

Molecular and Cellular Basis of Disease

PhD Training Program in Experimental Pathology

INTRODUCTION

The Molecular and Cellular Basis of Disease (MCBD) PhD program 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 the combined Molecular Medicine (Pathology Pharmacology, and Physiology) (MOMD/PPP) admissions program, or through the Medical Scientist Training Program (MSTP). Students from other BIMS programs would be accepted into the MCBD PhD program.

FIRST YEAR

The focus of the first year of studies is on core curriculum requirements that are shared by most programs (*e.g.* MOMD, MII, BMBG, CDB) at UVA. Generally, the equivalent accomplishments will be achieved during the first two years of medical education within the MST Program.

A total of at least 30 credit hours should be earned during the first year.

Research Rotations (First and Second Semester)

Generally, students complete 3 laboratory rotations (PATH 8440, up to 12 credit hours; 4 credit hours/per lab rotation) in different laboratories in their first year, as required by their admission program. By April 29 of their first year students are expected to select their research mentor and choose the department from which they will receive their degree.

First Semester

Combined Core Curriculum—

BIMS 5030: Macromolecular Structure and Function
(4 credits)

BIMS 8010: Gene Structure and Expression
(5 credits)

BIMS 5012: Cell Structure and Function
(5 credits)

PATH 8130: Topics in the Molecular Basis of Human Disease
(1 credit, *may be taken in second year*)

Orientation

The department of Pathology will organize a tour or meeting with the first year students within their first month into the MOMD/PPP program

Second Semester

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

BIMS 8320 Grad Physiology

(5 credits)

BIMS 7100: Research Ethics
(1 credit)

Electives

Students are required to take one elective from the following: Pharmacology, Practical Molecular Medicine, Genetics, Molecular Pathogenesis, Immunology, Molecular Basis of Carcinogenesis, Vascular Biology, Neurophysiology, Development and Reproduction, or others as relevant to their area of interest.

SECOND YEAR

During the second year, students have three main tasks:

1) Identify members of a thesis committee

In consultation with the Mentor, the student will select a committee of four or five faculty members who will serve as guides and readers of the qualifying examination and thesis. 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 Biomedical Sciences 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 participation courses related to the Molecular and Cellular Basis of Disease.

Twenty-four (24) credits must be completed during this year to satisfy the total requirement of 54 credits for the PhD, in addition to the 30 credits earned during the first year. Normally, no for-credit courses are allowed in the third year, so required coursework must be completed during the second year.

Advanced Electives

Students must complete at least 12 credit hours of didactic courses relevant to their interests and the Molecular and Cellular Basis of Disease. *Two of these courses must be—*

PATH 8058: Topics in Medical Pathology
(3 credits)

Students select subtopics of the Medical Human Pathology course

and

PATH 8060: Rotation in Medical Pathology
(4 credits)

Other didactic electives from Pathology or other Programs may be taken in addition. Didactic courses must be approved by the Program Director or Curriculum Director.

Required Participation Activities

Students must enroll and regularly attend—

PATH 8460: Seminars in Molecular Medicine and Human Disease
Seminar
(1 credit)

and

PATH 8050: Colloquium in Human Disease Research
Journal Club, and Research Progress Report
(1 credit)

Or, if a schedule conflict with PATH 8050—

PATH 8920: Topics in Human Disease Literature
Independent colloquium
(1 credit)

In addition, students must identify and participate in a topical journal club relevant to their research interests, or relevant to their training grant. In the case that no pre-existing journal club is available, PATH 8480 may be used to organize a special readings program—

PATH 8480: Research Correlation in Medical Pathology
(1 credit)

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.

3) Prepare for completion of the Qualifying Exam

In consultation with the student's mentor, the student will prepare for the Qualifying Exam, which consists of writing an NIH-style grant on the proposed thesis work. This Exam, specified in more detail elsewhere, will consist of a written document between 18 and 20 pages in length (double spaced) which will be defended orally before the thesis committee. The Exam should present a logical, achievable research plan for the Thesis, 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 presented by September of the Third 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
(1 credit each)

and

PATH 8050: Colloquium in Human Disease Research
Journal Club, and Research Progress Report
(1 credit)

The focus of subsequent years will be on laboratory research oriented toward the selected thesis topic. Students will spend more time in the lab developing their thesis project. Students should plan on completing their thesis within a 5-year time frame, meaning within 4 years after selection of their mentor. Students are expected to publish their findings in high quality peer-reviewed journals. At least one research paper as a first author on the thesis research should be accepted for publication before defense of the Thesis.

