeutics. Following completion of the Pharmacology Core Course in Molecular Therapeutics, trainees in the Cancer Therapeutics Track will be 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** (PHRM520). Basic concepts of cancer biology and the various therapeutic strategies used to treat this disease. 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.**
- **Cellular and Molecular Biology of Cancer** (PHRM420). 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 humans and animal models. *Course Director*, **Ed Stavnezer**

Both of these are 3 credit hour courses. PHRM520 offers a study of the pathology and therapeutics of cancer while PHRM420 delves deeply into the molecular basis of carcinogenesis. A therapeutics enrichment to

PHRM520 is also offered, which is a one credit hour class. Participants in this course will attend the Cancer Center "Blood Club" seminar series. Prior to each class, the students will be assigned a therapeutically-relevant cancer research journal article that is related to the topic of the seminar. They will prepare a one page critique of the paper prior to attending the seminar. This accomplishes multiple goals: 1) students are prepared to fully engage in the lecture; 2) during the semester, students are required to critically read and review modern literature in the field of cancer therapy; and 3) students will develop the skills necessary to compose a thorough written critique of another laboratory's research paper.

In addition to the course work associated with the Cancer Therapeutics Track, the principles of cancer therapeutics will be reinforced in two additional ways. The first involves participation in the Cancer Center's weekly seminar series ("Blood Club"), which attracts outstanding internal and external speakers with expertise in a wide variety cancer research disciplines. Representative speakers from previous years include Judah Folkman, John Cleveland, Charis Eng, Harold Moses, and Thea Tlsty. Trainers and trainees in the Cancer Therapeutics track also participate in a one-half day scientific retreat on an annual basis. Students will present their research in oral format and a luminary speaker in cancer therapy will be invited to present a key-note address. Students within the track comprise the retreat planning committee and are responsible for identifying the key-note speaker. They also have the opportunity to interact with the speaker at a concluding dinner at the Retreat. To enforce uniformity for each student's training program, it is anticipated that at least one of the thesis committee members, other than the student's mentor, will be a member of the cancer therapeutics track, and the chair of the committee will hold a primary appointment in Pharmacology.

Advanced Track in Membrane Structural Biology and Pharmacology (MSBP)- A core group of MTTP training faculty have primary interests in molecular aspects of membrane protein structure and function. Membrane proteins and their complexes are critical in signal transduction and transport processes, and their functions influence all aspects of cellular regulation. Also, they are crucial in energy production and energy transfer between cells and between compartments, including organ systems. 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.*

Despite their importance, study of the molecular mechanisms and structures of membrane proteins lag far behind information available about soluble proteins because of the inherent difficulty in studying proteins embedded in a membrane. Determining how membrane proteins act and how various drugs can modify those actions is a central theme of this advanced training track. Following completion of the two part core course in the *Physiological and Molecular Bases of Therapeutics*, students continuing in the *Membrane Biology and Pharmacology Track* will receive specialized training in membrane protein structure and function through a combination of specialized course work, journal clubs devoted to membrane proteins, and laboratory research focused on determining the structure and/or delineating the function of one or more membrane proteins. Specialized courses are chosen from a variety of opportunities depending on whether the student's primary interest lies towards structure, mechanism, or 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:** classification and structure and of membrane transport proteins, mechanisms of transport and physiological integration of transport processes (PHRM 412). *Course Director*, **Michael Maguire**.
- **Protein Biophysics**: Structural, thermodynamic and kinetic aspects of protein structure-function relationships (PHOL475). *Course Director*, **Matthias Buck**
- **Advanced Methods in Structural Biology I & II**: Applications of NMR, ESR, CD, Raman, Fluorescence, Mass spectrometry and X-ray crystallography to delineate protein structure and function. (PHRM 430/431). *Course Director*, **Menachem Shoham**.
- **Structural Biology of Proteins, Enzymes and Nucleic Acids:** Enzyme structure, kinetics, and mechanisms, structural biology of proteins and protein-DNA complexes, and techniques for structural analysis. (BIOC 434). *Course Director*, **Paul Carey**.

Advanced Track in Translational Therapeutics - The Translational Therapeutics Track (TTT) is designed to train students to utilize molecular and cellular biochemical approaches in 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 organism level. Such levels of sophistication will allow 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-bedside" orientation while the other represents the "bedside-to-bench" approach.

Students enrolled in the TTT will formulate a forward-looking vision of pharmacological research as it will be developed and applied over the next several decades. This track will endeavor 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 will be expected to master basic core tenets and principles of pharmacology as well as the application of newer technologies against this 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 will be 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 526, 3 credit hr)**: This course is aimed at providing students with a deeper understanding of the mechanisms of drug action and target validation. The first part of the course focuses on the basis for classical approaches in drug discovery, including kinetic and thermodynamic analyses of small molecule interactions with enzymes and receptors. The second part of the course focuses on new technologies and agents such as interference RNA and peptoids as therapeutic agents. The final section considers pre-clinical and clinical trials, as well as practical issues for start-up companies Students will use published literature and web resources to develop a written proposal for drug or target and licensing agreements. discovery with the aid of a mentoring committee that includes a member of the TTT training faculty. Evaluation is based on interactions with the Committee, quality of the written proposal and oral defense. (PHRM 526). *Course Director*, **Anthony Berdis**.
- **Pathways to Personalized Medicine (PHRM 527, 3 credit hr)**: Students select a problem from a list of clinically important therapeutic issues related to variability in drug responsiveness, and they design a research project to elucidate its molecular, biochemical, genetic and pathophysiological basis. Students assemble a mentoring committee for the process, including a member of the TTT training faculty along with a clinician and a basic scientist with relevant experience. The goal is to produce a written research proposal to be defended orally that takes the problem from bedside to the bench and back again. (PHRM 525). *Course Director*, **Jeffrey Blumer**.

