

Yale Medical Research Scholars Program (MRSP) Curriculum

MRSP students complete the curriculum below at the same time that they fulfil their regular academic requirements, which include required coursework and lab rotations in year one and coursework, a qualifying exam, and possibly teaching in year two. The MRSP courses will satisfy degree requirements in some of the BBS Ph.D. programs; in others they will be in addition to required courses. The MRSP curriculum will increase a student's responsibilities, and only the most committed and motivated students should apply for consideration.

Physiological Systems (C&MP 5500/MCDB 5500)

Students in Physiological Systems will develop a foundation in human physiology and the principles of feedback and homeostasis. The biophysical properties of cells, tissues and organs will be developed in context of the functions they perform, and the concept of homeostasis will be considered at the cellular and organismal level. Several physiological systems will be investigated. First, the respiratory system will be reviewed with emphasis on the mechanical interactions between the lung and the chest wall, gas exchange, the matching of ventilation and perfusion, and respiratory control. Because regulated transport of molecules through membranes underlies renal function as well, the functional organization of the kidney will be explored next. Urine composition and regulation as well as salt, fluid, and acid-base homeostasis will all be considered. This background will lead into the physiology of skeletal muscle, smooth muscle in hollow organs and cardiac muscle. The regulation of cardiac output, blood flow, and vascular exchange will be integrated into an overview of the responses to exercise. The digestive system will then be developed in the context of energy balance and temperature regulation, substrate and calcium metabolism, and its regulation by hormones. Energy production and its regulation will be integrated in the context of exercise physiology. Subsequently, the biology of nerve cells will be considered, with an emphasis on structure-function relationships within the central nervous system and the physiology of the special senses (vision, hearing, touch, taste, smell). The course will conclude by considering the integral link between physiological systems and biomedical engineering. Weekly discussion sections will provide a forum for in-depth exploration of questions and concepts. Graduate students will, in addition, evaluate pertinent research topics on a weekly basis through meeting with the instructor.

The Physiological Systems class will meet three times per week for 50 minutes and will have lectures, weekly quizzes, two midterm examinations, and final examination.

Physiologic Function and Cellular Structure of Organ Systems (PTB 5604)

This new course introduces students to the organization and function of cells within complex multicellular systems within the human body. The course will include a review of all major tissues and organs, with particular emphasis on the molecular and cellular bases of developmental processes and human diseases. The lectures are supplemented by electronic-based tutorials on the histology of tissues and organs. Below are the key learning objectives:

- To gain a working knowledge of identifying the key features of human cells, tissues and organs at the light and electron microscopic levels
- To be able to relate tissue and organ structure/organization to their function in normal and disease states
- To build an understanding of how tissues and organs interact via circulating molecules and cells
- To become familiar with the research that has led to our current understanding of the function of organs and systems, the most recent research developments, and the questions that remain open in diseases
- To appreciate how our understanding of disease mechanisms at the molecular level contributes to our knowledge of organ development and function, and conversely, how our knowledge of organ development and function helps us understand disease mechanisms

- To gain and understanding of how the immune system, stem cells and the microbiome, which are non-solid tissues engaged in cell migration, and in which signaling events are key to function, contribute to tissue/organ development and function as well as to diseases

Intro to Biostatistics in Clinical Research (IMED 5645)

This intensive 2-week summer course provides an introduction to statistical concepts and techniques commonly encountered in medical research. The course usually runs in July. Previous coursework in statistics or experience with statistical software packages are not a requirement. Topics to be discussed include study design, probability, comparing sample means and proportions, survival analysis, and sample size/power calculations. The computer lab will incorporate lecture content into practical application by introducing the statistical software package SPSS to describe and analyze data. This course is taken with physicians who are in the Investigative Medicine PhD program.

NOTE: The process for enrolling in the course requires multiple steps:

1. In the spring semester prior to the course, students must express interest in the course by registering at <https://medicine.yale.edu/investigativemedicine/courses/registration/>.
2. Students will then receive information from the Investigative Medicine Program about the exact course schedule.
3. Students must then enroll in the course (via the normal graduate school course enrollment process) in the fall semester immediately following completion of the course. Doing so will enable the instructor to enter a grade and is the only way in which the course will appear on a transcript.

Molecular Mechanisms of Disease (PATH 5690)

A central objective of the MRSP is to provide training in Pathobiology for Ph.D. students. The course surveys the mechanisms underlying the major human diseases, including infectious, metabolic, genetic, inflammatory, and neoplastic disorders. The primary objectives are to highlight the interface between clinical medicine and molecular and cellular biology, and to demonstrate how basic biology can be used to understand the mechanisms underlying human disease, and, increasingly, utilized to develop effective therapy.

Mechanisms of Disease meets twice weekly for one hour each session. The majority of sessions are didactic lectures, with ample time set aside for questions and comments by the students. The regular lecture sessions are interspersed with discussion sessions, led by a faculty member, in which the students can continue to ask questions and discuss further implications of the content introduced in the lectures, including opportunities for relevant research. The formal discussions are complemented with assigned readings and a term paper, for which students are first required to submit a series of research questions based on the lectures. In consultation with the student, the instructor selects one of these questions for which the student writes a discussion, including experiments proposed to address that question. Each student's performance in the course is evaluated based upon his/her participation in the discussion sessions and the term paper.

