

# Molecular and Cellular Basis of Disease

## *PhD Training Program in Experimental Pathology*

### *Curriculum Document*

Director: Janet V. Cross, PhD  
Administrator: Michael Kidd, MA

#### INTRODUCTION

The Molecular and Cellular Basis of Disease (MCBD) Graduate Program offers the PhD in Experimental Pathology and is designed to rigorously train students to excel in the research associated with elucidating the mechanisms of disease processes, with a particular emphasis on the skills necessary to perform translational research. Admission to the MCBD program is in most cases through Biomedical Sciences (BIMS) admissions clusters, or through the Medical Scientist Training Program (MSTP).

#### FIRST YEAR

The focus of the first semester is on core curriculum requirements that are shared by most BIMS programs at UVA, as well as laboratory rotations with a goal of identifying a research mentor and degree-granting program. A total of 24 credit hours are earned during the first year.

##### Research Rotations (Summer, First and Second Semester)

Generally, students complete three laboratory rotations in different laboratories during their first year. By mid February of their first year, most students select their research mentor and choose the department where they will earn their PhD degree. Rotations take place during set blocks of time defined yearly by BIMS.

Rotation 1: Early July – start of classes

Rotation 2: end of core course – ~December 22<sup>nd</sup>

Rotation 3: ~January 3<sup>rd</sup> – February 8<sup>th</sup>

##### BIMS Core Course:

Starts ~August 20<sup>th</sup>, ends in early November

##### Modular Coursework

Modular coursework begins on or about Feb 11<sup>th</sup> each year, after students select a research mentor and a degree-granting program. Modular coursework is selected in consultation with the mentor based on student interests, the research interests of the selected laboratory/ mentor, and the training grant(s) appointment that will be pursued. Final approval for the student's modular course of study must be received from the MCBD Program Director who ensures that it meets all MCBD and Graduate School of Arts and Sciences (GSAS) requirements. In this way, each student builds an individualized training program that best meets his or her needs and those of the mentor. Most students will take 3-4 modules in the Spring Semester.

Module S-1: ~Feb 11<sup>th</sup> – ~March 22<sup>nd</sup>

Module S-2: ~ March 25<sup>th</sup> – ~ May 3<sup>rd</sup>

### Additional Required Coursework

PATH 8140: Topics in the Molecular Basis of Human Disease II  
(2 credits, *may be taken in second year*)

BIMS 7100: Research Ethics  
(1 credit)

### SECOND YEAR

During the second year, students have three main tasks:

#### 1) Identify members of a thesis committee

In consultation with the Mentor, and subject to approval by the MCBD Program Director, the student selects a committee of four or five faculty members who serve as guides and readers of the qualifying examination and dissertation. The student's thesis committee must consist of the mentor and three or four other expert scientists.

- The Chair of the Thesis committee must be a Full Member of the training faculty of MCBD, and a faculty member of the Department of Pathology, but cannot be the research Mentor.
- At least two members of the Thesis Committee must be Full Members of the training faculty of MCBD, and at least one must be a trainer in another BIMS training program outside of MCBD/Pathology.
- Generally, one member should be an outstanding scientist with expertise outside the student's area of research interest.

#### 2) Take advanced electives and required courses / participation activities related to the Molecular and Cellular Basis of Disease.

Generally, required coursework must be completed during the second year, as no for-credit courses are allowed in the third year and beyond.

#### Advanced Electives

Students must complete the following didactic courses, as well as two semesters of each of the required participation activities. Other didactic electives from Pathology or other programs may be taken in addition to accommodate student interests and/or training grant requirements. Didactic courses must be approved by the MCBD Program Director.

PATH 8130: Topics in the Molecular Basis of Human Disease I  
(2 credits, Fall Semester)

PATH 8140: Topics in the Molecular Basis of Human Disease II  
(2 credits, Spring Semester, *if not taken in the first year*)

PATH 8058: Topics in Medical Pathology  
(3 credits)

*Course meets in the summer (early July – end August) to coordinate with Resident Summer Lecture Series, but students register in the Fall.*

PATH 8060: Rotation in Diagnostic and Interventional Medicine  
(4 credits)

*Course is individually arranged, "independent study", to meet students' needs and interests as well as the schedule(s) of involved faculty. Students may register in Fall or Spring.*

## Required Participation Activities

PATH 8460: Seminars in Molecular Medicine and Human Disease  
*Seminar*

(1 credit per semester, both Fall and Spring)

PATH 8050: Colloquium in Human Disease Research

*Journal Club and Research Progress Report*

(1 credit per semester, both Fall and Spring)

Other opportunities to supplement basic science training activities include workshops to promote skills in translational research, including Patents/Intellectual Property, Grant Writing/Review and others.