Other recommended advanced courses include:

- **Mechanisms of Drug Resistance**: Molecular, cellular and physiological mechanisms of resistance to antibiotics, anti-viral agents, and cancer therapeutic agents. (PHARM 434). *Course Directors*, **Eric Arts and Robert Bonomo**.
- **Cancer Biology and Therapeutics**: Seminar on the pathophysiology and therapeutics of cancer (PHRM520). *Course Director*, **David Danielpour**.

Dissertation Research (PHRM 701)

Upon written notification to the dean of graduate studies that a faculty member has been selected as a doctoral student's principal research advisor, the student will be acknowledged by the dean as eligible to register for one to nine credit hours of **"Dissertation Research"** (course # PHRM 701) each semester. After accumulation of 18 credits of 701, students must continue to register for 701 (*1 credit per semester constitutes full time enrollment*) until graduation occurs.

Pre-candidacy 701 hour(s) can only be taken concurrent with course work. However, since half-time (six credit hours) is required for the purpose of student loan deferment, a student who is not advanced to candidacy upon completion of all course work requirements must register for not less than six credit hours each semester until candidacy is achieved, regardless of the total of pre-candidacy 701 hours completed. Otherwise, without the need for deferment, a student must maintain registration as stated above. A student is permitted to register for a maximum of nine (9) credit hours (full-time status) of 701 each semester only after advancement to candidacy.

Statistics workshop – It is expected that every graduate student in the MTTP participate in a one-day workshop on practical statistical analysis of biological data. This is an important aspect of training that is beneficial for all biological scientists, and it is emphasized by training grant review panels. Typically, students who have completed Prelim II (see below) and are in the active phase of compiling and analyzing data for publication will participate in the workshop. The participants will supply actual data in advance to the workshop director, and the data of as many students as possible will be analyzed in real time during the workshop to illustrate alternative appropriate means for statistical analysis, focusing on the most effective approaches for different types of data sets. The workshop will be offered at least once each year. Potential directors of the workshop are faculty members affiliated with the Dept. of Epidemiology & Biostatistics, including Tomas Radivoyevitch, Susan Redline (MTTP Trainer), and Emma Larkin.

Dissertation Research (PHRM 703)

Students who need to have more than one hour on their transcripts are eligible to register for PHRM 703 so long as they have advanced to candidacy and are within the five-year time limit for completion of a degree, but have not yet completed the dissertation. Students can complete the Dissertation Fellowship 703 form. This course is designed for special instances where a student may need loan deferment or childcare and needs to carry over 1 credits of 703. In addition to registering for 703, the student must register for a minimum of 1 credit hour of 701. Prior to registering for PHRM 703, the rationale needs to be submitted to Cami Thompson for approval.

Examinations

Preliminary (Qualifying) Examination I for advancement to doctoral candidacy

University Policy on Examination (Preliminary) Requirements - In order to meet the requirements for the doctorate degree, a student must pass a general examination (or a series of examinations covering different fields) specified and administered by the student's department or supervising committee (**Prelim I in MTTP**). The examination generally precedes advancement to candidacy. A student must be registered during the semester in which any part of the general or qualifying examination is taken. If not registered for other courses, the student will be required to register for one semester hour of EXAM 700, General/Qualifying Examination, before taking the examination. A student who fails the examination on the first attempt may be permitted to take the examination a second time within one year (*one month in Pharmacology*) at the discretion of the Department. Except in unusual circumstances, a student who fails the examination a second time will be separated from further graduate study within the same department or supervising unit.

Pharmacology Policy - MTTP Preliminary Examination I – 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. 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 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 to a new dimension.

Format: Students are administered a two-part written examination, typically containing eight 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.

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

At the end of spring semester, Year 2, students will have completed the following courses: C3MB (Cell and Molecular Biology), Principles of Pharmacology I & II, Frontiers in Pharmacology Colloquia, 3 research rotations, initial thesis-related research, Prelim I, and two advanced courses. Successful completion of Prelim I in January of year 2 and achievement of a GPA $\geq$ 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 within the specified limits, 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 aspect of the training program (see below).

Unsuccessful performance in any one of these aspects constitutes probationary status with appropriate remedial measures defined on an individual basis. More than one unsuccessful performance may lead to dismissal from the program. Decisions on student status at this stage will be based on the decision of the MTTP Steering Committee and their recommendations to the full Faculty of Pharmacology.

Thesis proposal, Thesis Committee, and Preliminary Examination II (PHRM 525).

Once students successfully complete Preliminary Examination I, they are advanced to candidacy. They may begin immediately to identify their Thesis Committee and to prepare their thesis proposal, while completing remaining advanced coursework. This process takes place during the spring and throughout the summer of year 2. The thesis committee consists of at least 4 CWRU faculty of the School of Medicine. At least 2 must hold primary faculty 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 than the mentor, and be a primary faculty member of the Department of Pharmacology, thus facilitating consistency among thesis committees. In consultation 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 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 format for an NIH Individual Fellowship Application (PHS 416-5, available on the internet / *see URL in Appendix*), specifically section one of the application which includes the subsections listed 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 will 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 will receive 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 will 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 will convene the workshop. At the workshop, the Review Panel will 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 will be able to compare what they emphasized in their critiques to what the expert panel focused on. The panel will summarize the key points of the discussion and provide 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, 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 25-30 minute oral presentation of the proposal, highlighting 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 presen-

tation 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 (see Appendix for URL). 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 will be scored independently and anonymously by each committee member before the Exam Committee discusses the performance of the student.
    a. Each member of the Committee will score the written document, according to specific guidelines (see *Components of the Prelim II Proposal,* above*)*, and provide the score to the Committee Chair prior to the oral exam. The Committee Chair will record these initial scores, but not share or discuss them with the Committee until the oral exam is completed.
    b. Each member of the Committee will score the oral performance, according to specific criteria, namely: overall organization; breadth and depth of knowledge of published work relative to research plan and pilot data; quality of responses to questions and ability to respond to criticism of experimental design; quality of visual aids. These scores are provided to the Committee Chair before any discussion ensues. The Chair will record these initial scores.
2. The Committee Chair will share the initial scores for the written and oral segments of the Exam and invite discussion with the goal of reaching a consensus score on each component of the Exam.
3. The written score will contribute 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. $\geq$ 90% = A; $\leq$ 79% = C (failure).
5. **For an *Unconditional Pass* both component scores must be $\geq$ 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 to a deficiency in the oral component.
6. Each Committee Chair will report 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.

