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Preface

This Handbook provides an overview of the Graduate Program in Pharmacology at Case Western Reserve University under the auspices of the Molecular Therapeutic Training Program (MTTP), which is funded in part by an institutional NRSA training grant from the NIH (T32GM008803). 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 2016-2017 academic year and beyond. Students who began prior to 2016 follow the guidelines that were in effect during the year they began, except where the recent changes are designated for all students.

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

John Mieyal, Ph.D.
Vice-Chairman and MTTP Director
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 the biomedical sciences. In 1994, Alfred Goodman Gilman, an M.D., Ph.D. graduate of the Department, was awarded the Nobel Prize in Physiology or Medicine for his characterization of signal transduction via G-proteins. In 1998 the Nobel Prize in Physiology or Medicine was awarded to another alumnus of the Department, Ferid Murad, M.D., Ph.D., recognizing his discovery of the role of nitric oxide (NO) in intercellular signaling.

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

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

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

Current Departmental Information:

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

Important contacts:

Chairman:  
Krzysztof Palczewski, Ph.D. (kxp65@case.edu / 368-1300)

Vice- Chairman and Graduate Program Director:  
John Mieyal, Ph.D. (jm5@cwru.edu / 368-3383)

Graduate Program Coordinator:  
Kristine Basso (kristine.basso@case.edu / 368-4617)

Business Manager / Executive Asst. to the Chair:  
Vida Tripodo (vmt1@case.edu / 368-1300)

Accounts Payable:  
Rachael Griffis (rag120@case.edu)

Information Technology Support for Pharmacology:  
David Pilasky (CaseMEDhelp@case.edu / 368-4669)
Department of Pharmacology & Medical School Facilities

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

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

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

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

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

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

Other Facilities:

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

Pharmacology Conference and Seminar Rooms: The Department provides a seminar room with state-of-the-art features and seating for over 70 people. The seminar room’s features include a built-in projector, dry erase boards, and a complete electronic system that can be either self-sufficient or can accommodate both PC and Mac computers. In addi-
Cleveland Center for Membrane and Structural Biology (CCMSB): The CCSMB is a joint venture between Case Western Reserve University and the Cleveland Clinic Foundation, administratively overseen by the Department of Pharmacology (http://ccmsb.case.edu), and directed by Dr. Phoebe Stewart, Professor of Pharmacology. The Center provides access to sophisticated instrumentation which is housed at various sites in the School of Medicine and in the newly renovated building at the nearby West Campus. The NMR facility is well equipped with state of the art NMR instrumentation, ranging from 600 to 900 MHz. Two Bruker 600, an 800 and a 900 MHz are equipped with cryogenic probes for solution NMR work. The 800 MHz instrument can also be switched to solid-state operation. The X-ray core facility is equipped with a Rigaku MicroMax-007HF, second-generation microfocusing rotating anode generator, Osmic VariMax optics, a Saturn 944+ CCD detector and X-stream 2000 cooling system. The system is used for crystal screening and data collection. The high beam flux along with the CCD detector speedily collects images by exposing the crystals for a few seconds. The Electron Microscopy facility features two high-end 200 kV cryo-electron microscopes for high-resolution imaging of single complexes and 2D crystals and for cryo-electron tomography. A 120 kV EM is used for sample screening and conventional imaging of sections and negatively stained samples. The Facility also has sample preparation equipment for single particle cryo-EM, 2D crystallography and tomography.

The Protein Expression Purification Crystallization Core is a state-of-the-art robotic laboratory that facilitates the crystallization of soluble and membrane proteins for structure determination by X-ray crystallography. The PEPPC is located in the Department of Physiology and Biophysics within the School of Medicine, serving investigators throughout Greater Cleveland (http://pepcc.case.edu).

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

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

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

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

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

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

Cytometry & Imaging Microscopy Core Facility (Director: James Jacobsberger, Ph.D.) - The Cytometry core provides flow and laser scanning 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 experi-
mental design, teach the principles of cytometry, and develop protocols and approaches as a set of tools designed to assist cancer research.

Small Molecule Discovery Core (Director: Drew Adams, Ph.D.) - To propel translation of novel findings of disease biology toward effective therapies, CWRU has launched a small molecule drug discovery core (SMDDC), which is located on the west quad campus. Small-molecule high throughput screening (HTS) is a powerful unbiased method to find novel starting compounds for drug development. The state-of-the-art facility has 5 work stations dedicated for tissue culture, liquid handling, compound treatment, and microplate reading. The Enspire microplate reader is compatible with absorbance, fluorescence, luminescence, ALPHAlisa and Label-Free assays. The Operetta high-content imager is equipped with common fluorescence channels and capable of analyzing images of fixed or live cells in 384-well plates. Current setup allows both target-based and phenotypic HTS screens. The SMDDC currently has a 50,000-compound diversity set and a 1,280-compound bioactives set, which serve both small-scale pilot screens and large-scale HTS.

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 Departmental Journal Club which provides the opportunity for the students to present current research findings to the entire department. In addition, the Annual Departmental Retreat showcases the scientific accomplishments of the entire program and brings the community of faculty, students and 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 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 for guidance and constructive criticism of their written assignments and presentations. The listing of requirements and expectations that are detailed below may seem daunting at times, but the Pharmacology graduate student community here is an assembly of caring individuals who are very willing to help by providing notes for classes, tips for preparing for exams, and feedback on practice oral presentations. Collectively the faculty and students are proud of our program, because it holds everyone to a high standard of excellence, provides guidance and assistance through tough spots, and celebrates achievement!

Stipends, Tuition and Taxes

All registered Molecular Therapeutics Training Program (MTTP) students matriculating on a full-time basis are eligible to receive tuition and stipend support. The stipend level for the 2015-2016 academic year is $27,500; and this will increase to $28,500 in July 2016. 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.

As described under the Prelim II guidelines, all students are encouraged to revise and submit their thesis proposals to granting agencies for fellowship support (e.g., an NRSA from the NIH). Students who earn a fellowship that provides at least 75% of the current stipend amount will be awarded a stipend bonus of $2,000 per year in addition to the MTTP stipend, pro-rated to cover the period of extramural fellowship support. If the extramural fellowship provides a stipend higher than the current MTTP stipend plus $2000 (i.e., >$29,500 currently), the student will receive the full level of stipend provided by the fellowship award.

Stipend checks will be automatically deposited into student accounts once a month. Arrangements for direct bank deposit of funds may be made through http://hcm.case.edu.

Tuition rates are set annually by the CWRU Board of Trustees. The per credit hour rate for tuition during the academic year 2016-2017 is $1744.00. Tuition for MTTP graduate students is funded by NIH institutional training grants, individual fellowships, or university resources.

Neither CWRU nor the MTTP may advise students about their tax liability. Students can obtain information and tax forms and publications at local libraries and post offices. Additional tax concerns include: Individuals must take the initiative to identify themselves to their residential community to trigger the Regional Income Tax Authority’s awareness of their 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
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Please contact the MTTP Director or Coordinator for any other financial issues regarding tuition and stipends. In addition, students should contact Kristine Basso 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 Case Western Reserve University Student Medical Plan offered to students registered for one or more credit hours. Visit: http://students.case.edu/medicalplan for more information.

Students with private insurance, comparable to the Student Medical Plan, may submit a waiver online in the Student Information System (SIS). *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.*

Students registered for one or more credit hours are eligible to use the University Health Service Clinic for medical services. There is no charge for the visit. You do not need to have the Student Medical Plan to use the Health Service. For more information on the services provided, check the Health Services web site at http://students.case.edu/health/ If you are covered by the University insurance plan and are registered for the fall and spring semesters, your health insurance is also covered in the summer. However, if you are covered by private insurance and want to visit the University Health Service Clinic in the summer, you will be charged a one-time fee of $80 at your first appointment. If you never need service, you’ll never need to pay the fee. If you need service multiple times, the initial $80 fee will cover all visits. For more information, check the Health Services web site at: http://students.case.edu.

**Registration**

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

Consultation with the MTTP Graduate Program Director and Coordinator. Students will meet initially with the Director and Coordinator 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 Coordinator will supply information each semester prior to the registration period. *All electives, and any variations from the typical plan of study, need to be approved by Dr. John Mieyal.*

Registration. The Student Information System (SIS) is the system of record for student information and the university course catalog. Students use the SIS to register for classes, view grades, view their progress towards graduation, and for other important business.

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

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

**Planned Program of Study**

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

**Monitoring/facilitating student progress**

Besides regular interaction with the thesis mentor, there are two other major mechanisms in the MTTP to monitor student progress and provide assistance. The first mechanism involves the MTTP Steering Committee, which conducts an annual
review of all MTTP students, commending those who have excelled and providing specific feedback to those who have areas for improvement. All students who have passed Prelim II are expected to meet with their Thesis Progress Committees at least every 6 months (see below). These committees are applicable for Ph.D. students and for plan A (thesis) M.S. students.

**Thesis Progress Committee Meetings**

Thesis Progress Committees, chaired by a member of the primary Faculty of Pharmacology who can commit to this responsibility for the duration of the student's studies, are selected by the student and thesis advisor in consultation with the Director of the MTTP. Selection of the Committee should occur before the end of March in Year Two. Each Committee includes two primary members of the Faculty of Pharmacology and two other faculty members with expertise complementary to the student's thesis project. Students are required to meet with their Progress Committee for the first time at least two weeks in advance of submitting their final written proposal for Prelim II. Normally, this first meeting should occur before August of Year Two in order most effectively to provide helpful guidance for Prelim II (see description of Prelim II, below). Thus, the first committee meeting, along with the Grant Writing Workshop, is expected to facilitate the student's preparation of their thesis research proposal. Therefore, at the first meeting (scheduled for a 2-hr period) the student should present (in about 30-45 min) an outline of their research proposal, including background, specific aims, and supporting data, so that the Committee can provide feedback valuable to completing the full written proposal. The Chair of the Thesis Progress Committee (primary Pharmacology faculty member) is selected at this first meeting. The Committee Chair will coordinate the assessment of the Prelim II proposal and oral exam, and convene subsequent meetings of the Committee as described below.

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

One of the primary responsibilities of the MTTP Steering Committee (comprised of the MTTP Director and the co-Leaders of each of the Advanced Tracks) is to review, evaluate and recognize student performance and progress throughout their time in the Program. Each student is evaluated annually by the full Steering Committee, and at other times during the year as the need arises. It is the responsibility of the faculty mentors to provide evaluations for their students in a timely manner preceding the annual review of students. Confidential reviews and action plans, shared with the student and mentor, are recorded for each student at the time of the annual review and are maintained by the Program Coordinator in consultation with the Program Director. Multiple documents form the basis of this annual review, including academic coursework transcripts, planned programs of study, rotation reports, departmental retreat presentation evaluations, prelim exam evaluations, committee meeting evaluations, and evaluations provided by the research mentor.

In addition, self-prepared biosketches are collected for each student, documenting publications in print, in press, and in preparation, as well as honors and awards; and service to fellow students, the Training program, the Department, the School, or the University. On the basis of these reviews, students may be recognized for their accomplishments in the form of a letter of commendation from the Committee. One model student is chosen each year to receive the Graduate Student of the Year Award, which is presented at the Annual Pharmacology Retreat. Deficiencies in individual student progress are also identified and action plans are agreed upon to help the student overcome the deficiencies. In some cases, after formal consultation between the graduate student, mentor, and the Steering Committee, a student may be placed on academic probation to reflect the seriousness of the lack of progress (coursework and/or research). In most cases, the students are returned to good standing and complete the MTTP requirements for the Ph.D. In other cases, even with frequent intervention by the Thesis Progress Committee and/or the Steering Committee, the student is not able to fulfill the Ph.D. requirements. In these cases, the Steering Committee may recommend to the full primary Faculty of Pharmacology either that the resignation of the student be accepted, or that the student be dismissed from the Program. A majority vote of the primary faculty is required for these actions. In cases where there are difficulties with a student’s progress in research or research environment, the Steering Committee meets with both the student and the mentor privately to assess the basis and seek a resolution, which may include transfer to another laboratory or discontinuation in the Program.