In addition, the students must complete 18 hours of Non Topical Dissertation Level Research (PATH 9999), as required by GSAS.

### 3) Prepare for completion of the Qualifying Exam

In consultation with the student's mentor, the student prepares for the Qualifying Exam, which consists of writing an NIH-style grant on the proposed thesis work. This Exam, specified in more detail elsewhere, consists of a written document between 18 and 20 pages in length (double spaced, 0.5 inch margins) which is defended orally before the thesis committee. The Exam should present a logical, achievable research plan, outlining the biological problem with a relevant literature review, and providing literature evidence and preliminary laboratory results that demonstrate the achievability of the project. The Qualifying Exam must be completed by the end of June of the second year.

## SUBSEQUENT YEARS

Students must register for research credits—

PATH 9998: Non-topical Research

(variable credit up to 12)

*For students who have not completed their advancement to candidacy*

or

PATH 9999: Non-topical Research

(variable credit up to 12)

*Dissertation research credit for students who have completed their advancement to candidacy*

Students must attend—

PATH 8460: Seminars in Molecular Medicine and Human Disease  
*Seminar Series*

and

PATH 8050: Colloquium in Human Disease Research

*Journal Club and Research Progress Report*

*Students must continue to attend the Progress Report Series (PRPR) throughout their graduate career. In addition, they are encouraged to participate in the Journal Club, but are no longer required to attend once they have advanced to candidacy.*

## FURTHER EXPECTATIONS

The focus of subsequent years is on laboratory research oriented toward the selected thesis topic. Students will spend more time in the lab developing their thesis project. Continued participation in the research activities of the Program and Department is expected, specifically regular attendance at weekly departmental seminars, the PRPR student/postdoc seminar series, a welcome lunch to meet faculty members and other trainees in the department, and the annual Pathology Research Retreat with oral and poster presentations. Financial support of the student from the Department is contingent upon adequate participation in these activities and suitable progress in the student's research.

All students must maintain acceptable academic standing consistent with the guidelines established by the Graduate School of Arts & Sciences, MCBD, and the Department of Pathology. This requires a current and a cumulative grade point average of at least 3.00. Failure to meet these criteria will be handled individually by the MCBD Program Director after consultation with the mentor.

The Thesis Committee must meet at least annually through the term of the training. Under certain circumstances the MCBD Director may require more frequent Thesis Committee meetings and/or specific progress objectives from the student. The MCBD Director must be informed of the time of meetings, and at his/her discretion may attend the meeting at a mutually convenient time, and may participate as a voting member of the Committee. Thesis committee meetings are documented by the Committee Chair by email communications with the student, mentor, committee members, and graduate program administrator.

Graduation requirements include a written thesis that conforms to GSAS specifications, a closed oral defense of the document and research conclusions, and a public oral defense (seminar presentation). The written thesis document includes an adequate background information chapter and a chapter outlining future directions for the research. Students should plan on completing their thesis within a 5-year time frame, meaning within four years after selection of their mentor. Students are expected to publish their findings in high quality peer-reviewed journals appropriate for the student's field of study. At least one first author research paper describing original work must be accepted for publication before final defense of the dissertation.

# Molecular and Cellular Basis of Disease

## *Course Descriptions for Experimental Pathology*

### **PATH 8050: Colloquium in Human Disease Research**

(1 credit, offered Fall/Spring)

Instructor: Janet V. Cross, PhD

*(Formerly PRPR) The purpose of this course is to introduce new graduate students to the scientific literature in human disease, and to give them experience in interpreting, discussing, and presenting both research publications and their own progress on research projects. Enrollees will be expected to be present at each session and to be prepared to participate in the discussion. (MR5, Third Floor, Room 3005).*

### **PATH 8058: Topics in Medical Pathology**

(3 credits, offered Fall)

Instructor: Janet V. Cross, PhD

*Graduate students join the incoming class of residents for an introduction to concepts in the practice of Pathology. Lectures directed by Pathology faculty are complemented by a clinical perspective from the physicians who apply this information to make patient care decisions in their daily practice. In addition, students attend weekly conferences where a multidisciplinary team considers the total clinical picture to design treatment plans.*

### **PATH 8060: Rotation in Diagnostic and Interventional Medicine**

(4 credits, offered Fall/Spring)