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 deviation from 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.

Format and timing of Dissertation Defense

The thesis defense must be scheduled with the Office of Graduate Studies no later than two weeks before the date of the examination. *The candidate must provide to each member of the Thesis Committee and to the Chair of the Department of Pharmacology, a copy of the completed dissertation at least 10 days before the examination so that the committee members and the Chair may have sufficient opportunity to read the dissertation in advance of the oral defense.* Scheduled defenses are made known through on-campus publications and any member of the university may be present at that portion of the examination pre-designated by the chairperson of the examining committee.

YOU MAY NOW FILE ELECTRONICALLY - Please see following link for information:

http://www.cwru.edu/provost/gradstudies/etd/Index.htm

Two copies of each completed and accepted dissertation will be deposited in a library of the University by the School of Graduate Studies. The University assumes the cost of binding these 2 copies of the dissertation. One copy of the completed and accepted dissertation will be deposited in the Department of Pharmacology, and the Department will assume the cost of binding for this one as well as one copy for the student. The expense of any additional bound copies will be assumed by the student. In addition, the student must guarantee the reproduction of the dissertation through University Microfilms, Ann Arbor, Michigan, before certification for the doctorate. This includes the completion and submission of the annual "Survey of Earned Doctorates Awarded in the United States".

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 or dissertation 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 entrance into the Pharmacology Ph.D. program. A complete description of the Program can be obtained by asking for the *Guidelines for the CWRU MSTP* (revised 4/18/07) from the MSTP Office (Kathy Schultz, Administrative Director).

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 (**PHRM 402**). Note: Typically PHRM 401 would be waived because its contents are 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 402

YEAR TWO

- Medical School Curriculum, NBME Exam: USMLE I
- Selection of thesis advisor
- PHRM 402, 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 Pharmacology Track Course(s)
- Independent Research (PHRM 601)
- Preliminary Exam I / Advancement to Ph.D. candidacy, if not completed
- Possibly Prelim II (Thesis Proposal)

YEAR FOUR

- Independent Research (PHRM 701)
- Preliminary II (Thesis Proposal), if not completed

YEARS FIVE AND SIX (*or sooner*)

- 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 offered 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 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 proscribed 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 a 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:

Coordinated Curriculum in Cell and Molecular Biology (C3MB)	
Cell Biology (CBIO 453)	4 credits
Molecular Biology (CBIO 455)	4credits
The Physiological Basis of Therapeutics (PHRM 401)	3 credits

The Molecular 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

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 proscribe 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

Semester 1:	CBIO 453 (4) CBIO 455 (4)	Semester 2:	PHRM 401 (3) PHRM 402 (3) PHRM 601 (1)
Semester 3:	PHRM 511 (1) PHRM Elective (3) PHRM 601 (2)	Semester 4:	PHRM 511 (1) PHRM Elective (3) PHRM 601 (1) EXAM 600 (1)

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 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

Semester 1:	CBIO 453 (4) CBIO 455 (4)	Semester 2:	PHRM 401 (3) PHRM 402 (3) PHRM 651 (1)
Semester 3:	PHRM 511 (1) PHRM Elective (3) PHRM 651 (5)	Semester 4:	PHRM 511 (1) PHRM Elective (3) PHRM 651 (3)

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 has launched a new program that requires a fifth year of research within its medical training at the Lerner College of Medicine, and an increased emphasis on research training is incorporated into the revised University medical curriculum (WR2), beginning in 2006. These developments will spawn a growing interest by medical students in obtaining advanced degrees in addition to the MD during their usual course of study. This new combined MD/MS program is designed to specifically address this interest and 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 proposed 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 is 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, 6 graded credits of medical coursework, participation in a common seminar series, scientific integrity training, Qualifying Examination, and 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 College Medical Programs, and their admission to the medical curriculum 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, MCAT scores will be substituted for GRE scores and 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 MD/MS 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 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 Program plan 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 will 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
	Physiological Basis of Therapeutics (PHRM 401) / Spring		3 credits
	Molecular Basis of Therapeutics (PHRM 402) / Spring		3 credits
	Advanced Elective Course complimentary to research focus		3 credits
Year 3	Independent Research (PHRM 601) / Fall & Spring	(9 cr each)	18credits

	Frontiers in Pharmacology Seminar Series (PHRM 511) Fall & Spring (1 cr each)	2 credits
	Scientific Integrity Training (IBMS 400)	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. The Department of Pharmacology subsidizes the purchase of these computers for every Pharmacology student in our training program. For the 2008-2009 academic year and beyond, the Department provides one-half the purchase price of the computer, up to $750.00. The mentor's laboratory 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. This is sometimes an uncomfortable issue for new students to address with their new mentors. Therefore, 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 Vicki Grace (X-5997) to begin this process.

Computing Resources

Getting connected
This is the page that most of you will need. In this section, instructions and assistance on connecting and setting up your computer to the CWRU network are provided. Whether it is secure wireless, or a gigabit on-campus connection, how to setup email, or software downloads... It's all here!
http://help.case.edu/

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 XP Professional, Windows Vista Business, Windows Vista Ultimate (also in x64), 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.

Planned Program of Study Form: (see sample form) Submit electronically after advancing to candidacy. **A paper version is also required by the Department of Pharmacology**.