Steering Committee Roster (2015-2016)

John Mieyal, Director of the Molecular Therapeutics Training Program (MTTP)
Phoebe Stewart, co-Director of the MTTP; co-leader of the Membrane and Structural Biology and Pharmacology Track
Derek Taylor, co-Leader of the Membrane and Structural Biology and Pharmacology Track
Ruth Keri, co-Leader of the Cancer Therapeutics Track
Scott Welford, co-Leader of the Cancer Therapeutics Track
George Dubyak, co-Leader of the Molecular Pharmacology and Cell Regulation Track
Johannes vonLintig, Co-Leader of Molecular Pharmacology and Cell Regulation Track
Marvin Nieman, co-Leader of the Translational Therapeutics Track
Goutham Narla, co-Leader of the Translational Therapeutics Track
Harry Scott and Leslie Cuellar Vite, Student Representatives / 2016/2017: Leslie Cuellar Vite and Deoye Tonade

Student Records

The MTTP Coordinator maintains a file of the progress of each graduate student. A student may request, in writing, an opportunity to review the contents of their educational file. Certain materials are excluded from review as specified in the Family Educational Rights and Privacy Act of 1974 (FERPA). The FERPA contains several provisions that are important to students. Specific provisions are printed in the University’s General Bulletin. Students may also obtain from the Office of the Provost a copy of the policy, which the University has adopted to meet the requirements of FERPA. As noted above, students are expected to provide periodically updated biosketches for review by the MTTP Steering Committee and for publication on their personal websites linked to the Department website.
The MTTP Graduate Student Organization

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

GSO Officers, 2016-2017
President: Leslie Cuellar-Vite, and Graduate Student Council representative
Vice President and President-Elect: Deoye Tonade
Secretary: Tessianna Misko
Past President: Harry Scott
Biomedical Graduate Student Organization (BGSO) Representatives: Sahil Gulati and Melyssa Shively
Biomedical Graduate Student Symposium (BGSS) representative(s): Caitlin O’Connor and Tessianna Misko
Social Chairs: Corey Emerson and Chris Sander
Student-Invited Seminar Series Chairs: Caitlin O’Connor and Abbey Perl
Career Series Chair: Mary Kelly with help from Christine Lee and Phil Ropelewski

Seminar Programs/Lectures

All MTTP students are required to attend the weekly seminars and special lectures offered by the Department of Pharmacology.

Weekly Frontiers in the Pharmacological Sciences
Seminars are arranged according to faculty recommendations and student recommendations. Student invitees are arranged and hosted by the GSO. Students may invite as many seminar speakers as the seminar schedule will allow. The rationale for student-invited speakers is several-fold. The students are engaged directly, the speakers are especially honored by student-initiated invitations, and the student speaker interactions are an important part of the Training Program, expanding the students’ awareness beyond CWRU. Pharmacology Seminar meets every Tuesday at 12 noon in the Webster conference room, W331. For each invited outside speaker a luncheon is arranged with one sub-group of the graduate students on a rotating basis, providing opportunities for the students to interact in an informal setting with investigators from other academic institutions or industrial companies to gain perspective on career advancement options as well as to initiate potential networking contacts.
Weekly Pharmacology Journal Club

Students, postdoctoral fellows, faculty, and other research personnel convene to review frontier topics in the pharmacological sciences on a weekly basis. The schedule is organized according to the Advanced Training Tracks of the MTTP. To encourage discussion, all regular attendees are provided a copy of the published article to read in advance. Formal participation in Journal Club is an integral part of the MTTP curriculum (see PHRM 511 on p. 19). Advanced students and postdocs are encouraged to relate their current research findings in the context of their Journal Club presentations. Students are also encouraged to participate in journal clubs sponsored by their thesis laboratory or by other programs especially pertinent to their research interests. Pharmacology Journal Club meets every Thursday at 3:00 pm in the Webster Conference Room/W331.

Sternlicht Family Memorial Lectureship in Cancer Biology and Pharmacology

This annual lectureship was originally established as a mechanism to honor the memory of Robert Sternlicht, late son of Himan and Mona Sternlicht, by helping to promote scientific interactions and dissemination of knowledge in cancer biology and pharmacology. In 2008 Himan Sternlicht, Ph.D., Professor of Pharmacology, also died of cancer. In 2009 his wife and research partner Mona Sternlicht died in her sleep. Both Hi and Mona were long-term members of the Department of Pharmacology, and the lectureship now honors all three members of the family.

Nathan S. Greenfield Family Lecture

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

Weekly Seminar Series in BSTP Programs and the School of Medicine

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

Frontiers in the Biological Sciences Lecture Series

This long-standing lecture series brings at least eight distinguished scientists to the medical school campus each year. The Pharmacology Department hosts one speaker each year.

SURP Seminar Series

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

Other Departmental Events

Annually

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

BSTP Graduate Student Orientation – The MTTP Director and/or MTTP Recruitment and Admissions Director, along with GSO officers, meets with the first year BSTP students before the Fall Semester to provide an overview of the Department and the Program, and to invite students to visit posters representing the research of MTTP trainers and their students.
Pharmacology Winter Holiday Celebration and/or Summer Picnic—Usually during mid-December or summer 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. Inaugurated in 1998, the Departmental Retreat is held off-campus and typically is scheduled for two days. The purpose of the retreat is fourfold. First, it provides a training opportunity for students and post-doctoral fellows to hone their presentation skills. Second, it fosters collaborative interactions and unity among all those affiliated with the Department. Third, it provides a unique opportunity for the entire Department to participate in workshops on leadership, mentoring, teaching, and other departmental initiatives. Fourth, it showcases the Department to potential benefactors. All Pharmacology graduate students and selected post-doctoral fellows are invited to make either an oral or poster presentation. The oral presentations are 10 minutes in length and are followed by 5 minutes of questioning. A separate session is set aside for poster presentations. These scientific presentations simulate the atmosphere of a national/international professional meeting. Although all faculty members attend the retreat, the focus of this event is on the work that the students have accomplished. Therefore, as a general rule, principal investigators do not give presentations. However, each session is overseen by a session chair who may be a faculty member. The job of the session chair is to provide a 5 minute overview to the audience of that research track and the type of research being done. In addition, two to three "provocateurs" are assigned to each session (usually a mixture of faculty, postdocs, 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 150 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.

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

Leave of Absence from Graduate Study

MTTP students undertaking graduate work are expected to pursue their studies according to a systematic plan each year, registering for credit according to the guidelines for a typical program of study (as delineated below).

Occasionally a student finds it necessary to interrupt his or her studies before completion of the graduate program. Under such circumstances the student must request, in writing, a leave of absence for a period not to exceed one calendar year, explaining the circumstances. This request, which requires endorsement by the student’s advisor, the MTTP Director, and the Department Chairperson, must be approved by the Dean of Graduate Studies.

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

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

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

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

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

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

**The SBBTP** emphasizes quantitative methods and equips students to study cell and protein structure and function using state-of-the-art instrumentation and computing. SBB-TP spans research areas from several of Case’s departments and centers. Students can enter this training program by admission to the Interdepartmental Structural Biology and Biophysics Training Program. The first semester curriculum is designed to give students without much background in biology an introduction to cell and molecular biology, with two courses known as C3MB (CBIO453/455). Three short laboratory rotations in the first semester and attendance of seminars of the participating departments and a journal club co-organized by the Cleveland Center for Membrane and Structural Biology offer in-depth information about ongoing research projects and opportunities for thesis research projects. After the first semester, students join the graduate program in either Biochemistry, Pharmacology, Physiology & Biophysics, or in Systems Biology. (For more information on this alternative track, see: [http://sbb-tp.case.edu](http://sbb-tp.case.edu).

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

**Thesis advisor selection** is coordinated through each program (MTTP, BSTP, or MSTP). It has been the policy of the Pharmacology Department to base Training Faculty status and the opportunity to accept a graduate student for Ph.D. training on the demonstrated or potential training skills of the mentor with emphasis on a training environment that provides opportunities for regular interaction with other students and faculty in the Department as well as access to major research facilities. At the time of selection, the advisor is expected to be conducting an active, independently funded re-
search program. All student-advisor matches are approved by the MTTP Director and the Chairman of Pharmacology to ensure a departmental commitment to the student throughout the training period. In some cases, based on the collaborative nature of the project a student may have more than one mentor providing complimentary expertise. In such cases, one of the mentors provides the primary lab environment and assumes the primary responsibility for facilitating the student’s progress through the program.

INTRODUCTION TO THE MTTP

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

Overview of MTTP Design

The Molecular Therapeutics Training Program is developed in three progressive phases (Figure 1). Stage 1: At the outset, all students are enrolled in the Core Curriculum in Cell and Molecular Biology (C3MB) [or the equivalent in the medical curriculum for M.D. /Ph.D. students] to provide a common foundation in the principles and practice of cell and molecular biology and biochemistry, including protein chemistry and enzymology. Concurrently the students explore at least three different mentoring opportunities and laboratory environments (research rotations) to gain research experience and select a thesis laboratory. Stage 2: Students focus on research and study pertinent to evolving their thesis project, and they immerse themselves in an intensive two-part core course in pharmacology, emphasizing the physiological and molecular bases for understanding the actions of drugs, and then placing the study of particular drug classes in the context of the targeted diseases. Upon selection of a thesis lab, each student is assigned to a particular advanced track according to the interests of the student and the mentor and the anticipated nature of the thesis project. An elective course pertinent to the advanced track is selected each semester to be completed along with one of the components of the Pharmacology Core Course (see Fig. 3, below). Stage 2 culminates in a comprehensive written exam (Prelim I) that assesses each student’s ability to demonstrate understanding of the core principles of their coursework by responding to questions that challenge them to apply key concepts in new contexts, including situations derived from assigned literature articles. Success in Stage 2 results in advancement to Ph.D. candidacy. Stage 3: Students are now focused on developing their specific thesis project. During the initial period of stage 3, students participate in a Grant Writing workshop and incorporate their pilot data into a specific research plan written in the style of an individual NRSA proposal which they defend orally (Prelim II) (see Prelim Exam I & II descriptions, below). The benchmarks of success in Stage 3 are research accomplishments and knowledge sufficient to foster at least two first author original research publications and an erudite thesis presentation and defense. Success in Stage 3 results in award of the Ph.D. degree.

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

Each of the Advanced Training Tracks are well-represented by interactive, collaborative trainers in Pharmacology and other basic and clinical departments throughout the Medical School. The trainers in each track are proposed by the co-leaders of the track and confirmed by the entire Steering Committee which includes the leaders of the Tracks (see Administration, Fig. 2, below). According to research focus, expertise, and collaborative interactions each trainer may be included in one or two of the Advanced Training Tracks. Besides the opportunity to serve as primary thesis advisor for students within the Track, each trainer has the responsibility of serving on Prelim II Exam and Thesis Progress committees, as well as teaching in advanced courses and participating in journal clubs associated with the respective tracks. Besides scientific interactions, students and faculty of each track share in social functions at the Track, Program, and Department levels, adding to the cohesiveness and camaraderie of the training environment.

Figure 2. Administration of the Training Program

As director, Dr. Mieyal oversees all aspects of the program, in collaboration with Dr. Stewart. Scheduling and clerical responsibilities are accomplished by the Program Coordinator, Ms. Basso, who 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 / evaluation of program faculty, quality control of coursework, student performance, and oversight of admissions. The Recruitment & Admissions Committee participates in recruiting efforts, evaluates applicant credentials and interview performance, and makes all admissions decisions 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.
Graduation Requirements for a Ph.D.

Overview

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

Typical Training Program

The objective of the MTTP is to provide students with outstanding training in the cellular, molecular, and physiological basis for therapeutics both in the classroom and in the laboratory, with the ultimate goal of preparing them for independent careers in research and teaching.