Course Coordinator: Janet V. Cross, PhD

Students will spend 4 weeks, selecting from 3 or 4 Sections, at least one of which should be Surgical Pathology. Given their extensive clinical experiences, MSTP Students in the MCBD Program should select their sections from the first 8 options, excluding the Rotation in Interventional Medicine. The rotations will expose students to clinical problems and hands-on techniques such as tissue procurement, processing and diagnosis. Students will attend Clinical Conferences in which cases of human diseases related to the students' areas of thesis research are discussed. Discussions focus on the etiology of the disease, its stage, progression, and clinical treatment. The purpose of attending such clinical conferences is to develop a full appreciation of the major issues that characterize a specific disease and to provide an understanding of how the current means of disease treatment could be improved by advances in cellular or molecular therapeutics. This rotation will allow students to utilize clinical faculty members as resources to further discuss the relevance of their thesis research to the understanding of human disease. Students are encouraged to select one of these faculty members as member of their thesis committee.

To document participation in the rotation, students will be expected to maintain a "journal" with daily entries briefly summarizing the individuals that they interacted with (faculty, fellows, residents, etc) and what they observed/learned (3-4 sentences). A final summary of the experience with feedback on how the student might apply their experiences to their future work will complete the journal, which should then be submitted to the MCBD Director for evaluation.

## **Sections**

### **1. Hematopathology (Adam N. Goldfarb, MD)**

For the rotation in Hematopathology, the student will attend the daily diagnostic sessions known as "signout". These sessions encompass analysis of blood, bone marrow, and lymph node specimens by light microscopy. Additional signout sessions are held for flow cytometric analysis of similar specimens. The student is expected to gain an understanding of the basic morphology of normal blood, bone marrow, and lymph nodes. In addition the basic principles of multiparametric flow cytometric analysis of samples will be covered. The student is also expected to develop a basic understanding of the molecular abnormalities underlying leukemia and lymphoma. Correlations will be made the fun-

damental questions being addressed in current research on normal and malignant hematopoiesis. Clinical hematology journal club occurs weekly. Basic science lab meetings occur weekly with presentation of work in progress and discussion of cutting edge articles.

**2. Neuropathology and Autopsy (M. Beatriz S. Lopes, MD and James W. Mandell, MD, PhD)**

Students participate in the diagnostic service of the Division of Neuropathology, which includes the examination of intra-operative consultations (brain smears and frozen sections) and permanent sections of neurosurgical specimens, the gross and microscopic examination of brains obtained from the autopsy material in the Department, and gross and microscopic examination of muscle and nerves. Students essentially function as residents in studying at first hand the neuropathological material under the guidance and supervision of a faculty member, and participate in the regular weekly microscopic conference in which current neuropathological material and consultation case material submitted from outside centers are reviewed and discussed. In addition, the students participate in the interdepartmental conferences with the Neuro-Oncology Center team of clinicians and neurosurgeons. Projects in clinicopathologic correlation and/or experimental neuropathology may be possible during this rotation by pre-arrangement.

**3. Clinical Microbiology and Microbial Pathogenesis (Melinda D. Poulter, PhD)**

This rotation is designed to familiarize the student with microbial pathogenesis from the “bench to the bedside”. Students will attend daily “plate rounds” in Clinical Microbiology during which diagnostic interpretations are considered. Attendance of the Infectious Diseases attending rounds at least twice per week and Infectious Diseases case conference is required. Students are expected to become familiar with biochemical, morphologic, serologic, and molecular methods used for diagnosis of infectious diseases and for evaluation of antimicrobial efficacy. During the rotation, students will become acquainted with microbial virulence mechanisms that contribute to progression of bacterial, fungal, and viral infections. Mechanisms of inducible and intrinsic antimicrobial resistance will also be covered. Ongoing basic science questions about microbial pathogenesis and host response addressed in current research will be discussed. Research lab meetings involving presentations of work in progress and review of current literature are held weekly.

**4. Immunology and Renal Pathology: Renal disease mechanism in the clinical setting (Kenneth S.K. Tung, MD and Helen P. Cathro, MBChB, MPH)**

Students will learn the clinicopathologic presentation of the following diseases based on case studies: The Alport syndrome; Goodpasture’s disease; Glomerulonephritis of systemic lupus erythematosus; Renal allograft acute rejection. Students will learn the following concepts and techniques: Pathophysiological basis for the clinical presentations; Introduction to histology and histopathology of kidney and inflammation; Electron microscopy and ultrastructural findings of immune complexes; Immunohistology and appearance of immune complexes. Finally, students will learn the disease mechanism pertaining to each disease by addressing the following issues or questions: Biochemistry of glomerular basement; Why do autoantigens stimulate autoantibody response? How is self tolerance maintained and terminated? How do autoantibodies mediate tissue injury and disease? How do antigens stimulate allogeneic T cell response? What are the mechanisms of renal allograft rejection? Read a good review on each topic, following by discussion. Students are expected to participate in the diagnosis of ongoing renal biopsy cases.