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.

Dissertation Fellowship 702 Form: Ph.D. students are eligible for Dissertation Fellowship 702 when they have met all of the following requirements: 1) completed all required course work; 2) completed 18 hours of 701 dissertation research credits; 3) advanced to candidacy; 4) achieved a minimum 3.00 G.P.A.; 5) are within the 5 year time limit. Students cannot take any other course work for credit while registered for 702.

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 which 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 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 which 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
http://www.case.edu/

CASE Directory
http://cnswww.cns.case.edu/phone/phonebook/local/

CWRU Registrar
http://www.case.edu/provost/registrar/registrar.html

CWRU academic regulations for doctoral degrees
http://www.case.edu/provost/gradstudies/ar_doct.htm

National Library of Medicine's PubMed
http://www.ncbi.nlm.nih.gov/PubMed/

NIH home page
http://www.nih.gov/

Ruth L. Kirschstein National Research Service Awards for Individual Predoctoral Fellowships
http://grants.nih.gov/grants/guide/pa-files/PA-05-151.html

More About PHRM #702...

The appointment is available for a maximum of four consecutive semesters, renewable prior to the beginning of each of those semesters upon recommendation by the department chair to the graduate dean. If the dissertation is not completed and defended in the fourth semester of the Fellowship, the Fellow must resume registration for course 701 at a minimum of one credit hour each semester through the allowed five-year limit.

Doctoral students have five consecutive calendar years from the semester of the first credited 701 registration 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.

To register for course 702, the following actions must occur:
1 A completed and endorsed "Ph.D. Date Sheet" must be submitted to the Office of Graduate Studies recommending the candidate for appointment to a Dissertation Fellowship before the beginning of each effective term
2 Appointment by the graduate dean is required each semester of the four-semester fellowship based on:

- Advancement to candidacy
- Completion of all course work
- Completion of a minimum of 18 credits of 701
- Receipt of department chair's recommendation (via "Date Sheet")

1 Upon the dean's approval of each recommendation, the Graduate Studies Office will validate the Dissertation fellowship status every semester to permit registration for 702 by the candidate
2 When re-appointment for the fourth and final semester of the fellowship occurs, the candidate will be sent a letter from the dean, with a copy to the department, indicating that unless the dissertation is completed and defended by the end of that semester, resumption of registration for course 701 is required in each of the remaining semesters of the five-year time limit for completion of all degree requirements.

Although completion of all course work is a requirement for appointment, the Dissertation Fellow may desire to take a course, for example, one not previously offered. Registration for such a course while in fellowship status is limited to a maximum of 4 credit hours in each semester, and the additional tuition is assessed at the per credit hour rate.

In the event that a candidate receives a grade of "U" in 702, the fellowship is forfeited and the candidate formally is placed on academic probation. Requirements for removal from probation may differ from those stipulated in the regulations (repetition of the same number of credits with a grade of "S"), but in all cases the subsequently needed dissertation research credit will require registration for course 701 until all degree requirements are fulfilled within the time allowed.

Sample Planned Program of Study Form (Year 1-2)

Graded Courses are indicated with an asterisk*

Term	Course #	Course Name	Hrs.
	PHRM 400	Research Rotations	0
Fall	CBIO 453	Cell Biology	4*
	CBIO 455	Molecular Biology	4*
	PHRM 400	Research Experience (Rotations) #2	0
	PHRM 601	Independent Study and Research	1
Spring	Pharm 401	Physiological Therapeutics	3*
	Pharm 402	Molecular Therapeutics	3*
	Pharm 511	Frontiers in Pharmacology Seminar Series	0
	PHRM 601	Independent Study and Research	3
Summer	IBMS 500	On Being a Professional Scientist	0
	RSCH 750	Independent study and Research	0
Fall	PHRM ??	Advanced Track Elective 1	3*
	PHRM 511	Frontiers in Pharmacology Seminar Series	1*
	PHRM 601	Independent Study and Research	5
		Prelim 1 (During January, Year 2)	

Term	Course #	Course Name	Hrs.
Spring	PHRM 511	Frontiers in Pharmacology Seminar Series	1*
	PHRM ??	Advanced Track Elective 2	3*
	PHRM 701	Independent Study and Research	5
Summer	PHRM 750	Independent Study and Research	0
Fall/Spring	PHRM 701	Independent Study and Research	1-9
	Optional Coursework		
	PHRM 525	Grant Writing Workshop	0
	PHRM 525	Prelim II Thesis (by 9/30 Yr. 2	2*
	PHRM 525	Responsible Conduct of Research (yr 3/4)	0
	PHRM 525	Dissertation Research	0
	PHRM 525	Formal Statistics Workshop	0
	PHRM 525	Publications/Thesis Defense (Yr 5)	0

PHARMACOLOGY TRAINERS

Focco van den Akker, Ph.D., Assistant Professor of Biochemistry, member of the Membrane Biology Track.

Dr. van den Akker's laboratory is mainly focusing on the natriuretic peptide receptors and related receptors. These receptors are guanylyl cyclase receptors involved in blood pressure regulation and bone growth and their activation leads to the production of the intracellular second messenger cGMP. Determination of the crystal structure of the ligand binding domain of the atrial natriuretic peptide receptor revealed many unexpected discover is such as its structural similarity with periplasmic binding proteins, possible dual allosteric regulation, the hormone binding site, and dimer interfaces. Current projects range from site-directed mutagenesis and activity assays to probe specific mechanistic questions, biochemically characterizing and crystallizing the remaining individual domains, and finally the long term goal of crystallizing the entire receptor which may lead to discovery of new pharmacologically interesting effectors.

Anthony J. Berdis, Ph.D., Assistant Professor of Pharmacology, co-Leader of the Translational Therapeutics Track, member of the Molecular Pharmacology Track.