To accomplish this goal, we have devised an intensive, multi-faceted training experience composed of:

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

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

The immersion in the rigorous, seminar-style two-part core course in Pharmacology during the spring semester of year one and the fall semester of year two provides a broad based foundation in the principles of pharmacology which is complimented by concurrent elective courses in the chosen area of specialization. The Pharmacology core courses and the elective courses have a common focus on challenging students to develop the scientific insight that is required to meet the demands of independent research. As indicated in Fig. 3, all students entering the Program with a bachelor's degree must complete 24 credit hr of graded coursework and 12 credit hr of pass / no credit (P/N) coursework (e.g., independent study, PHRM 601). Upon satisfactory performance in the coursework and seminar presentations, all students are eligible to advance to Ph.D. candidacy at the middle of their second year by successfully completing the comprehensive qualifying exam (Prelim I, see below). Remaining formal coursework is completed in spring of year 2, except for Prelim II. Thus, by the beginning of their third year, most students devote essentially 100% of their efforts towards dissertation research. The thesis proposal (Prelim Exam II) is preceded by a special workshop on grant writing and a meeting of each student with their Prelim II/Thesis Committee. Completion of Prelim II should occur no later than September 30 of Year 3. An important goal is for students to complete the Training Program in about 5 years. Specific courses and other training activities for the program are described below.

<table>
<thead>
<tr>
<th>Figure 3</th>
<th>Typical MTTP Curriculum / 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summer Year 1</td>
<td>* = Graded Courses (≥ 24 cr. hr.)</td>
</tr>
<tr>
<td>Research Rotation 0 - 1 credit hr</td>
<td>+ = P/N Courses (≥ 12 cr. hr.)</td>
</tr>
<tr>
<td>Fall Year 1</td>
<td># = Thesis research (≥ 18 cr. hr.)</td>
</tr>
<tr>
<td>CBIO 453 Cell Biology .............. 4 hr*</td>
<td>PHRM 401 Molec. Therap. ....... 3 hr*</td>
</tr>
<tr>
<td>CBIO 455 Molecular Biol. ........... 4 hr*</td>
<td>Advanced Track Elective 1 ...... 3 hr*</td>
</tr>
<tr>
<td>Research Rotation 2,3 .............. 0 hr</td>
<td>Research Rotation 2,3 .............. 0 hr</td>
</tr>
<tr>
<td>PHRM 601 Indep. Study .............. 1 hr*</td>
<td>PHRM 601 Indep. Research ....... 2 hr*</td>
</tr>
<tr>
<td>Selection of Thesis Adviser</td>
<td>PHRM 601 Frontier Pharmac. ..... 0 hr</td>
</tr>
<tr>
<td>IBMS 500 Profess’l Scientist ..... 1 hr*</td>
<td>IBMS 500 Profess’l Scientist ..... 1 hr*</td>
</tr>
<tr>
<td>Spring Year 1</td>
<td>Summer Year 2: Research in thesis lab (no formal registration)</td>
</tr>
<tr>
<td>Fall Year 2</td>
<td>Spring Year 2</td>
</tr>
<tr>
<td>PHRM 402 Physiol.Therap. ...... 3 hr*</td>
<td>Prelim I (during Jan.-Feb.); Admission</td>
</tr>
</tbody>
</table>
| Advanced Track Elective 2 ...... 3 hr* | Prelim II Thesis Proposal (by Sept. 30, Yr 3); PHRM 701, 16 credit hr 
| PHRM 601 Indep. Research ....... 2 hr* | PHRM 501 Frontier Pharm. ...... 1 hr* |
| PHRM 601 Frontier Pharm. ....... 1 hr* | PHRM 601 Indep. Research ....... 5-8 hr* |
| Summer/Fall Year 3: Independent research; PHRM 526, 2 hr* = grant writing workshop, Prelim II Thesis Proposal (by Sept. 30, Yr 3); PHRM 701, 16 credit hr |
| Years 3 - 5: Responsible Conduct of Research Seminars. |
| ....... Dissertation Research (PHRM 701, 18 hr total); Publications; Thesis Defense. |
Coursework

Planning the Study Program

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

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

Coursework and Hour Requirements

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

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

Core course requirements for the Ph.D. in Pharmacology

The first summer and fall consists of research rotations, the C3MB courses, and independent study (9 credit hours). The spring semester of year 1 includes the molecular therapeutics core course, the responsible conduct of research course, an elective course, seminars and independent study (9 credit hours). In fall of year 2 the physiological therapeutics core course, an elective course, the course in seminar presentation, and independent research are completed (9 credit hours). Coursework is completed in spring of year 2 along with Prelim I and admission to candidacy, permitting registration for independent research and study (9 credit hours). One to two additional graded credits are assigned to the completion of Prelim II (PHRM 526) by Sept. 30 of year 3. These requirements are presented in the Table below.

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Credits</th>
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<tbody>
<tr>
<td>1) Three Rotations (PHRM 400)</td>
<td>0</td>
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<tr>
<td>2) C3MB (CBIO 453)</td>
<td>4</td>
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<tr>
<td>3) C3MB (CBIO 455)</td>
<td>4</td>
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<tr>
<td>4) Becoming a Professional Scientist– Responsible Conduct of Research (IBMS 500)</td>
<td>1</td>
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<tr>
<td>5) Principles of Pharmacology I: Molecular Basis of Therapeutics (PHRM 401)</td>
<td>3</td>
</tr>
<tr>
<td>6) Principles of Pharmacology II: Physiological Basis of Therapeutics (PHRM 402)</td>
<td>3</td>
</tr>
<tr>
<td>7) Frontiers in Pharmacology, J Club Series (PHRM511)</td>
<td>2</td>
</tr>
<tr>
<td>8) Two advanced electives (from the Advanced Track offerings)</td>
<td>6</td>
</tr>
<tr>
<td>9) Prelim I Comprehensive Examination</td>
<td>0</td>
</tr>
<tr>
<td>10) Independent Research and Study (PHRM 601)</td>
<td>12</td>
</tr>
<tr>
<td>11) Prelim II Dissertation Proposal, including grant-writing workshop (PHRM526)</td>
<td>2</td>
</tr>
</tbody>
</table>

Descriptions of core courses

Each MTTP or BSTP student spends the first summer doing a research rotation in a particular lab; the direct-admit MTTP students choose 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; however, all students should begin their first rotation before the end of July. The fall semester is spent taking comprehensive coursework in cell and molecular biology and rotating through second and third research labs. Before the beginning of the second semester, MTTP and BSTP students choose a Ph.D. mentor, and BSTP students identify a specific Ph.D.
program. Each year, several BSTP students choose Pharmacology as their degree-granting program, and then they continue in step with those directly admitted to Pharmacology to fulfill the requirements of the MTTP.

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

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

**Description of Pharmacology Courses:**

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

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

**Principles of Pharmacology II: The Physiological Basis of Therapeutics (PHRM 402).** This course focuses on human physiology of organ systems including the central nervous system, cardiovascular system, and those systems (gastrointestinal, hepatic, and renal) that are involved in determining the pharmacokinetics or time course of drug action in vivo. A second major emphasis is placed on disease-based sessions where normal physiology, pathophysiology, and key drug classes to treat pathophysologies are discussed. The students learn key concepts in endocrine pathologies, inflammatory disorders, pulmonary diseases, infectious diseases, and cancer. The main learning objectives are for the student to gain an understanding of basic principles of modern pharmacology and physiology and to
build self-directed learning skills. This is a highly interactive course in which faculty lectures are minimized. A heavy emphasis is placed on student-directed learning experiences including presentation and discussion of primary literature, problem solving applications, small group discussion and team-based learning. This 3-credit hour course meets 3 hr per week during the fall semester of year 2. Course Director: Paul N. MacDonald, Ph.D.

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

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

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

Responsible Conduct of Research Seminars.

It is important that the foundation in bioethics that is provided to all students during year 1 (IBMS500) be reinforced throughout their years of training in research. Accordingly, as an integral component of the weekly Frontiers in Pharmacology Journal Club, two sessions per year are devoted to issues of responsible conduct of research. Each of these sessions is focused on one or more cases where ambiguities in research conduct have been documented. All faculty, staff and students are invited to these sessions; however, students in training are required to sign in. All graduate students are required to document participation in at least six of these sessions during their matriculation in the MTTP. The focal cases are distributed at the beginning of the session, and the participants are divided into groups of 6-10 individuals, with at least one primary member of the Faculty of Pharmacology and one other Faculty Trainer participating in each small group discussion. Texts: F.L. Macrina, Scientific Integrity 3rd Edition, Text and Cases in Responsible Conduct of Research, ASM Press, 2005; Research Ethics: A Philosophical Guide to the Responsible Conduct of Research by Gary Comstock (2013, Cambridge University Press).

Advanced Training Tracks, Associated Courses

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

- **Cell Signaling** (PHOL/CLBY 466, 3 credits). This is an advanced lecture/journal/discussion format course that covers cell signaling mechanisms. Includes are discussions of neurotransmitter-gated ion channels, growth factor receptor kinases, cytokine receptors, G protein-coupled receptors, steroid receptors, heterotrimeric G proteins, ras family GTPases, second messenger cascades, protein kinase cascades, second messenger regulation of transcription factors, microtubule-based motility, actin/myosin-based motility, signals for regulation of cell cycle, signals for regulation of apoptosis. **Course Director, George Dubyk.**

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

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

- **Phosphorylation and Cell Regulation** (MBIO 522, 3 credits). This intensive seminar course will emphasize signaling pathways mediated by protein phosphorylation/dephosphorylation. Bacterial signaling mediated by histidine/aspartate phosphorylation and regulation of cellular physiological events will be reviewed. Then eucaryotic cell signaling will be reviewed from the surface of the cell and into the nucleus. This includes receptor-dependent phosphorylation/dephosphorylation reactions, cytoplasmic signaling intermediates, protein translation processes dependent upon phosphorylation, and nuclear regulatory events with emphasis on transcriptional mechanisms. In addition to faculty lectures, students will be reviewing the current literature and will present a research proposal based on the current concepts in the field that they choose to cover. **Course Director, Jonathan Karn.**
Advanced Track in Cancer Therapeutics – Many of the Training Faculty for the MTTP are members of the Case Comprehensive Cancer Center, which is one of 40 NCI designated Comprehensive Cancer Centers. The Cancer Center is comprised of faculty from Case Western Reserve University, University Hospitals of Cleveland, The Cleveland Clinic Foundation, MetroHealth Medical Center and the Cleveland Veterans Affairs Medical Center. Dr. Keri is the Associate Director for Basic Research within the Center. To build on this considerable strength in cancer biology and cancer therapeutics, the Cancer Center has recently developed a cancer biology Ph.D. training program. This program serves as a hub for cancer biology training that occurs in two departments: Pharmacology and Pathology. Selection of a specific training track is dependent upon the students’ interests in either the fundamental basis of cancer therapeutics (Pharmacology) or mechanisms underlying the pathogenesis of cancer (Pathology). Following completion of the Pharmacology Core Course in Molecular Therapeutics, trainees in the Cancer Therapeutics Track are required to take two advanced courses, at least one of which must be one of the specialized courses on cancer biology:

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

- **Molecular Genetics of Cancer** (PHRM / BIOC 420, 3 credits). The molecular basis of cancer is covered in lectures and discussion of scientific literature. The principal topics are cellular and viral oncogenes and tumor suppressors, including their identification, function, and roles in cellular transformation and malignant progression in humans and animal models. Cancer is a genetic disease, not only in the Mendelian sense of inheritance, but also in the sense that it is caused by somatic mutation. The targets of mutation are a set of proto-oncogenes and tumor suppressor genes whose products govern cellular proliferation, death, and differentiation. The objectives of this course are to examine the types of genes that are the targets of mutational activation or inactivation and the mechanistic outcome of mutational changes that lead to oncogenesis. The course will also probe viral mechanisms of oncogenesis related to the products of cellular proto-oncogenes or tumor suppressor genes. In the course of these examinations we will explore the genetic and molecular genetic approaches used to identify and study oncogenes and tumor suppressor genes. Students should be prepared to present and discuss experimental design, data and conclusions from assigned publications. There will be no exams or papers but the course will end with a full-day, student-run symposium on topics to be decided jointly by students and instructors. Grades will be based on class participation and symposium presentation. **Course Director**, Yu-chung Yang

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

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 Case Comprehensive Cancer Center’s weekly seminar series (“Blood Club”), which attracts outstanding internal and external speakers with expertise in a wide variety of cancer research disciplines. Representative speakers from previous years include Dan Haber, Max Wicha, Robert Weinberg, and Chris Contag. Trainees are also expected to attend the Cancer Center’s annual scientific retreat which includes oral presentations by faculty spanning the breadth of the Center as well as trainee career development and poster sessions. Students also participate in a monthly meeting of cancer trainees from all departments in a seminar series that involves paired presentations by a student on their research and a clinical faculty member that presents an introductory lecture on the clinical management of a specific type of cancer. 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 as usual the chair of the committee will hold a primary appointment in Pharmacology.