**5. Molecular Diagnostics (Mani S. Mahadevan, MD and Lawrence M. Silverman, PhD)**

This rotation is designed to get the students familiar with various aspects of molecular diagnostics. The application of molecular diagnostics to infectious diseases, genetic diseases, and hematopathology will be emphasized. Students will attend weekly laboratory meetings and clinical genetics conferences. They will also have an opportunity to become familiar with the cytogenetics laboratory and will have an opportunity to generate a karyotype. Students are expected to become familiar with the fundamentals of molecular genetics, real-time PCR and quantitative RT-PCR, DNA sequencing, automated fragment analysis, Southern blotting, etc. They will get exposure to the issues of genetic counseling. In addition, they will get an opportunity to understand and interpret HIV genotyping, fragment analysis as it applies to identifying clonal processes and genetic disorders. Emphasis will be placed on the underlying molecular basis of the various disorders and genotype-phenotype correlations.

#### 6. Surgical Pathology (Robin D. LeGallo, MD and Christopher A. Moskaluk, MD, PhD)

The purpose of this rotation is for the student to gain an understanding of the role of microscopic examination and special techniques in the diagnosis and study of human disease. Accordingly, the student will attend daily “sign-out” sessions, during which patient tissue specimens from the clinical Surgical Pathology service are examined microscopically, discussed and diagnosed. These clinical specimens demonstrate a diverse variety of neoplastic and non-neoplastic human diseases. Also, the student will attend weekly Surgical Pathology and Autopsy conferences, where clinical cases are presented and discussed in detail. In addition, the student will rotate through the clinical and research Surgical Pathology laboratories to gain exposure to a variety of the special techniques used in diagnostic and investigational pathology, specifically tissue procurement, tissue processing, immunohistochemistry, microdissection, and microarray analysis. Upon completion of this rotation, the student will have gained an appreciation for the role of microscopic examination and special techniques in the diagnosis and investigation of human disease.

#### 7. Cytopathology (Henry F. Frierson, Jr, MD)

This rotation is an introduction to the technical and professional skills involved in the field of cytopathology. Students will learn how a variety of cytologic specimens (cervical, urine, ascites, fine-needle aspiration, etc) are prepared in and outside the laboratory for microscopic examination. Also, students will accompany cytopathology fellows to the clinic, bedside, and radiology suite to observe how fine-needle aspiration specimens are obtained from patients and the nuances of immediate cytopathologic interpretation. In addition, they will learn general cytopathologic criteria that allow the diagnosis of cancer, infectious diseases, and benign conditions. Students will participate in the daily sign-out of cytopathologic cases with residents, fellows, and faculty, and gain an appreciation for the implications of various diagnoses on patient management.

#### 8. Clinical Chemistry/Biochemistry, Toxicology/Therapeutic Drug Monitoring and Medical Informatics (James C. Boyd, MD; David E. Bruns, MD; and Doris M. Haverstick, PhD)

Testing done in these areas of the laboratory provides the largest portion of diagnostic results in medicine. The rotation will address (a) the types of clinical questions that can be answered by chemical and biochemical measurements, (b) the performance of those measurements, and the reporting and (c) the interpretation of the results of the tests. Thus, the rotation will first provide an introduction to the principles of formulating clinical questions that can be addressed by laboratory testing and the principles of formulating these questions. Next we will explore principles of analytical science (what we should have learned in chemistry class, had we been paying attention – in two easy lessons) and examples of modern measurement techniques used in the care of patients and in monitoring of health status. This will include a laboratory tour to see the automation and robotics in current use. We will then address the interpretation of clinical laboratory data in individual patients. This will be done by use of discussion, readings and examples. In the various areas of this rotation (a through c), we will use examples from clinical toxicology, therapeutic drug monitoring, clinical chemistry and clinical biochemistry, including biochemical genetics and tests of endocrine signaling.

#### 9. Rotation in Interventional Medicine (Coordinated by Janet V. Cross, PhD)

After learning about the diagnostic challenges facing physicians in the practice of Pathology, the Rotation in Interventional Medicine will allow the student to learn more about the challenges facing physicians as they interact with patients. The students will select two clinical specialties from the list below and spend two to three days interacting with the faculty and staff, learning about the challenges that they face in their practice and observing procedures first-hand. Some direct patient contact may be part of the rotation, at the discretion of the supervising physician.