Inhibition of nucleic acid metabolism is a powerful chemotherapeutic strategy that has one significant pitfall non-selective killing of both diseased and healthy cells. The Berdis laboratory has developed a unique strategy to potentiate the effects of existing chemotherapeutic agents by using their recently developed series of non-natural nucleosides which are preferentially inserted opposite damaged DNA. These non-natural nucleosides inhibit replication opposite damaged DNA and induce apoptosis only in the presence of other chemotherapeutic agents.

Jeffrey L. Blumer, M.D. ,Ph.D., Professor of Pediatrics and Pharmacology, co-Leader of the Translational Therapeutics Track.

Clinical research focuses on the evaluation of the efficacy, safety, and pharmacokinetics of new antimicrobial agents in infants and children. Other studies include detailed evaluation of the pharmacokinetics and pharmacodynamics of intravenous catecholamines in patients undergoing open heart surgery, the rational dosing of sedative agents in mechanically ventilated children, and evaluation of the pharmacokinetic and pharmacodynamic interactions of loop diuretics in children with volume overload. The Blumer lab also investigates the genetic aspects of drug metabolism as they relate to the development of birth defects and pediatric neoplasms.

Robert Bonomo, M.D. Associate Professor of Medicine and Pharmacology, member of the Molecular Pharmacology and Translational Therapeutics Tracks.

Research in the Bonomo laboratory investigates the molecular and clinical aspects of bacterial resistance to betalactams antibiotics. One area involves understanding the structure function relationships of the class A beta-lactamase, SHV-1. This chromosomal and plasmid encoded beta-lactamase confers high level resistance to third generation cephalosporins which can render ineffective the most frequently used drugs to treat serious nosocomial infections. The goals are to understand what amino acid substitutions permit evolution of novel substrate profiles and what factors control expression of these periplasmic enzymes.

Matthias Buck, Ph. D., Assistant Professor of Physiology & Biophysics, member of the Membrane Biology & Pharmacology Track.

Dr. Buck's research program characterizes the structures and the dynamics of proteins involved in protein-protein interactions. Our system of primary interest are the plexin and the Eph family of transmembrane receptors. Both 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. Protein-protein interactions
determine the basic mechanisms by which signals are transmitted in cells and how signaling is disrupted by mutation in diseased states. Knowing at near-atomic resolution which residues interact in protein-protein interactions will allow us to rationalize their interaction affinity and
specificity. Furthermore, it will provide an opportunity for us to alter the proteins for diagnostic or therapeutic purposes.

Kevin Bunting, Ph.D., Associate Professor of Medicine-Hematology/Oncology and Pathology, member of the Cancer Therapeutics Track.

Dr. Bunting's main area of research is in the field of hematopoietic stem cell biology. Since stem cells are potential targets for treating a wide variety of blood diseases, understanding the basic mechanisms regulating their proliferation, differentiation, self-renewal, mobilization, and
migration is extremely important. His lab has recently identified a STAT5 modifier locus on murine chromosome 7 that modulates engraftment of hernatopoietic stem cells during steady-state hematopoiesis. The critical role of STAT5 and potential modifier genes in this function has led to collaborations with Drs. Tse, Auletta, and Letterio to explore pharmacological suppression of STAT5 activity as a novel new adjuvant for non-myeloablative stem cell transplant..

Martha Cathcart, Ph.D., Professor of Molecular Medicine and Director of the Hughes Training Program in Molecular Medicine, The Cleveland Clinic Foundation and CWRU, member of the Translational Therapeutics Track.

Research in the Cathcart Lab is focused on many aspects of the inflammatory response, including human monocyte activation, regulation of NADPH oxidase generation of superoxide anion, mechanisms of lipid oxidation, expression of 15-lipoxygenase, signal transduction, and regulation of monocyte chemotaxis to MCP1. Current research objectives include Identifying and characterizing the signal transduction pathways regulating superoxide anion production by activated monocytes, exploring the mechanisms involved in IL-13 stimulation of 15-lipoxygenase expression in primary human monocytes, and investigating the regulation of monocyte chemotaxis to MCPI.

Mark Chance, Ph.D., Professor and Director of the Proteomics Center, member of the Membrane Biology 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.

Pamela Davis, M.D., Ph.D., Dean, School of Medicine, Professor of Pediatrics & Vice Dean for Research, member of the Membrane Biology and Translational Therapeutics Tracks.

The laboratory's goal is to understand the pathophysiology of cystic fibrosis (CF) and ultimately to ameliorate or cure it. CF is caused by defects in a gene that encodes a chloride channel, CFTR, but patients succumb to pulmonary infection and inflammation. CF airway epithelial cells and CF mice model the excessive cytokine responses to bacterial stimulation. We found that high dose ibuprofen ameliorates the excessive inflammation clinically, possibly by binding to PPAR-a, a nuclear receptor which can interact with the proinflammatory transcription factor NF-kB to inhibit it. A second line of work is to devise means to deliver normal CFTR gene to the airways of patients. We have constructed DNA nanoparticles consisting of plasmid DNA compacted with polylysine, stabilized with polyethylene glycol, that can transfect airway epithelium *in vivo* in CF mice and correct the CF chloride transport defect. Promising phase I clinical trials have been completed and Phase II trials are beginning. We are extending the molecular targets for this approach to delivery of siRNA directed against respiratory viruses. Finally, we are interested in the role of FXYD proteins which are induced in CFTR-deficient cells as these proteins
appear to have tissue specific consequences for regulation of Na+,K+-ATPase and consequently electrolyte homeostasis.

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-b 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. Our 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-b 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-b-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 of Pharmacology

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. Our approach is to use a multidisciplinary cycle to study the structure-function relationship of proteins. We also use structure-based drug and protein design to develop novel therapeutics against cancer, Alzheimer's disease and microbial infections. Biophysical tools such as x-ray & neutron crystallography, molecular modeling, CD, MS, fluorescence spectroscopy and ultracentrifugation are the techniques used in our lab.