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

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

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

- **Membrane Transport Processes** (PHRM412, 3 credits). The classification and structure of membrane transport proteins and channels. Examination of the common mechanistic features of all systems and the specific features of different classes of transporter. The goals are to understand the role of transport processes in cell homoeostasis and to consider transporters and channels as drug targets. *Course Co-Directors, Michael Maguire & Vera Moiseenkova-Bell.*

- **Protein Biophysics** (PHRM475, 3 credits). An in-depth understanding of the molecular biophysics of proteins. Structural, thermodynamic and kinetic aspects of protein function and structure-function relationships are considered at the advanced conceptual level. *Course Director, Matthias Buck*

- **Advanced Methods in Structural Biology** (PHRM430 / BIOC430, 1-6 credits). This course is divided into 6 specific modules, including X-ray crystallography, nuclear magnetic resonance spectroscopy, optical spectroscopy, mass spectrometry, cryo-electron microscopy, and computational and design methods. Modules are scheduled so that students can take all the offered modules in one semester. Each section is given in 5 weeks and is worth 1 credit. Modules encompass the area of structural biology at an advanced level such that the student is prepared for graduate level research in that topic. *Course Director, Menachem Shoham*.

- **Structural Biology of Proteins, Enzymes and Nucleic Acids** (BIOC 434, 3 credits). Introduction to the basic chemical properties of proteins and the physical forces that determine protein structure. Topics include: the elucidation of protein structure by NMR and by X-ray crystallographic methods; the acquisition of protein structures from databases; and simple modeling experiments based on protein structures. *Course Director, Paul Carey.*

**Advanced Track in Translational Therapeutics** - The Translational Therapeutics Track (TTT) is designed to train students to utilize molecular and cellular approaches to addressing problems related to the inter-individual differences in drug responsiveness, including variations in drug effectiveness and toxicity. The goal is to interface and ultimately integrate basic science trainees with physician-scientists and clinicians who share an interest in developing and/or employing therapeutic agents in a rational and individualized manner. The proposed integration is designed to promote both the study and understanding of disease and drug action within the context of disease at the molecular, biochemical, genetic, cellular, tissue and organismal levels. Such stages of sophistication 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 formulate a forward-looking vision of pharmacological research as it will be developed and applied over the next several decades. This track endeavors to foster research spanning from “proof-of-concept” approaches to therapeutic principles in model systems through the completion of formal Phase 1 and 2 trials in humans. In conjunction, students are expected to master basic core tenets and principles of pharmacology as well as the application of newer technologies upon the strong background of traditional thought. Throughout this process both faculty and peers mentor students. The goal is a careful blending of the principles of drug action with the language of molecular biology to yield expertise in the personalized therapeutics that will be the hallmark of medical practice for the next several decades. The advanced curriculum of the TTT is designed to stimulate students to use multiple and innovative approaches to solve biologically-based therapeutic problems in a pathophysiological setting. In this context the overall goal is to provide students with a critical approach to performing excellent scientific research, based on their foundation in the core courses (described above for all MTTP students), coupled to specialized advanced courses and continuous education opportuni-
Contemporary Approaches to Drug Discovery (PHRM 528, 3 credits): This course is designed to teach
students how lead compounds are discovered, optimized, and processed through clinical trials for FDA approval.
Topics will include: medicinal chemistry, parallel synthesis, drug delivery and devices, drug administration and
pharmacokinetics, and clinical trials. A special emphasis will be placed on describing how structural biology is
used for in silico screening and lead optimization. This component will include hands-on experience in using so-
sophisticated drug discovery software to conduct in silico screening and the development of drug libraries. Each
student will conduct a course project involving in silico screening and lead optimization against known drug tar-
ggets, followed by the drafting of an inventory disclosure. Another important aspect of this course will be inclusion
of guest lectures by industrial leaders who describe examples of success stories of drug development. Course
Directors, Yoshi Imanishi and Chris Dealwis.

Pathways to Research in Translational Therapeutics (PHRM527, 3 credits): Students will spend time in the
clinical or community setting that most directly relates to their area of research interest. Based on this "bedside"
experience and in collaboration with basic science and clinical mentors, students will identify a significant thera-
peutic challenge in the treatment of the related patient population and will write a review based on the available
literature in this field. The course will culminate with presentation of this review at a symposium for the Transla-
tional Therapeutics Track of the MTTP. Students with outstanding review articles will be encouraged to submit
them for publication. The goals of this course include 1) to provide the research student with an opportunity to in-
teract with health care professionals and with patients, 2) to enhance graduate student understanding of the chal-
lenges that patients face in dealing with imperfect therapeutic options, 3) to immerse students in an area of litera-
ture that is relevant to their research interests and will potentially inform the way they think about improving thera-
peutic strategies, 4) to disseminate their semester-long experience to their graduate student peers through public
defense of their review article, 5) to produce a scholarly manuscript on a problem in therapy that conceptually
takes the therapeutic challenge from bedside to the bench and back again. Course Directors, Amy Wilson-
Delfosse & John Mieyal.

Other recommended advanced courses include:

Mechanisms of Drug Resistance (PHRM434 / MBIO434, 3 credits). Molecular, cellular and physiological
mechanisms of resistance to antibiotics, anti-viral agents, and cancer therapeutic agents. Resistance to drugs is
an important health concern in the new millennium. Over the past century, modern medicine has developed and
prescribed drugs for various ailments and diseases with known therapeutic benefit. Since the discovery of antibi-
otics by Dr. Fleming, we have struggled with a new complication in infectious diseases, development of drug re-
sistance. This course will focus on and compare the drug resistant mechanisms selected by viruses, bacteria,
parasites, fungi, and tumor cells. Topics to be covered include antiretroviral resistance (e.g., AZT and protease
inhibitors), antibiotic resistance (e.g., ß-lactams), resistance to chemotherapeutic agents, and resistance to anti-
malarial drugs (e.g., chloroquine). Course Directors, Robert A. Bonomo.

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

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

MTTP Preliminary (Qualifying) Examination I for advancement to Doctoral Candidacy—The exam is scheduled for all eligible students typically after completion of the core courses in Pharmacology and at least one advanced course. It is designed so that the students are able to complete the process in approximately one month. Eligibility is defined by two criteria: (A) Successful completion (grade of B or better) in all of the core courses [currently defined as (1) the Correlated Curriculum in Cell & Molecular Biology (C3MB = CBIO 453/455); (2) Student Seminar Course PHRM 511, (3) Molecular and Physiological Bases of Therapeutics (PHRM 401 and PHRM402)]; (B) Satisfactory performance in all research rotations, and consistent research effort in the thesis laboratory of their choice. *Satisfactory progress in the lab must be documented by an email confirmation from each Ph.D. mentor during the fall semester preceding the Prelim I exam.* Students who have not fulfilled the two eligibility criteria as expected are placed on formal probation by the MTTP Steering Committee for a defined period of time not to exceed one year. No student on probation may sit for the Prelim I Exam. If remedial work for course requirements or research performance is not completed satisfactorily during the one-year probation period, the student is subject to dismissal from the Ph.D. program with the opportunity to fulfill requirements for the M.S. degree.

Purpose of the Exam: The exam is designed to assess each student’s comprehension of core principles, ability to critically evaluate data, and integrative thinking capacity, 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 will be administered a multi-component essay exam to be completed on site. The exam is designed to assess understanding of core principles and their application in specific research contexts. To facilitate a focus on applications of principles in research, the students will be assigned a published article chosen by the Prelim I Exam Committee which is comprised of faculty and students who are well informed about core principles of the required courses. The article will be assigned two weeks in advance of scheduled exam, and care will be taken to minimize the possibility that any individual student would have a particular advantage based on his/her current research focus. Questions fitting one or both of the following two question types are solicited from the Primary Faculty of Pharmacology and Training Faculty associated with the MTTP and edited in a collaborative fashion by the Prelim I Exam Committee. Type I questions are stand-alone challenges to the student’s ability to display understanding of core principles from the courses in contexts that the students have not previously encountered (not associated with the assigned article or previous course exams). Type II questions are inspired by specific aspects of the assigned article, and they test the student’s critical thinking and integrative capacity. (In exceptional cases a student who receives a grade of “C” in one of the sections of the C3MB may balance that grade with an “A” in another course, however in no case will a student be allowed to stand for the Prelim I exam whose G.P.A. is less than 3.0.)
ability to recognize core principles in practice. Further, they require the students to extend their thinking to suggesting experimental designs not included in the published article. Examples of each type of question are shown in a copy of a previous Prelim I Exam appended to this description.

Quality Control of Exam Questions, Conduct of the Exam, and Uniformity of Grading: One month in advance of the Prelim I Exam Period all MTTP Faculty are invited to submit Type I questions and Type II questions based on the article selected by the Exam Committee. Every submitted question must be accompanied by a succinct model answer. Then the Prelim I Exam Committee (comprised of multiple faculty members and at least one advanced student) will review the articles and questions, solicit clarification if necessary from the authors, and craft the exam. The exam will include multiple Type I questions, one assigned article, and an appropriate number of corresponding Type II questions. A key criterion in selecting and editing questions is that they investigate integrative thinking rather than simple regurgitation of factual information. The exam will be designed so that it should take approximately 3-4 hours for each student to provide thoughtful answers to all of the questions. In fact, more time will be allowed as necessary so that time constraint would not be a factor for any student.

As indicated above, the published article for the exam will be distributed to all eligible students two weeks in advance of the scheduled exam day. Students are encouraged and expected to begin preparation for Prelim I by reviewing their class notes from the core courses well before they receive the first published article, which denotes the beginning of the exam process. Students are expected to read and critically evaluate the assigned articles privately, independent of any input from fellow students or faculty. On the day of the exam students may not bring any notes or textbooks to the examination room. Fresh copies of the published article will be provided to facilitate reference to specific items of data or descriptions that are addressed by the exam questions. Each student will mark each question with his/her pre-assigned anonymous identification number before starting to write answers.

After the exam is completed, answers to each question from all of the students will be collated and distributed to the original authors of the questions for grading (0-100% for each question). Grading of all student responses by the original authors of the particular questions will provide uniform assessment. In addition, the Exam Committee will assign a second faculty member to grade each question, so that two independent scores are generated for each question from each student. The Exam Committee will review all scoring for consistency. Then the Committee will calculate the mean ± S.D. for each question on the exam and for the entire exam. The entire grading process is expected to be limited to < three days. The mean +/- SD will be used as the guideline for evaluation. Any student whose overall score is above the (mean minus 1 SD) AND whose scores on ALL individual questions are at or above the (mean minus 1 SD) will receive an unconditional pass and fulfill the requirement for admission to PhD candidacy. All students whose overall score on the exam is at or above the (mean minus 1 SD) BUT whose score on any individual question is either below the (mean minus 1 SD), or substantially < 50%, for that question will receive a conditional pass (see Removing the Condition, below). Any student whose overall score is substantially below the (mean minus 1 SD) will receive a failure on the exam (see Failure of Prelim I, below). [Obviously, the fewer the number of students sitting for the Exam in any year the less reliable will be a statistical approach to assessing performance. Therefore, in all cases consensus judgment of the Prelim I Exam Committee will be used to decide the basis for unconditional versus conditional pass, or failure].