Continued participation in the research activities of the Program and Department is expected, specifically regular attendance at PATH 8460, PATH 8050, the chosen Journal Club (usually PATH 8050), and the annual Pathology Research Retreat. Financial support of the student from the Department is contingent upon adequate participation in these activities and suitable progress in the student's thesis research.

The Thesis Committee must meet at least annually through the term of the training. Under certain circumstances the Graduate Director may require more frequent Thesis Committee meetings and/or specific progress objectives from the student. The Graduate Director must be informed of the time of meetings, and at his discretion may attend the meeting at a mutually convenient time, and may participate as a voting member of the Committee. Thesis committee meetings should be 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 University specifications, a closed oral defense of the document and research conclusions, and a public oral defense (seminar presentation). The written thesis document should include an adequate background information chapter and a chapter outlining future directions for the research.

EXPECTATIONS

Students are expected to attend and participate in research activities and seminars in the Department of Pathology. These include a bi-monthly Research in Progress that focuses on student research presentations, weekly departmental seminars, a Welcome lunch to meet faculty members and other trainees in the department and an annual research retreat with oral and poster presentations.

Molecular and Cellular Basis of Disease

Course Descriptions for PhD in 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 present at least one research literature report each semester (*MR5, Third Floor, Room 3005*)

PATH 8058: Topics in Medical Pathology

(3 credits, offered Spring)

Instructor: Donald J. Innes, Jr., MD

From the Medical course in Human Pathology, students will select General Pathology (required) and three other subtopics based on their research program, summing to at least 45 hours of in-class time.

General Pathology (10 hours in-class time)

Pulmonary Pathology (15 hours)

Dermatopathology, Bone, Toxicology, Endocrine (6 hours)

Gastrointestinal Pathology (12 hours)

Cardiovascular Pathology (9 hours)

Breast and Reproductive Pathology (4 hours)

Renal Pathology (12 hours)

Hematopathology (30 hours)

Neuropathology (15 hours)

Microbiology and Forensic Pathology (10 hours)

PATH 8060: Rotation in Medical Pathology

(4 credits, offered Fall/Spring)

Generally Fall only, since scheduling is more difficult in Spring– Students will spend 4 weeks, selecting from 3 or 4 Pathology Sections. These 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.

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 fundamental 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. Lopez, 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 (Kevin C. Hazen, 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 (Julia C. Iezzoni, 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. 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.

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

(1 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.

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

(1 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.

PATH 8280: Clinical Immunology and Immunopathology

(3 credits, offered Fall every other year)

Instructor: Timothy N. Bullock, 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

(3 to 12 credits, offered Fall/Spring)

Instructor: Isa M. Hussaini, PhD

Research rotation projects for students pursuing a graduate degree 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 8480: Research Correlation in Medical Pathology

(1 credit, offered Fall/Spring)

Instructor: Isa M. Hussaini, PhD

Self-organized journal club. Participation in other organized journal clubs is encouraged when available.

PATH 8620: Advanced Topics and Technologies in Cell Signaling

(3 credits, offered Spring every other year, cross-listed as BIMS 8620)

Instructor: Janet V. Cross, PhD

Prerequisite: BIMS 812 or permission of the instructor –

This course uses contemporary literature in the field of cell signal transduction as a foundation for student driven discussion. Each class session focuses on a single signaling pathway, with particular attention paid to the techniques and technologies applied. Understanding the specific signaling pathway shares emphasis with critical examination of the data and the chosen approach, and consideration of possible alternatives.

PATH 8640: Clinical Oncology for Basic and Translational Scientists

(1 credit, offered Spring every other year)

Instructor: Dennis J. Templeton, MD, PhD

This is a 6-week seminar course designed to present an overview of selected aspects of the clinical cancer diagnosis and care by cancer practitioners. Selected vignettes demonstrating issues and technologies will be presented, together with a discussion of cutting edge approaches and current problems confronting clinicians and patients. There will also be an emphasis on investigator-clinician collaborations.

PATH 8920: Topics in Human Disease Literature

(1 credit, offered Fall/Spring)

Instructor: P. Prabhakara Reddi, PhD

This course weekly presents the opportunity to participate in a weekly journal club on selected topical research areas of relevance to the student's interests. Areas of participation include cancer, signal transduction, transcription and differentiation, immunology, infectious disease, reproduction, and neuropathology. The instructor will coordinate with the student a schedule of participation including presentations in at least one area, and the student will document participation with short summaries of the topics presented.

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

EXPECTATIONS

Students are expected to attend and participate in research activities and seminars in the Department of Pathology. These include a bi-monthly Research in Progress that focuses on student research presentations, weekly departmental seminars, a Welcome lunch to meet faculty members and other trainees in the department and an annual research retreat with oral and poster presentations.