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 gluco-

corticoids induce apoptosis in order to provide novel insight into a fundamentally important mechanism of apoptosis induction. Understanding the mechanism(s) accounting for apoptosis will allow for the development of novel therapies to overcome resistance to glucocorticoid-induced apoptosis.

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

The laboratory is investigating multiple aspects of nucleotide-based signaling during inflammation with a particular emphasis on the P2X7 receptor, an ATP-gated ion channel that is predominantly expressed in the lymphocytes and macrophages that mediate local proinflammatory responses. We study natively expressed P2X7 receptors, recombinant P2X7 receptors ectopically expressed in various model cell types, and the inflammatory cells derived from P2X7-knockout mice. A current focus is analysis of the signaling mechanisms - and proteins that couple P2X7 receptors to the activation of caspase-family proteases involved in either the maturation of inflammatory cytokines (IL-1b and IL-18) or induction of regulated cell death.

Andreas Engel, Ph.D. Visiting Professor, Membrane Structural Biology and Pharmacology (co-Leader)

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

John Feng, Ph.D. Assistant Professor of Pharmacology

Dissecting the genetic mechanisms of dopamine neurotransmission-related human diseases, such as Parkinson's Disease (PD). The main research interest of my lab is to dissect the genetic mechanism of dopamine neurotransmission-related human disease, such as PD. We are also interested in in vivo screening for potential therapeutic drugs to treat these diseases. We are using C. elegans as a model organism and a combined approach of molecular genetics, biochemistry, cell biology, in vivo calcium imaging and bioengineering. C. elegans is a facile genetic model widely used in biomedical area including research of human diseases.

Stanton Gerson, M.D., Professor of Medicine and 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 alkyguanine-DNA alkyltransferase (AGT) in mediating resistance to several chemotherapeutic agents, and they have led in the discovery and development of the AGT modulator O6benzylguanine 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 methoxamine 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 of Pathology, member of the Membrane Biology and Translational Therapeutics Tracks.

Antigen processing converts protein antigens to peptide-MHC complexes that can be recognized by T cells. Class I MHC (MHC-I) and class II MHC (MHC-II) molecules are loaded with peptides *via* two distinct "conventional" processing pathways. MHC-II molecules target to endocytic compartments or phagosomes to bind peptides from exogenous antigens that are cleaved by vacuolar proteases. In contrast, MHC-I molecules are loaded in the endoplasmic reticulum (ER) with peptides that are produced by proteosome cleavage of cytosolic antigens and imported into the ER by TAP. In addition to these "conventional" pathways, The Harding research group is are studying "alternate" pathways with different processing mechanisms. Much of their effort is now directed to understanding regulation of antigen presenting cell (APC) function in the context of infectious diseases, *e.g.* tuberculosis and HIV infection. APCs sense pathogens by innate immune receptors, including Toll-like receptors (TLRs), and are regulated by cytokines and interferons that are produced during infection. For example, they are studying recognition of Mycobacterium tuberculosis by TLRs and the dysregulation of type I interferon responses by APCs from HIV-infected patients.

Charles Hoppel, M.D., Professor of Pharmacology and Medicine, Chief of Clinical Pharmacology, Director of the Center for Mitochondrial Diseases, member of the Membrane Biology & Pharmacology and Translational Therapeutics Tracks.

The main focus of the laboratory is mitochondrial fatty acid oxidation. The organization of the pathway for mitochondrial fatty acid oxidation is of particular interest as a potential site for control of the system. Mitochondrial contact sites contain the protein translocases for protein translocation into the mitochondria and the peripheral benzodiazepine receptor. They have data that support the localization of key enzymes, such as the long-chain acyl-CoA synthetase and carnitine palmitoyltransferase of fatty acid oxidation to these contact sites. They have proposed a fatty acidlcarnitine shuttle through the contact sites. The characterization of this shuttle coupled with the determination of its localization within the mitochondria will be essential steps. In addition to the primary basic science focus of the lab which is pertinent to the Membrane Biology Track, Dr. Hoppel's roles as Chief of Clinical Pharmacology and Director of the Mitochondrial Diseases Center put his laboratory at the natural interface of Translational Therapeutics. He oversees many clinical studies

aimed at understanding the cell and molecular basis of diseases and devising and testing novel interventions.

Jonathan Karn, Ph. D., Professor and Chair of Molecular Biology & Microbiology, member of the Molecular Pharmacology & Cell Regulation and Translational Therapeutics Tracks.

Dr. Karn joined the CWRU Faculty as Chair of Molecular Biology & Microbiology after spending 22 years at the Laboratory of Molecular Biology at the Medical Research Council (MRC) in Cambridge, England, which is the United Kingdom's equivalent of the NIH. His research on the molecular signals that trigger HIV growth led to the discovery of several novel drug targets and the formation in 1997 of the UK-based, private biotech company Ribo-Targets Ltd. Current research is focused on circumventing the HIV viral defenses against anti-viral agents. If HIV hides in the host cell's DNA in a latent state, existing anti-HIV drugs cannot destroy the virus. In order to flush the virus out so that it can be targeted by drugs, we need to understand the process whereby HIV can be activated. Dr. Karn's group is studying the LTR promoter region of the HIV virus that is responsible for auto-activation of viral replication. They will assess which human and viral proteins transduce signals to the LTR and in which sequence, in order to more fully understand how HIV could be activated as a therapeutic strategy to target otherwise latent virus.