Removing the Condition - All students who receive a conditional pass will be advised about which conceptual areas gave them particular difficulty on the exam, and they will be instructed to focus on those areas during the next two weeks in preparation for a follow up re-test specifically on those types of questions. The Prelim I exam Committee will select another published article, if necessary, and design only the type and number of questions necessary to re-test the areas identified by student scores below the cutoffs for those questions. The following example illustrates the approach to the re-test.

Description of the original Prelim I Exam:

<table>
<thead>
<tr>
<th>Question</th>
<th>Type of Knowledge</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>General knowledge of drugs</td>
</tr>
<tr>
<td>#2</td>
<td>Fundamental principles of peptide biochemistry pertinent to the assigned article</td>
</tr>
<tr>
<td>#3</td>
<td>Interpretation of data and design of experiments pertinent to the assigned article</td>
</tr>
<tr>
<td>#4</td>
<td>Fundamental principles of Enzyme Kinetics and Antibiotic Biochemistry</td>
</tr>
<tr>
<td>#5</td>
<td>Fundamental principles of Pharmacodynamics pertinent to the assigned article</td>
</tr>
<tr>
<td>#6</td>
<td>Pharmacokinetics calculations</td>
</tr>
<tr>
<td>#7</td>
<td>General knowledge of Cell Biology</td>
</tr>
<tr>
<td>#8</td>
<td>Specific knowledge of G-protein Coupled Receptors pertinent to the assigned article</td>
</tr>
</tbody>
</table>

Performance:

<table>
<thead>
<tr>
<th>Student ID</th>
<th>Question 1</th>
<th>Question 2</th>
<th>Question 3</th>
<th>Question 4</th>
<th>Question 5</th>
<th>Question 6</th>
<th>Question 7</th>
<th>Question 8</th>
<th>Overall Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Points</td>
<td>10</td>
<td>13</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>13</td>
<td>14</td>
<td>14</td>
<td>14</td>
</tr>
</tbody>
</table>
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#### Analysis of the Sample Exam Performance:

Students XXX1 and XXX5 would receive an *unconditional pass* and be admitted to candidacy. According to the guidelines, Student XXX6 technically would fail the Exam; however, this student’s overall score is close to the cutoff and he/she scored at or well above the mean on 4 of the 8 questions. Therefore, this student would receive a *conditional pass* and be required to take a Re-test of 4 questions focused on the topic areas represented by questions 1, 4, 5 & 8.

Students XXX2, XXX3, and XXX4 would also receive a *conditional pass*. Student XXX2 would remediate and be re-tested on the subject areas represented by questions 2 & 8; Student XXX3 would be re-tested on the topics represented by questions 2 & 6. Student XXX4 would be re-tested on the topics represented by questions 6, 7, & 8.

#### Design of the Re-test:

In the sample analyzed above, the Re-test would require the Exam Committee to provide seven total questions, covering the topics represented by the original questions 1, 2, 4, 5, 6, 7, 8. According to the Committee's judgment of the basis for low scores related to questions on the assigned article, the Re-test may or may not require the assignment of an additional published article.

The Re-test for those who received a conditional pass will be administered two weeks after evaluation of the Prelim I Exam and distribution of another assigned article (if necessary). Grading of the Re-test will be performed in the same manner as the Prelim I Exam. Because of the smaller number of students answering each question (sometimes only one), the criterion for successful remediation is a score of at least 60% on each question.

#### Failure of Prelim I and consideration of remediation or dismissal:

Any student whose composite score on the Prelim I Exam is substantially below 1 S.D from the overall mean for all participating students shall be reviewed by an Ad Hoc Committee of the MTTP Steering Committee and placed on formal probation; or recommended for dismissal from the program. Final decision for dismissal is considered by the full Steering Committee of the MTTP and by the Assembly of the Faculty of Pharmacology. If probationary status is assigned to a student who has failed Prelim Exam I, this can be removed by successful remediation and re-examination, as designed by the Prelim I Exam Committee. Various individualized approaches to remediation may be conducted. For example, a student may be given a defined period of time to study with the assistance of a tutor, and then a broadly-based Re-test, analogous to the original Prelim I exam would be administered, including a new assigned article. Emphasis would be placed on particular areas of deficiency identified by the original exam. A student who fails a remediation exam is automatically subject to dismissal from the program.

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

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

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

Dissertation Research (PHRM 701)

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

Thesis proposal, Thesis Progress Committee, and Preliminary Examination II (PHRM526, 1-2 hr.).

Once students successfully complete Preliminary Examination I and are advanced to candidacy, they may begin immediately to prepare their thesis proposal, while completing any remaining advanced coursework; and they should identify their Thesis Progress Committee which also serves initially as the Prelim II Exam Committee. This process takes place during the spring and throughout the summer of year 2. The composition of the Committee is determined by the Director of the Graduate Program in consultation with the student and the mentor, based on prescribed criteria. Namely, the Thesis Progress Committee shall consist of at least 4 CWRU faculty members. At least 2 must hold primary appointments in the Department of Pharmacology, and at least one must hold a primary faculty appointment outside the Department. The chair of the thesis committee must be someone different from the mentor, and be a primary faculty member of the Department of Pharmacology, thus facilitating consistency among thesis committees. **The Thesis Progress Committee should be constituted no later than March 30 (spring, year 2).** Through interactions with the mentor and other members of the thesis committee, the student develops a set of specific aims that will constitute an original research plan. It is understood that some students may have only limited preliminary data at this point in the program. However, the purpose is to propose a well-conceived research plan in which the hypothetical framework emanates from previously published work and current supporting data and leads naturally to the specific aims. Each student is expected to schedule a meeting of his/her Thesis Progress Committee no later than June 30 (last day of year 2) for the purpose of presenting a preliminary research design and receiving constructive criticism. Two weeks before the Prelim II oral defense (no later than September 15 (summer, year 3), 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). Students are encouraged to complete the written and oral components of Prelim II well in advance of the final deadline of September 30. 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 and Coordinator of the MTTP. Note: 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.

Grant Writing Workshop — Integral to the process of preparing an individual NRSA-type proposal on their thesis research for the Prelim II exam, students participate in a grant-writing workshop, which may adopt different formats depending on the instructors. The workshop is focused on how to identify a problem, generate specific aims, and frame the experimental approach for the reviewers. The workshop also describes the peer review process focusing on the perspective of the reviewer and study section discussions. As noted, all students completing Prelim II will be enrolled for 1-2 credit hr. of PHRM526, and the grant writing workshop is one of the required components of this exercise.

In one approach, students would receive a copy of an actual grant proposal that was reviewed by a national panel and received a written summary statement with critiques to illustrate effective strategies for organizing the grant application. The students would independently score the proposal; and then be able compare their assessment with that of the na-
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Recommended Format for Prelim II Proposals: Proposals should not exceed 10 single-spaced pages in length (excluding references) and should follow the general format for an NIH Individual Fellowship Application (http://grants.nih.gov/grants/guide/pa-files/PA-14-147.html) (see Components of the Prelim II proposal, below). Completed proposals must be submitted to the members of the Prelim II Exam/Thesis Committee at least seven days in advance of the scheduled oral defense of the proposal.

Components of the Prelim II Proposal

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

Student-Mentor Interaction in the Prelim II Process - The written proposal will be developed by the student in close consultation with the thesis mentor. This generally involves a series of discussions between the student and mentor where details of the specific aims page are formulated. The general mechanics of effective grant writing and grant formulation are also discussed early and emphasized throughout the process, thereby reinforcing the Grant Writing Workshop (described above). It is appropriate to use the mentor’s own grant applications as useful models. However, the proposal should be written independently by the student, and the mentor should not contribute text to the written document. This should be a student-driven and mentor-guided process, where the mentor asks probing questions and offers suggestions rather than providing explicit direction. For example, the mentor and student might discuss general methods, approaches, and reagents that could be used or developed to accomplish the aims. However, the student should provide the overall plan of attack, the written details, rationales, appropriate controls, potential outcomes and interpretations. General areas of weakness or gaps might be identified by the mentor, but specific approaches to fill these gaps should be the student’s responsibility. Following the Prelim II examination, the mentor and student are encouraged to meet and discuss the strengths and weaknesses of the examination and the final written proposal. The intent of this meeting is to emphasize the strong points and identify areas where further development would be useful. Students and Mentors are expected to follow up on the Prelim II experience by applying for Ruth L. Kirstein NRSA Individual predoctoral fellowship awards, or analogous fellowships from other granting agencies (e.g., American Heart Association, Department of Defense, etc.). Receiving such an award is a special honor for the student, and a benefit for the laboratory, the MTTP, and the Department. Further benefit is provided by a $2000 salary bonus per year during the fellowship award.

Grading of Prelim II – Guidelines for formal, consistent grading of the written and oral components of the Prelim II Exam are delineated below:
1. Each component of the Exam is scored independently and anonymously by each committee member before the Exam Committee discusses the performance of the student.
Each member of the Committee scores the written document, according to specific guidelines (see Components of the Prelim II Proposal, above), and provides the score to the Committee Chair prior to the oral exam. The Committee Chair records these initial scores, but does not share or discuss them with the Committee until the oral exam is completed.

Each member of the Committee scores the oral performance, according to specific criteria, namely: overall organization; breadth and depth of knowledge of published work related to the research plan and pilot data; quality of responses to questions and ability to respond to criticism of the experimental design; quality of visual aids. These scores are provided to the Committee Chair before any discussion ensues. The Chair records these initial scores.

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

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

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

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

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

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

Composite scores corresponding to grades of B or better are reported by the thesis advisor through the SIS system as the grades for the 1-2 credit hr. of PHRM 526.

A composite score corresponding to a grade of C (failure) for the first attempt at Prelim II is reported by the thesis advisor as a grade of I (incomplete); and remediation and re-examination must be completed by the end of the next semester to achieve a grade of B. A second failure on Prelim II is recorded as a grade of C, and the student’s progress must be reviewed by the MTTP Steering Committee for consideration of a terminal MS degree.

Required Foundation in Biostatistics, and Consultation — Students who have completed their required coursework and Prelims I & II are expected to have a foundation in fundamental biostatistics for appropriate analysis of their data. This is the stage in thesis research when students are expected to have generated sufficient data to develop manuscripts for publication. All students in the Molecular Therapeutics Training Program of the Department of Pharmacology are expected to take advantage of opportunities organized by the SOM Office of Graduate Studies to review fundamentals of biostatistics, or to provide documentation for completion of an equivalent experience in another context. Currently a foundation is provided as part of the Core courses in Cell and Molecular Biology.

In addition, access to private consultation with statisticians is provided for investigators in the School of Medicine. This service is open to our students for questions relating to specific study design, statistical software, and data analysis and interpretation. Technically, each investigator is allowed only one free hour of consultation for each project, but the statistician (schedule permitting) may provide additional consultation on a project (no more than 4 hours).

Individual Development Plans

In response to the NIH expectation (NOT-OD-14-113) for Institutions to develop Individual Development Plans (IDP), The CWRU SOM has adopted the following policy to ensure that all NIH-supported trainees utilize IDPs to identify professional development goals and plan their future careers. IDP Policy: All PhD students and post-doctoral fellows will complete an IDP within 6 months of arrival in their permanent mentor’s lab. Completing an IDP is an interactive process that involves face-to-face meetings and frank discussions between the junior researcher and mentor. The IDP will evolve through annual meetings between mentee and mentor. Copies of all graduate student and postdoc IDPs as well as all annual updates will be submitted electronically to the CWRU SOM Graduate Education Office. To ensure compliance, Graduate Program Directors in the SOM will be notified annually about trainee compliance with this policy. The MTTP Steering Committee will follow up as necessary during its annual review of trainees and mentors.
Recommended IDP Format: The CWRU SOM IDP format is available on-line. Final submission requires that both the trainee and mentor have viewed the document and have met to discuss it. All IDPs include a career planning component and an assurance that the trainee and mentor have discussed the content. The SOM strongly encourages trainees to develop their CWRU SOM IDPs by exploring the myIDP web tool package that is available at http://myidp.sciencecareers.org. To facilitate preparation of the IDP, the MTTP provides trainees with information and perspective regarding the broader range of career opportunities (beyond direct scientific research and education) that are relevant to the biomedical enterprise. These opportunities include scientific writing, academia-industrial liaison, health and research policy, research commerce, legal consultation, investment consultation, administration of scientific peer review organizations, and specialized roles in biotechnology companies. Perspectives on career evolution are provided by invited speakers who meet with MTTP students and describe their own paths of career development. In addition, two seminar series on career development were initiated in 2014, namely Career Opportunities for Trainees Series (COTS) and Professional Enrichment for Trainees Series (PETS). The schedule of speakers for the 2015/2016 academic year is shown.