Some background reading prior to the first day of the rotation may be required, and attendance at a relevant Case Conference expected as part of the rotation. The specifics of each opportunity are detailed below.

If selecting this rotation, the student should be aware that, in order to accommodate complex schedules of the physicians, clinics, procedures etc., some flexibility will be required. The expectation for this rotation will be one “week-equivalent” but it will likely not be possible to schedule everything to fit in a standard week.

*Radiation Oncology (Paul W. Read, MD, PhD and James M. Lerner, MD; with Admin Charlotte A. Gilbert)*

The practice of Radiation Oncology involves the treatment of cancer patients with ionizing radiation. UVA has four state of the art instruments central to the practice, and this rotation will offer the students the opportunity to learn about how these machines work and to observe how they are deployed. Through interactions with the physicians, medical physicists, and staff, students will observe the treatment planning process as therapeutic approaches are discussed and developed by this collaborative team. Attendance at a 'morning conference' where the complete medical picture of ongoing cases is presented and discussed will be expected. Some direct interaction with the patients will be possible as the students observe in the clinic.

*Gynecologic Oncology (Linda R. Duska, MD)*

This rotation will allow a self-directed exploration of the specialty, coordinated through discussion with Dr. Duska. Opportunities will include observation at clinic visits, interactions with patients considering participation in clinical trials and observation in the operating room, including laparoscopic, open and robotic surgical procedures. Attendance at a minimum of one Tumor Board (weekly on Wednesday) where the pathology, radiology etc of interesting cases is discussed will be required. In addition, attendance at a monthly "Clinical Trial Meeting" will expose students to the ins and outs of conducting clinical trials from the specialty that has been most successful at establishing trials and recruiting patients here at UVA.

### **PATH 8130: Topics in the Molecular Basis of Human Disease I**

(2 credit, offered Fall, cross listed as BIMS 8131)

Instructor: James W. Mandell, MD, PhD

*Students may take 8130/8140 out of sequence, if needed. This is a series of joint lectures by basic and clinical scientists that focuses on the clinical context of a specific biomedical problem and the contemporary research that has resulted in major advances and treatment of the disease. Possible topics include: Osteoporosis, Infertility, Allergy, Muscular Dystrophy, Rett Syndrome, Atherosclerosis, Malnutrition, Iron Metabolism and Hematopoiesis.*

### **PATH 8140: Topics in the Molecular Basis of Human Disease II**

(2 credit, offered Spring)

Instructor: James W. Mandell, MD, PhD

*Students may take 8130/8140 out of sequence, if needed. This is a series of joint lectures by basic and clinical scientists that focuses on the clinical context of a specific biomedical problem and the contemporary research that has resulted in major advances and treatment of the disease. For list of potential topics, please see PATH 8130 (above).*

### **PATH 8280: Clinical Immunology and Immunopathology**

(3 credits, modular)

Instructor: Timothy N. Bullock, PhD, Larry Borish, PhD

*Lecture course designed to provide participants with an appreciation of contemporary clinical problems associated with the immune system. Students will be introduced to diseases associated with aberrant performance of the immune system, gain an understanding of the etiology, clinical presentation, and consequences of diseases, and discuss current research in disease prevention and therapy.*

### **PATH 8440: Pathology Projects**

(1 credit, offered Fall/Spring)

Instructor: Dennis J. Templeton, MD, PhD

*Research rotation projects for medical or graduate students with an interest in Pathology*

### **PATH 8460: Seminars in Molecular Medicine and Human Disease**

(1 credit, offered Fall/Spring)

Instructor: Janet V. Cross, PhD

*Weekly presentations from speakers within and outside of UVA presenting descriptions, problems, and current approaches to diagnosis, molecular basis, and treatment of human disease. Presentations will usually*

*contain both clinical and laboratory research, though occasionally reports of disease model systems will be presented. (AP Conference Room, New Hospital Expansion Bldg., Third Floor, Room 3025)*

**PATH 9995: Topical Research**

(variable credit up to 12, offered Fall/Spring)

*Original research on approved problems.*

**PATH 9998: Non-topical Research**

(variable credit up to 12, offered Fall/Spring/Summer)

*For students who have not completed their advancement to candidacy*

**PATH 9999: Non-topical Research**

(variable credit up to 12, offered Fall/Spring/Summer)

*Dissertation research credit for students who have completed their advancement to candidacy*