Thomas Kelley, Ph.D. Assistant Professor of Pediatric Pulmonology and Pharmacology, member of the Molecular Pharmacology 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 regulation of Smad3 expression as a modulator of fibrotic disease* - Having observed reduced expression of Smad3 in CF airway epithelial cells, the Kelley lab has pursued studies of regulatory mechanisms that may explain this observation. These studies revealed the potential role of isoprenoids in modification of small GTPase proteins Ras and Rho that in turn may regulate Smad3 signaling. In addition they determined that a protein involved in MAPK activation is essential in maintaining Smad3 promoter function. Identifying other modes of Smad3 promoter regulation and determining methods of modulating the severity of fibrotic diseases by manipulating Smad3 expression are the current objectives of this project.

Ruth Keri, Ph.D., Assistant Professor of Pharmacology, co-Leader of the Cancer Therapeutics Track, member of the Molecular Pharmacology and Cell Regulation Track.

Research in 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. We have recently found that an inhibitor of mTOR action, rapamycin, induces regression of HER21Neu induced mammary tumors in mice. We 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 and Pharmacology, 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 our present understanding of this retinopathy. 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. We have 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.

Alan Levine, Ph.D., Professor of Medicine and Pharmacology, member of the Molecular Pharmacology & Cell Regulation Track.

The intestinal mucosa is the largest lymphoid organ, as assessed by antibodies produced, resident leukocytes, and surface area exposure to the environment. Further, the wall of the gut 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 gut, 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 in response to gut injury; (2) mechanisms by which co-stimulatory and accessory molecules direct the development of immune tolerance; (3) biochemical, spa-

tial, 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 nai've and memory T cells by the interstitial extracellular matrix; (5) biochemical signaling pathways emanating from integrin mediated adhesion of intestinal epithelial cells to the basement membrane; and (6) evaluation of a gene targeted murine model of colitis associated colorectal cancer.

John Letterio, M.D., Professor of 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-13 in hematopoietic and immune cell function. The prototype of this family, TGF-131, 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 in the TGF- 131-1- mouse allowed the Letterio lab to provide the first direct evidence that a TGF-131-deficiency state predisposes to multiple pathogenic manifestations of autoimmunity. Furthermore, endogenous TGF-131 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-131- deficiency.

Johannes von Lintig, Ph.D Assistant Professor of Pharmacology, Molecular Pharmacology & Cell Regulation

Danny Manor, PhD Associate Professor of Nutrition . Associate Professor of Pharmacology

My research team aims to gain molecular-level answers to basic questions that surround the etiology, treatment and prevention of cancer. Our research interests can be divided to 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').

Michael Maguire, Ph.D., Professor of Pharmacology, Co-Leader of the Membrane Biology Track, member of the Molecular Pharmacology Track.

Dr. Maguire's laboratory, in collaboration with the Structural Genomics Consortium of the University of Toronto, has recently solved the structure of a closed form of the CorA Mg2+ channel from *Thermatoga maritima.* CorA is the first divalent cation channel to have it's structure solved. It is a homolog of the mitochondrial Mg2+ channel, Mrs2p. Current work focuses on a) determining the structure of an open form of the CorA channel, b) functional studies on CorA using site-directed mutagenesis, transport assays and electrophysiology, c) the structure of the Mrs2p channel and d) the role of CorA in *Salmonella* pathogenesis. Further knowledge of the structure/function of Mg2+ transport systems and their role in Mg2+ homeostasis will lead to better understanding of the role of Mg2+ in pathogenesis, mitochondrial function and electrolyte disorders.

Shigemi Matsuyama, Ph.D., Assistant Professor of Medicine-Hematology/Oncology and Pharmacology, member of the Cancer Therapeutics Track.

Dr. Matsuyama studies (1) the molecular mechanism of programmed cell death, and (2) the development of drug-delivery system using cell penetrating peptides. His group found that Ku70 keeps Bax (a key protein inducing apoptosis) at 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 brake repair. Dr. Matsuyama's laboratory is investigating how apoptotic stress such as DNA damage modifies Ku701s activity to regulate Bax activity. The understanding of the mechanism of Ku70 modification will contribute the understanding of apoptosis-resistance mechanism of cancer cells. Dr. Matsuyamals laboratory found a new series of cell permeable penta-petides. Dr. Matsuyama's laboratory is investigating the mechanism of membrane penetration by the cell permeable penta-peptides, and the potential application of these peptides for drug delivery into the cell.

Paul N. MacDonald, Ph.D., Associate Professor of Pharmacology, Co-Leader of the Molecular Pharmacology Track, member of the Cancer Therapeutics Track.

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 my laboratory is to understand the molecular details and signaling mechanisms involved in VDR-mediated gene expression. We are currently focusing 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.

John J. Mieyal, Ph.D., Professor and Vice-Chair of Pharmacology, Director of the MTTP, member of the Molecular Pharmacology & Cell Regulation and Membrane Biology & Pharmacology Tracks.

Recently it has been recognized that 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 known 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. Our lab is focused on delineating the enzymatic mechanisms of reversible glutathionylation, and understanding how these link extracellular stimuli to downstream cellular events in health and disease.

Monica Montano, Ph. D., Assistant Professor of Pharmacology, member of the Molecular Pharmacology & Cell Regulation and Cancer Therapeutics Tracks.

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 this 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 (HEXIMI). Animal models have been generated that support the role of HEXlMl as a tumor suppressor and anti-angiogenic factor. We have also defined the mechanistic basis for HEXlMl regulation of mammary gland tumorigenesis/angiogenesis.

Noa Noy, Ph.D. Professor of Pharmacology, Molecular Pharmacology & Cell Regulation AND Cancer Therapeutics (co-Leader)

Various lipid-soluble nutrients and hormones, such as vitamin A, vitamin D, cholesterol, and long chain fatty acids, regulate cellular behavior by modulating the rates of transcription of multiple genes. The biological activities of these compounds are mediated by transcription factors termed nuclear hormone receptors. These proteins bind to regulatory regions of particular target genes, and they modulate the transcription of these genes in response to the specific hormones that activate them. Consequently, nuclear receptors and their activating hormones have profound effects on cell growth, metabolism, and differentiation, and they are involved in numerous physiological processes. Nuclear receptors also play key roles in various pathologies, and ligands that activate them are in current use as therapeutic and preventive agents in diseases ranging from dermatological disorders to cancer. Work in my laboratory aims to obtain molecular-level understanding of the mechanisms of action of nuclear hormone receptors and their accessory proteins, and to elucidate the consequences of the activities of these proteins for cell function in health and in disease. Of special interest to us are the roles of nuclear receptors in cancer development, in adipose tissue biology, and in diabetes.