<table>
<thead>
<tr>
<th>Date</th>
<th>Series</th>
<th>Speaker</th>
</tr>
</thead>
<tbody>
<tr>
<td>September 18</td>
<td>COTS</td>
<td>Lori Taylor (From the Bench to Business)</td>
</tr>
<tr>
<td>October 9</td>
<td>PETS</td>
<td>Paul MacDonald (Biomedical PhD Outcomes: Developing a Plan for your Future)</td>
</tr>
<tr>
<td>November 12</td>
<td>COTS</td>
<td>Joe Lawcock (Life on the other side; Pursuing a career in Biotech or Big Pharma)</td>
</tr>
<tr>
<td>December 11</td>
<td>PETS</td>
<td>Emily Roberts (The Graduate Student's Guide to Personal Finance)</td>
</tr>
<tr>
<td>January</td>
<td>COTS</td>
<td>Thomas Magaldi (Humble PhD and Postdoc: Avoid Career Mistakes by Adapting)</td>
</tr>
<tr>
<td>January</td>
<td>PETS</td>
<td>Thomas Magaldi (Professional Development on a PhD's Schedule)</td>
</tr>
<tr>
<td>March</td>
<td>COTS</td>
<td>Craig Nard &amp; William Merrick (Patent Practice and other future dual degrees for Biomedical PhDs)</td>
</tr>
<tr>
<td>April 21</td>
<td>PETS</td>
<td>Ruth Keri (K99/ R00 Awards)</td>
</tr>
<tr>
<td>May 26</td>
<td>COTS</td>
<td>John Hildebrand (Career Trajectories in Academia: An open discussion)</td>
</tr>
</tbody>
</table>

Dissertation Defense

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

Publication Guideline and Dissertation Defense

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

MTTP Specific Guidelines

Composition of the Final Defense Committee - The Dissertation Defense Committee shall be comprised of the Thesis Progress Committee and one more member with expertise in the focal research area added to the Committee at the time of the thesis defense. As described (above) the Thesis Progress Committee typically is comprised of four members, at least two of whom hold primary faculty appointments in the Department of Pharmacology; however, some committees may have an additional member – e.g., committees for MSTP students are required to include a clinical scientist. The additional defense committee member shall be named by the Director of the Graduate Program from a list of at least three investigators who have not been former mentors or collaborators of the Ph.D. candidate. There is no restriction on the affiliation of the additional member. Thus, the additional member may be from outside the Department, outside CWRU, and even outside the USA. The list of three potential thesis reviewers will be provided by the candidate and/or mentor, and the selection will be made by the Co-Leaders of the MTTP track with which the candidate is affiliated in consultation with the MTTP Director.

Composition and Format of the Dissertation – All dissertations are expected to contain the following chapters: Introductory Chapter, providing the broad background of the research topic and culminating in the specific aims of the thesis project; Research Chapters, providing specific introduction, methods, results, and discussion for each subproject of the overall work - typically the individual research chapters are replicates of manuscripts that have been published or submitted for publication; Concluding Chapter, providing an overall discussion of the work and how the findings have advanced understanding in the focal area of research, and identifying in detail future directions of the research and experimental approaches; Bibliography, providing a complete list of all cited references. In addition to these broad guidelines, The CWRU Office of Graduate Studies requires all dissertations to follow specific formatting guidelines, including Table of Contents, List of Abbreviations, margins, font size, etc. These guidelines may be found at the following url: http://case.edu/gradstudies/current-students/electronic-theses/. Drafts of dissertations must be approved by the Graduate Studies Office to confirm adherence to formatting guidelines.

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

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

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

Proclamation:
Name of Candidate - you have fulfilled the requirements for the award of the Ph.D. degree in Pharmacology to be conferred by Case Western Reserve University.
We welcome you to the community of professional scientists. With this honor comes the important responsibility to uphold scientific integrity. As you go forth as an independent scientist we trust that you are committed to this responsibility. Congratulations!

Steps to Completion [Excerpt from Graduate Studies Website]
See [http://gradstudies.case.edu/current/graduation/phd.html](http://gradstudies.case.edu/current/graduation/phd.html) for further instructions

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

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

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

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

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

Delayed Graduation
A doctoral or master’s thesis applicant who meets all deadlines for commencement in one semester except for the deadline for submission to the Office of Graduate Studies of approved copies of the thesis 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 by completing a Waiver of Registration form*. 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. More information and forms can be found at gradstudies.case.edu.

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 as described above. A complete description of the Program can be obtained by contacting the MSTP Office (Kathy Schultz, Administrative Director) or by consulting the MSTP website: http://mstp.cwru.edu/

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

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

2. Sample schedule for MSTP students in the MTTP:

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

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

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

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

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

YEARS SEVEN AND EIGHT (or sooner)
  - Clinical Rotations
  - M.D. degree awarded
Getting a M.S. Degree in Pharmacology:

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

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

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

A. Required Courses:

<table>
<thead>
<tr>
<th>Course</th>
<th>Credits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coordinated Curriculum in Cell and Molecular Biology (C3MB)</td>
<td></td>
</tr>
<tr>
<td>Cell Biology (CBIO 453)</td>
<td>4</td>
</tr>
<tr>
<td>Molecular Biology (CBIO 455)</td>
<td>4</td>
</tr>
<tr>
<td>The Molecular Basis of Therapeutics (PHRM 401)</td>
<td>3</td>
</tr>
<tr>
<td>The Physiological Basis of Therapeutics (PHRM 402)</td>
<td>3</td>
</tr>
<tr>
<td>Frontiers in Pharmacology Seminar Series (PHRM 511)</td>
<td>2</td>
</tr>
<tr>
<td>Two Advanced Courses in Pharmacology (see list)</td>
<td>6</td>
</tr>
<tr>
<td>Master's Qualifying Examination (EXAM 600)</td>
<td>1 credit / typically this is equivalent to the Prelim I Exam (described above under the Ph.D. program)</td>
</tr>
</tbody>
</table>

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

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

C. Sample Plan of Study for Plan B

<table>
<thead>
<tr>
<th>Semester 1</th>
<th>Semester 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBIO 453 (4)</td>
<td>PHRM 401 (3)</td>
</tr>
<tr>
<td>CBIO 455 (4)</td>
<td>PHRM 601 (3)</td>
</tr>
<tr>
<td></td>
<td>PHRM Elective (3)</td>
</tr>
<tr>
<td>Semester 3</td>
<td>Semester 4</td>
</tr>
<tr>
<td>PHRM 511 (1)</td>
<td>PHRM 511 (1)</td>
</tr>
<tr>
<td>PHRM 402 (3)</td>
<td>PHRM Elective (3)</td>
</tr>
<tr>
<td>PHRM Elective (3)</td>
<td>PHRM 601 (3)</td>
</tr>
<tr>
<td></td>
<td>EXAM 600 (1)</td>
</tr>
</tbody>
</table>

Course work M.S. degree (Plan B) for students entering as former Ph.D. candidates - This program is aimed at students who have taken most or all of the courses required for the Ph.D. but have not accomplished sufficient research to write a Ph.D. or Master’s thesis. Passing the qualifying exam (Prelim Exam I) required for admittance to candidacy in the Ph.D. program in Pharmacology and registering for 1 credit of EXAM 600 satisfies the requirements for a Comprehensive Exam for the M.S. degree. A total of 27 credit hours (18 credit hr graded) are required, fashioned analogously to Plan B for students admitted directly to the M.S. program (above).
Masters Plan A (Research, direct admit)

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

Sample Plan of Study for Plan A

<table>
<thead>
<tr>
<th>Semester 1</th>
<th>Semester 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBIO 453 (4)</td>
<td>PHRM 401 (3)</td>
</tr>
<tr>
<td>CBIO 455 (4)</td>
<td>PHRM Elective (3)</td>
</tr>
<tr>
<td>PHRM 511 (1)</td>
<td>PHRM 651 (1)</td>
</tr>
<tr>
<td>PHRM 402 (3)</td>
<td></td>
</tr>
<tr>
<td>PHRM 651 (2)</td>
<td></td>
</tr>
<tr>
<td>PHRM Elective (3)</td>
<td></td>
</tr>
</tbody>
</table>

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

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

1. Academic Rationale and Purpose.

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

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

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

c. Admissions and Sample student program. All students will begin the University or the Lerner College Medical Programs, and their admission to the medical 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 credits obtained from the medical curriculum. Portions of the medical curriculum will earn graded credit toward the joint MD/MS degree as Integrated Biological Science (IBIS) coursework, as in existing IBIS 401-405 courses for the Medical Scientist Training Program. Normal rules, as established by faculties, for advanced standing shall also apply such that only 6 IBIS credits total will be applied toward the joint MD/MS. For students to receive graduate credit for medical coursework, they must register for IBIS credit at the beginning of the semester. Further, it is strongly recommended that students pursue rotation research between the first and second year of medical school, or during the first year as an elective in preparation for the full year of laboratory research, and 1-3 non-graded (601) elective credits may be earned for this activity. Students in the MD/MS joint degree program must attain a cumulative GPA of 3.0 in their graduate courses.

Students are likely to complete the required two semesters of research 601 after the pre-clinical years in medical school, although the research could occur in other years. Before initiating full time research, the trainee must submit a final program of study 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 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.
Appendix

Computer Policy
The computer policy for graduate students in the Department of Pharmacology is that all students receive a new personal laptop computer for their exclusive use throughout the training program at the time that they join their thesis research lab. The Department of Pharmacology subsidizes the purchase of these computers for every Pharmacology student in our training program. The Department provides one-half the purchase price of the computer, up to $750.00. The mentor's laboratory budget provides the remainder of the cost. It is important to note that this computer is the property of the PI's laboratory and stays with the PI when the student graduates. We expect the mentor to initiate this process as soon as the student has chosen a lab. The mentor and student should decide on a computer and then contact Kris Basso (368-0248) or Rachel Griffis (368-0701) to initiate this process.

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

Free “useful” downloads
The CASE Software Library gives students free use of many of the latest software packages on their own computers, provided they have network access. Other programs are available at a discounted price. Students may also use the software in the library from campus computer labs. A complete list of available programs is available at: https://softwarecenter.case.edu

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

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

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

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

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

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

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

Bound Copy of Dissertation: MTTP doctoral students are required to submit one hard-bound copy of their dissertation to the MTTP Coordinator. As stated previously, this copy and one additional copy for the student will be sponsored by the department. CWRU contracts with FedEx to handle university and student printing needs. Orders can be placed by accessing the url: https://www.case.edu/printing/. Students are also welcome to make other arrangements for binding their thesis.
Student Policies

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

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

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

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

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

Student Resources

University Counseling Services: 368-5872 - 220 Sears Library Building
Students with Mental Health concerns for yourself or a friend, which include depression, anxiety, eating problems, alcohol issues, sleep problems or any other school adjustment situations, can schedule an appointment at the Health Service to be seen by a health care provider. To schedule an appointment at the Health Service, call 368-2450. If it is an emergency, students will be referred to a local hospital.

Students may also schedule appointments in the counseling center for the same issues without first seeing someone at the Health Service. Call 368-5872 to schedule an appointment.

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

Housing and Residence Life: 368-3780 - Room 4, Yost Hall
The Department of Pharmacology can direct students to available housing options in the area. It is also available on line @ http://studentaffairs.case.edu/living/services/aloha/

Office of Student Affairs; 368-2020 - 110 Adelbert Hall
The University Office of Student Affairs provides leadership in the development of services and programs that supplement the classroom experiences of university students and enrich student life. The staff of the Office of Student Affairs attempts to promote an environment that provides positive, developmental experiences for all students.