Paul S.-H. Park, Ph.D. Assistant Professor of Ophthalmology and Visual Sciences and Pharmacology, member of the Molecular Pharmacology and Membrane Biology & Pharmacology Tracks.

The goal of Park laboratory is to understand the mechanism of signal transmission at the molecular level in phototransduction and other G protein-coupled receptor-mediated signaling systems. The specific aims of our research that will help us achieve our goal 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 formed by 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 the mechanism by which mutations in rhodopsin lead to vision-related disorders. We use modern biophysical approaches to tackle these issues including atomic force microscopy (AFM), single-molecule force spectroscopy (SMFS), and fluorescence-based methods.

Kris Palczewski, Ph.D., Professor and Chair of Pharmacology, Director of the Center for Membrane Biology, Co-Leader of the Membrane Biology Track, and member of the Translational Therapeutics Track.

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 baseline information for further studies of retinal disease processes.

Susan Redline, M.D., M. P.H., Professor of Pediatrics and Epidemiology and Biostatistics, member of the Translational Therapeutics Track.

Professor Redline's research program is multifaceted with a primary focus on the study of sleep disorders. She heads a Sleep-Heart Health Center that has pioneered approaches for collecting, processing, and analyzing complex polysomnography data and assisted in protocol development, centralized scoring, and quality control for sleep studies to better understand cardiovascular morbidity occurring with sleep apnea. Outcomes of sleep disorders in adolescents is special interest of her research group. This study assesses the prevalence, risk factors, and associated co-morbidity (neurocognitive, behavioral, and metabolic) of sleep disorders in children, ages 13 to 16 years. The study will also determine the rate or progression, and determinants of progression, of sleep disordered breathing from middle childhood through adolescence. Dr. Redline is an important asset to the Advanced Training Track in Translational Therapeutics because of her experience in design and oversight of clinical studies and her expertise in statistical analysis.

Alvin Schmaier, M.D., Professor of Medicine and Chief of Hematology-Oncology, member of the Translational Therapeutics Track.

Basic research efforts in the Schmaier laboratory examine the influence of the kallikrein/kinin system on vascular biology and its relation to blood pressure regulation and thrombosis. His translational research interests are in anticoagulant development of selective thrombin and thrombin receptor activation antagonists for treatment of cardiovascular disease and cancer. He is the founder and CEO of Thromgen, Inc., Ann Arbor, MI, and currently has an IND study underway.

Bingcheng Wang , Ph.D., Associate Professor of Medicine-Nephrology, member of the Cancer Therapeutics and Translational Therapeutics Tracks.

The primary interest of the Wang laboratory is understanding the molecular mechanisms governing tumor metastasis, a frequently fatal phase of tumor progression in cancer patients. Agents that can suppress either cell motility or MAPK activity can be exploited to prevent andlor treat metastasis. The Wang laboratory has found that agonists of EphA kinases, including EphAl and EphA2, possess the unique ability to inhibit cell motility and suppress the Ras/MAPK cascade. Current research involves the isolation and characterization of new and more potent agonists of Eph kinases as novel therapeutics to prevent and/or treat tumor metastasis. In addition, the Wang laboratory is searching for small compounds that can bind and modulate Eph kinase function through virtual screening using super computers. Candidate compounds are then tested *in vitro* and *in vivo* for anti-cancer activities.

Yu-Chung Yang, Ph.D., Professor of Biochemistry, member of the Cancer Therapeutics and Molecular Pharmacology & Cell Regulation Tracks.

Dr. Yang and her former colleagues at Genetics Institute were responsible for the cloning of three cytokines: human interleukin (IL)-3, -9 and -11. FDA approved IL-I I in 1997 for treating cancer patients with severe chemotherapy-induced thrombocytopenia. It is the first thrombopoietic agent to be approved for clinical use in the United States. They have been interested in studying signaling molecules that may determine cytokine specificity and redundancy. While studying cytokine-dependent signal transduction, Dr. Yang's laboratory cloned Cited2, a transcription factor induced by many biological stimuli and a transforming gene when overexpressed. The laboratory generated Cited2- knockout mice and showed that Cited2-null embryos die at mid-gestation, with defects in heart, lung, liver, eye and hematopoietic development. More recently, the laboratory has also shown that Cited2 is a coactivator of Smads and a negative regulator of HIF-1, is overexpressed in the mammary tumor of MMTV-neu and MMTV-PyvMT transgenic mice and plays an important role in epithelial-mesenchymal transdifferentiation (EMT). Mechanistic studies are underway to study the role of Cited2 in embryonic development and tumorigenesis.

Vivien Yee, Ph.D., Assistant Professor of Biochemistry and Pharmacology, member of the Membrane Biology & Pharmacology Track.

Dr. Yee's laboratory uses X-ray crystallographic methods to determine and analyze the structures of medically important proteins and of 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:substrate peptide structures, to provide some 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. We are also investigating the 1.2 million Dalton transcarboxylase multienzyme complex. Our structures of its large 5s and 12s catalytic subunits serve as models for related mammalian metabolic enzymes, and allow us to speculate on mechanisms and the structural consequences of disease mutations. Finally, in collaboration with the Maguire laboratory, studies are underway on the structure of the CorA Mg2+ channel, specifically to determine the structure of the open form of the channel and the structure of CorA homologs

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