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

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

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

[https://sis.case.edu/psp/saprd/](https://sis.case.edu/psp/saprd/)

Program: Pharmacology (PhD)

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(9 total)
QUESTION 1 [Total 10 points]  Graders: Maguire / Moiseenkova-Bell

Parts A - D are 1 point each

A. **CIRCLE** the pairing of agent and receptor that does **NOT** normally occur in typical individuals.
   - acetylcholine – muscarinic receptors
   - acetylcholine – nicotinic receptors
   - epinephrine – dopamine receptors
   - epinephrine – α-adrenergic receptors
   - norepinephrine – β-adrenergic receptors

B. **CIRCLE** the enzyme that digoxin binds to in exerting its therapeutic effect.
   - heart Ca\(^{2+}\)-ATPase
   - heart Na\(^+\)-Ca\(^{2+}\) exchanger
   - heart Na\(^+\),K\(^+\)-ATPase
   - kidney Na\(^+\),K\(^+\)-ATPase
   - skeletal muscle Ca\(^{2+}\) ATPase

C. **CIRCLE** the drug that should **NOT** be used for treatment of allergic rhinitis (hay fever).
   - Claritin/loratadine
   - Epinephrine
   - Intranasal corticosteroid
   - Oxymetazoline
   - Pseudoephedrine

D. **CIRCLE** the agent whose body level is directly altered by ACE inhibitors.
   - Acetylcholine
   - **Angiotensin II**
   - Angiotensinogen
   - Atrial natriuretic peptide
   - Epinephrine

Parts E - G are 2 points each  **[Use only the space provided]**

For each group of drugs below, state: **(1)** primary therapeutic use; **(2)** receptor(s)/protein(s) that mediate their therapeutic effect; **(3)** tissue(s) where these receptor(s)/protein(s) reside; **(4)** classification, *i.e.*, agonists/substrates/activators or antagonists/inhibitors. For example, “Sildenafil (Viagra) & Tadanafil (Cialis)” would be answered **(1)** to treat male erectile dysfunction and female anorgasmia, **(2)** PDE5, phosphodiesterase 5, **(3)** primarily in the genitals and **(4)** inhibitors.

E. Captopril (Capoten), Enalopril (Vasotec), Benazepril (Lotensin)
   **(1)** Hypertension treatment
   **(2)** Angiotensin converting enzyme
   **(3)** Vasculature
   **(4)** Inhibitors

F. Ibuprofen (Advil), Naproxen (Naproxyn, Aleve)
   **(1)** Pain, inflammation, fever
   **(2)** Cyclooxygenase/PGH Synthase
   **(3)** Most tissues and cell types
   **(4)** Inhibitors

G. Indinavir (Crixivan), Saquinavir (Invirase), Ritonavir (Norvir)
(1) HIV/AIDS
(2) HIV protease
(3) Virally infected cells, primarily lymphocytes
(4) Inhibitors

QUESTION 2 [Total 15 points]

In the manuscript by Moellering et al., measure Kd values for the RAMANK-CSL bio-SAHM1. Another research group method to measure the binding affinity titration measurements. In this type of intrinsic fluorescence of one protein is binding of its protein partner. The isotherm for the binding of RAMANK-CSL at the right.

*Use only the space provided on this page

**BERDICHIN NOYES**

Part A:

1. What is the equation used to define this curve? (1 points)

Answer: Bound = (Bmax * [Ligand])/ (Kd + [Ligand])

2. Indicate on the graph where Kd and Bmax values would be empirically measured. (1 points)

3. What are the Kd and Bmax values? (1 points)

Answer: Bmax ~ 110 ng/mL

   Kd ~ 0.01 μM

4. Is the Kd value measured here different than that reported in the manuscript? (1point)

Yes

5. In fact, Moellering et al. did use 2 independent methods to determine the binding affinity of SAHM1 to the CSL-binding domain of ICN1. Describe the principles for these methods and explain what they measure. How are they conceptually distinct? (3 points)

(1) Fluorescence polarization titrations (Fig. 2b). SAHM peptides were labeled with the fluorophore fluorescein. The labeled peptide was titrated with RAMANK and fluorescence polarization was measured. Fluorescence polarization reflects the rotational volume of a fluorophore. Polarization values of the complex are therefore larger than that of free SAHM. The resulting titration curve can be analyzed to yield Kd.

(2) Surface Plasmon resonance. RAMANK-CSL is immobilized on a surface and a solution containing SAHM peptides flown over the surface. The instrument senses changes in the characteristics of the immobilized component upon association and the time course of these changes, reflecting the rate of association of the two components, is recorded. Following saturation, the solution is exchanged with clean buffer, and the rate of dissociation of the peptide from its immobilized partner is measured. Kd is obtained from the ratios of the rate constants (Kd= koff/kon).

So: Method (1) directly measures equilibrium situations while method (2) derives the equilibrium constant from kinetic parameters.
6. If a difference is observed between the value of $K_d$ obtained by the SPR technique and another approach such as fluorescence quenching, provide at least one explanation for this apparent discrepancy. (2 points)

Berdis Answer: The $K_d$ of $0.01 \, \mu M$ measured here is 10-fold lower the $K_d$ of 0.12 mM reported using SPR. One possible explanation invokes the negative influence of "steric hindrance" using SPR, i.e., ligand has less access to immobilized binding partner. In other words, there are potential differences in reactions measured in solution versus on a surface.

Part B:

Scatchard plots are provided below for the binding of the RAMANK-CSL complex to SAHM1 (top graph); and for the RAMANK-CSL complex to a derivative of SAHM1 in which one histidine, which is known to be in the binding pocket, is replaced by alanine (denoted as SAHM1-HA, bottom graph).

1. Indicate whether there is cooperativity (none, positive, or negative) for each ligand. (1 point)

Answer: No cooperativity

2. Indicate on the Scatchard plots where $K_d$ and $B_{\text{max}}$ would be measured empirically. (1 point)

3. What are the $K_d$ and $B_{\text{max}}$ values? (1 point)

Wild-type SAHM1: $B_{\text{max}} \sim 100 \, \text{ng/mL}$

$K_d \sim 0.012 \, \mu M$

Mutant SAHM1: $B_{\text{max}} \sim 100 \, \text{ng/mL}$

$K_d \sim 0.120 \, \mu M$

4. Is there a difference in $K_d$ values between SAHM1 and SAHM1-HA? Yes

5. Provide a molecular explanation to rationalize any differences in binding affinity and indicate how this would affect the free energy of binding. (2 points)

There is a 10-fold decrease in binding affinity caused by the substitution of alanine for histidine. This difference in affinity corresponds to a loss in Gibb's free energy of $\sim 1.8 \, \text{kcal/mol}$, consistent with a loss in hydrogen-bonding interactions upon the replacement of histidine.

QUESTION 3 [Total 14 points] *Use only the space provided on this page

Consider the manuscript by Moellering et al.:
A. The equilibrium dissociation constant for the SAHM1-RAMANK-CSL association was found to be 0.12 μM. However, the IC50 for inhibition of the transcriptional activity of NOTCH by SAHM1 in cells was 6.5 μM.

1. Is such a difference common? (1 point)
   
   Yes

2. How can such a difference be explained? (3 points)

The reported Kd was measured in vitro under conditions of constant concentrations and in the absence of other components. In a cell, a higher concentration may be needed because: (1) compartmentalization of SAHM1 may result in different concentration at different subcellular locations, (2) SAHM1 may be metabolized or degraded, 3) affinity towards intact full length NOTCH may differ from the affinity towards the partial peptide.

B. The authors were concerned regarding possible off-target effects of the inhibitor.

1. What approaches were used to examine specificity? (2 points)

- SAHM1 directly binds to the NOTCH-CSL complex and competitively inhibits coactivator binding.
- SAHM1 inhibits the activity of a luciferase reporter driven by NOTCH
- Global expression profile demonstrated that the inhibitor repressed known NOTCH target genes.
- A strong correlation was found between effects on gene expression of SAHM1 and a small molecule inhibitor of g-secretase, known to inhibit the NOTCH pathway (GSI)
- SAHM1 inhibits the growth if leukemia cells that depend on NOTCH signalling but has no effect on proliferation of NOTCH-insensitive cells.

2. Are these approaches sufficient? Explain why/why not (2 points)

These approaches strongly support the conclusion that SAHM1 inhibits NOTCH signalling. However, they do not prove that this is the only effect. This point is, inherently, extremely difficult to prove.

3. Suggest an additional approach to examine whether the anti-leukemic effects of the drug were indeed specifically mediated by inhibition of the transcriptional activity of NOTCH. (2 point)

Use leukemia cells whose growth is inhibited by SAHM1. Decrease the expression of NOTCH (siRNA) and examine effects of SAHM1 on growth.

C. Consider the chemical nature of the SAMH1 inhibitors.

1. Why do peptides usually have a short half-life when administered to living organisms and require relatively high concentrations to exert their actions? (2 points)

Peptides usually have a short half-life because they are quickly digested by the proteases present in the stomach and small intestine (if they are administered orally) or by the proteases in the blood and target cell (if they are administered IV and can reach the target cell). Therefore, peptides require relatively high concentrations to exert their action.

2. How can one improve the half-life of peptides as therapeutic agents? (2 points)

The half-life of peptides could be improved either by chemical modification or by incorporation of unnatural amino acids to resist the proteolysis.

Question 4 [Total 12 points] *Use only the space provided on this page*

Consider the article by Moellering et al.: MONTANO / MACDONALD
A. Discuss structural features of SAMH1 that allow for:

1. its enhanced cellular uptake (2 points)

*SAMH1 contains several arginine amino acids that are cell permeable. Stapling may also increase the peptide's hydrophobicity and allow for better penetration of the cell membrane.*

2. its decreased susceptibility to proteolytic cleavage (2 points)

*Stapling constrains the polypeptide to an alpha-helical conformation. The constrained secondary structure may increase the peptide's resistance to proteolytic cleavage.*

3. its selective inhibition of Notch signalling despite the ability of MAML1 to function as a coactivator for other transcription factors (4 points)

*Stapled helix docks into the Notch-CSL surface groove, inhibiting the binding of Notch-CSL to MAML1, but does not inhibit MAML1 binding to other transcription factors.*

B. Would you expect therapeutics that target Notch signalling to be effective against solid tumors? Explain why or why not. (4 points)

*Notch signalling has also been reported to be oncogenic in solid tumors. However, solid tumors are highly dependent on angiogenesis and notch signalling decreases angiogenesis, thereby limiting the effectiveness of therapeutics targeting Notch in solid tumors.*

Question 5 [Total 12 points]  *Use only the space provided on this page*

DISTELHORST / SABO

A. Consider Figure 4, panel b in the Nature paper by Moellering et al. about Notch signalling. The authors monitored "effects of SAHMs on apoptosis of T-ALL cells using Caspase-glo 3/7."

1. What does this assay measure? (1 point)

*The Caspase-Glo® 3/7 Assay provides a homogeneous luminescent assay that measures caspase-3/7 activities. The assay provides a proluminescent caspase-3/7 DEVD-aminoluciferin substrate and a proprietary thermostable luciferase in a reagent optimized for caspase-3/7 activity, luciferase activity and cell lysis. Adding the single Caspase-Glo® 3/7 Reagent in an "add-mix-measure" format results in cell lysis, followed by caspase cleavage of the substrate. This liberates free aminoluciferin, which is consumed by the luciferase, generating a "glow-type" luminescent signal. The signal is proportional to caspase-3/7 activity.*

2. Why is it considered to be an assay for apoptosis? (1 point)

*Caspases are a class of protease commonly activated during the process of apoptosis. For example, activation of the intrinsic apoptotic pathway (i.e., mitochondrial pathway) involves release of cytochrome c from mitochondria, which in turn binds to APAF-1, activating the upstream caspase, caspase-9, which in turn cleaves and thereby activates downstream caspases, including caspase-3 and caspase-7. These caspases cleave a wide variety of proteins, resulting in cellular destruction characteristic of apoptosis.*

B. Regarding these same data, in the text the authors carefully state their conclusion, "In sensitive T-ALL cell lines, SAHM1 exposure prompted activation of caspase 3 and 7, consistent with the induction of apoptosis (Fig. 4b)."

1. Is caspase activation indicative only of apoptosis? Explain (2 point)
(This may not be an obvious question to many students, and should be graded liberally.) The answer is that while caspase activation is one feature of apoptosis that is often used, as in this paper, to determine if apoptosis has occurred, it is not 100% proof of apoptosis. This is because there may be some basal caspase activity in cells, particularly in tumor cells, that is not necessarily related to apoptosis. Also, capases can perform normal cellular functions unrelated to apoptosis, including for example the processing of certain proteins.

2. Briefly describe two assays to distinguish between apoptosis and necrosis. (4 points)

Apoptosis is a form of genetically programmed death in which a cell is active in its own destruction. It is an orderly process that involves activation of caspases and endonucleases, which are responsible for dismantling the cells. It is an energy-dependent process. The purpose of apoptosis, in physiological sense, is to get rid of unwanted cells in a manner such that cellular contents are not released into the intercellular space. The latter might stimulate a self-immune reaction. Apoptotic cells are engulfed by macrophages, at very early stages of the apoptotic process, thus preventing release of cellular constituents into the intercellular space.

Necrosis is a process involving plasma membrane damage, and is generally not thought to be a genetically programmed process. Rather, necrosis is thought to be a non-physiological process resulting from cellular damage (e.g., by toxins, by complement activation). Unlike apoptosis, specific proteases and endonucleases are not activated, at least early in the process. Also, in contrast to apoptosis, necrotic cells are not engulfed by macrophages during early stages of the process. Thus, cellular constituents can be released into the intercellular space.

Question 5, continued

C. The authors have shown in Figure 4 that the peptide treatment inhibits cell proliferation. One potential explanation is that the cells are undergoing autophagy rather than apoptosis, or undergoing both autophagy and apoptosis.

1. What is autophagy? (2 points)

Autophagy is a genetically regulated, physiological process in which cells form a double membrane structure, the autophagosome, which encircles organelles (e.g., mitochondria). Fusion of autophagosome to lysosomes exposes engulfed proteins and organelles to lysosomal proteases. The purpose of autophagy is to provide substrates for energy production (i.e., ATP) at times of cellular starvation. Thus, autophagy is primarily a survival mechanism, although if allowed to go to completion will induce cell death. Autophagy is a highly conserved process. It is not only induced by nutrient starvation, but also by many other processes that lead to cell stress.

2. Describe at least one assay that selectively detect autophagy. (2 points)

LC3 is a protein that undergoes post-translational modifications during autophagy, involving conversion of LC3I to LC3II. The latter is involved in autophagosome formation and its accumulation can be detected by immunoblotting, a convenient marker of autophagy.

Autophagy can also be detected by monitoring GFP-LC3 by fluorescence microscopy. During autophagy, GFP-LC3 converts from a diffuse cytoplasmic appearance to a punctate appearance, as the GFP-LC3 becomes localized in the autophagosome membrane. Thus, conversion from a diffuse to punctate pattern is indicative of autophagy.

Electron microscopy can be used to detect the characteristic double membrane autophagosome, indicative of autophagy.

Question 6 [Total 13 points]  

MIEYAL / BERDIS

Recently, a newly hired biochemical pharmacologist was mining the older literature for a rational lead to develop more effective immunosuppressive agents, and he came upon an article describing inhibitors of the enzyme Inosine 5’-Monophosphate Dehydrogenase (Franklin et al. (1999), cited below). In his musings he began to consider the analog of Inosine (IIK) whose structure is shown here:

Inosine Iodoketone (IIK)
A. Describe what metabolism this analog would have to undergo within the cells in order to target it to the active site of the Inosine 5'-Monophosphate Dehydrogenase (IMPDH) enzyme? Specify with an arrow what site on the molecule would be modified by this metabolism. (3 points)

This purine analog needs to be converted to the corre-ribosyl-5'-monophosphate metabolite

B. At the right is an X-ray crystal structure of the enzyme (from: Nimmegsmergern (2000), cited below), displaying the key active site. Given a [125I]-labeled derivative of the actual inhibitor (IIK- and a sample of the isolated enzyme, explain how the radiolabel used to determine the stoichiometry of covalent modification of (3 points)

Upon reaction with the enzyme active site, the [125I]-label is displaced as iodide. By separating iodide from the parent compound and knowing the specific radioactivity of the iodine, one molecule of enzyme is inactivated for each molecule of iodide that is displaced.

C. Identify the nucleophile, the electrophilic center and the leaving group responsible for covalent inactivation of the enzyme. (3 points)

Nucleophile = Cys331 thiolate; Electrophilic Center = C-atom bonded to I and C=O; Leaving Group = I

D. What type of inhibition pattern would you expect for the interaction of the IIK-metabolite with the IMPDH enzyme? Draw the double reciprocal plot for velocity versus IMP for no inhibitor and for several different concentrations of the IIK-metabolite, and explain why this pattern would be obtained. Note that the experimental design involved pre-incubation of the IIK-metabolite with the enzyme before testing residual activity in the presence of excess substrate. (4 points)

Although this is an active-site directed irreversible inhibitor which is potentially competitive with the substrate, the most likely inhibition pattern is non-competitive, because during pre-incubation some of the enzyme is irreversibly inactivated - therefore decreased Vmax because the active enzyme concentration is decreased. For the remaining active enzyme Km is unchanged. Pattern = increasing y-intercept (1/Vmax) for increasing inhibitor concentration; common x-intercept (-1/Km).


Question 7 [Total 12 points] *Use only the space provided on this page

A. Match the following proteins with their primary structures/residences from the list below. Note: only 6 matches are correct out of the list of 12. (3 points)

A) Apaf-1 _____ 2 _____ KERI / MAGUIRE

B) Cadherins _____ 1 _____

C) Citrate Synthase _____ 7 _____

D) Connexins _____ 9 _____

E) GroEL _____ 4 _____

F) β-tubulin _____ 3 _____
1) Adherens Junction
2) Apoptosome
3) Centrosome
4) Chaperonin
5) Endoplasmic Reticulum
6) Focal Adhesion
7) Mitochondria
8) RNAPolymerase Holoenzyme
9) Gap Junction
10) Peroxisome
11) Synapse
12) Lysosome

B. **For each match**, describe in **no more than 1-2 sentences** the **PRIMARY** function of each subcellular structure/protein complex. (9 points)

A) **Answer:** The apoptosome is a complex of proteins (Apaf-1 and cytochrome C) that activates caspases necessary for the induction of apoptosis.

B) **Answer:** The adherens junctions are structures at intracellular interfaces that tightly bind cells together through homotypic interactions of cadherins. These structures also control signalling within a cell to inform the cell of whether it is attached to another cell.

C) **Answer:** mitochondria are the respiratory centers of the cell where electron transport is coupled reduction of oxygen and production of energy in the form of ATP. Mitochondria also serve as an initiation site for apoptosis.

D) **Answer:** Gap junctions are comprised primarily of connexins and are specialized structures that provide a means for the transport of cytoplasmic constituents from one cell to another, allowing direct cell-cell communication.

E) **Answer:** Chaperonins are protein complexes that are necessary for the proper folding of nascent polypeptide chains and refolding of misfolded proteins.

G) **Answer:** The centrosome is the nucleating center for microtubules that attach to the chromosomes and ensure proper segregation during mitosis. Also accepted: the centrosome is a nucleating center for microtubules that establishes polarity of cells.

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**Question 8 [Total 12 points]** *Use only the space provided on this page*

Consider the article by Moellering et al.:

A. Notch signalling has a simple framework that is highly conserved in metazoans. Please explain the following details regarding this signalling pathway:

1. What is the core Notch signalling pathway? Name the components / individual steps in the pathway and sketch a diagram. (4 points)

*Notch signalling components: both the Notch receptor and its ligands, Delta and Serrate (known as Jagged in mammals), are transmembrane proteins with large extracellular domains that consist primarily of epidermal growth factor (EGF)-like repeats. Ligand binding promotes two proteolytic cleavage events in the Notch receptor. The first cleavage is catalysed by ADAM-family metalloproteases, whereas the second is mediated by γ-secretase, an enzyme complex that contains presenilin, nicastrin, PEN2 and APH1. The second cleavage releases the Notch intracellular domain (Nicc), which then translocates to the nucleus and cooperates with the DNA-binding protein CSL (named after CBF1, Su(H) and LAG-1) and its coactivator Mastermind (Mam) to promote transcription.*
Binding of the Delta ligand (green) on one cell to the Notch receptor (purple) on another cell results in two proteolytic cleavages of the receptor. The ADAM10 or TACE (TNF-α-converting enzyme; also known as ADAM17) metalloprotease (yellow) catalyses the S2 cleavage, generating a substrate for S3 cleavage by the γ-secretase complex (brown). This proteolytic processing mediates release of the Notch intracellular domain (Nicd), which enters the nucleus and interacts with the DNA-binding CSL (CBF1, Su(H) and LAG-1) protein (orange). The co-activator Mastermind (Mam; green) and other transcription factors are recruited to the CSL complex, whereas co-repressors (Co-R; blue and grey) are released.

2. Describe the mechanism of transcriptional regulation, including specific protein-protein interactions. What are the end results of activation of the Notch pathway? (4 points)

The key transducer of the Notch-signalling pathway is a DNA-binding protein, CSL (CBF1, Su(H) and LAG-1). CSL is similar to the Rel family of transcription factors. However, CSL differs from Rel in the insertion of a central modified β-trefoil domain (BTD) between the two Rel-homology regions (RHR-N, RHR-C). DNA contacts are predominantly made through the RHR-N and BTD domains. The BTD domain contains a hydrophobic pocket that is thought to mediate the interaction with the Notch intracellular domain (Nicd). To activate transcription, the co-activator Mastermind (Mam) is required. Mam proteins from different species share little sequence homology apart from an N-terminal region that forms an extended α-helical domain that contacts the RHR-N and RHR-C domains of CSL and the Ank domain of Nicd in a trimeric complex. This results in transcription of desired genes.
B. Describe the main finding of the Moellering et al. article and how it affects understanding of the Notch signalling cascade. (4 points)

A new type of molecule, stapled peptide derived from MAML1 (Mam) direct binds to the pre-assembled form of the NOTCH1–CSL complex and competitively inhibit MAML1 co-activator binding. Analysis of direct NOTCH1 target gene levels and the global expression profile induced by that peptide confirmed specific repression of the NOTCH signalling program in human and murine T-ALL cells.

MTTP TRAINERS

Molecular Pharmacology & Cell Regulation

- Robert Bonomo, M.D., Professor of Medicine, Pharmacology, Molecular Biology and Microbiology, CWRU
- Marcin Golczak, Ph.D., Assistant Professor of Pharmacology, CWRU
- Maria Hatzoglou, Ph.D., Professor of Genetics, CWRU
- Thomas Kelley, Ph.D., Associate Professor of Pediatrics and Pharmacology, CWRU
- Ruth Keri, Ph.D., Professor and Vice Chair, Department of Pharmacology, CWRU
- Qingzhong Kong, Ph.D., Associate Professor of Pathology and Neurology, CWRU
- Gary Landreth, Ph.D., Professor of Neurosciences, CWRU
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- Stephen Lewis, Ph.D., Professor of Pediatrics, CWRU
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- Irina Pikuleva, Ph.D., Professor of Ophthalmology and Pharmacology, CWRU
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- Nicole Steinmetz, Ph.D., Assistant Professor of Biomedical Engineering, CWRU
- Gregory Tochtrop, Ph.D., Associate Professor of Chemistry and Pharmacology, CWRU
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Cancer Therapeutics

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- William P. Schiemann, Ph.D., Goodman-Blum Professor in Cancer Research, Professor, General Medical Sciences-Oncology;
- Nima Sharifi, M.D., Professor of Cancer Biology, Cleveland Clinic Lerner Research Institute
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