Medical Physiology Case Conference (C&MP 5600)

This full-year course for medical students enables MRSP students to apply basic concepts of physiology to clinical syndromes and disease processes. All students are expected to participate actively in a weekly discussion of a clinical case that illustrates principles of human physiology and pathophysiology at the whole-body system, organ, cellular, or molecular level. The class is divided into groups of 10-12 medical students, with one MRSP student embedded per group to maximize interactions with the medical students.

NOTE: The course schedule does NOT follow the typical schedule for graduate level courses and is highly variable in when it meets each week and how frequently it meets each semester. The schedule is usually announced just prior to the start of classes.

Physiology in Medicine (C&MP 5700)

This discussion-based course makes use of medical case studies and scientific literature to illustrate key physiological concepts at the whole-body, system, organ, cellular, and molecular levels. Students are expected to actively participate in small-group discussions to deepen their understanding of human physiology and pathophysiology and how it relates to laboratory findings. It is taken as an alternative to Medical Physiology Case Conference (C&MP 5600).

Topics in Human Investigation (B&BS 6680)

Taking advantage of the extraordinary and unique facilities available at the School of Medicine, the Human Investigation course teaches students about the process through which novel therapeutics are designed, clinically tested, and approved for human use. It is divided into two main components, with the first devoted to moving a chemical agent from the bench to the clinic, and the second to outlining the objectives and methods of conducting clinical trials. The latter section also includes a discussion of the FDA approval process.

The first component describes aspects of structure-based drug design and offers insight into how the drug discovery process is conducted in the pharmaceutical industry. The format includes background lectures with discussions, labs, and computer tutorials. The background lectures include a historical perspective on drug discovery, the current paradigm, and important considerations for future success. Because two key features of structure-based drug design are the appreciation of three-dimensional protein structure via X-ray crystallography, and how one uses the structure to design and optimize drugs, students in the course grow protein crystals, collect X-ray diffraction data at the core X-ray facility at the School of Medicine, and learn basic molecular modeling. Complementing this exercise is discussion of relevant clinical examples of proteins for which structure-based drug design was essential for the development of successful therapeutics. Some examples include: (1) HIV protease for the design of AIDS drugs, (2) BCR-Abl tyrosine kinase for the design of the anticancer agent, Gleevec, (3) thymidylate synthase and dihydrofolate reductase as molecular targets for antimicrobials and anticancer agents, and (4) COX-1 and COX-2 inhibitors for inflammation and the Vioxx story.

The second component of the course provides students with knowledge of the basic tools of clinical investigation and how new drugs are tested in humans. A series of lectures and discussions provide an overview of the objectives, research strategies, and methods of conducting patient-oriented research, with a focus upon design of trials to test therapeutics. Student participation is key, and preparation and active participation in each session is expected. These sessions are followed by discussion of topics that are central to the conduct of clinical investigation including ethics of, and development of protocols for, human investigation. Practical experience is part of these latter sessions, with opportunities for students to observe the Human Investigations Committee at Yale, and the enrollment of patients in clinical protocols in the NIH-supported General Clinical Research Center at Yale, Yale-New Haven Hospital, or its outpatient clinics. These sites enroll patients in different stages of clinical trials for diseases ranging from type II diabetes mellitus to cancer. Each student is required to write and review an HIC protocol, in addition to participating actively in class. In the final lectures, clinical trials and data analysis are discussed in the context of the FDA new drug approval process.

Mentored Clinical Experience (C&MP 5610)

Through the other courses in the MRSP curriculum, students will become versed in the cell biology of tissues, human physiology, and the pathophysiology of human disease. While critical components of our proposed training program, these didactic experiences are not by themselves sufficient to ensure that participating students will gain a deep understanding of and appreciation for the interface between basic biomedical research and its application in clinical practice. There is no more powerful teaching tool in medical education than mentored exposure to patients and patient materials, which is the objective of the Mentored Clinical Experience course.

Students participate in a Mentored Clinical Experience that includes both classroom and “bedside” instruction. The class meets throughout both semesters of the students’ second and third years. The students meet with each of eight highly selected physician-scientist mentors (two mentors

per semester). In the first of these sessions, the faculty mentor leads a seminar-based discussion through which the students are introduced to a particular disease process. This first session reviews the relevant tissue cell biology, physiology, and pathophysiology. Emphasis is placed on the molecular mechanisms responsible for the disease and on the experimental approaches through which these mechanisms were elucidated. Students are expected to prepare for these sessions by reading handout material or designated sections of relevant textbooks.

In the second of the three sessions, the physician-scientist mentor leads the students in a seminar-based discussion of papers from the primary literature that report basic or translation research focused on the disease of interest. The students present these papers and are expected to discuss their experimental approaches, their strengths, and their weaknesses. The papers are chosen to cover as broadly as possible the spectrum of disease-related research, including the identification of pathogenetic mechanisms, the creation and characterization of animal or cell culture model systems, the search for possible therapies, and the evaluation of these therapies at the pre-clinical and clinical level.

The third session with each physician-scientist mentor brings the students into contact with patients afflicted with the disease of interest and/or with pathological specimens derived from such patients. The physician-mentor conducts an interview of the patient, and the students are encouraged to ask questions and make observations. Where possible and useful, the students also observe microscopic or macroscopic samples of tissues from affected patients in the setting of a clinical pathology laboratory under the guidance of the mentor and a member of the faculty of the Department of Pathology. The goal of these sessions is not to teach the students the skills involved in taking a medical history or performing a physical exam. Rather, it is to provide the students with an experience that will cement their understanding of a pathological process and make them aware of the impact that disease and its treatment can have on the lives of patients.

The Mentored Clinical Experience course is fortunate to have recruited some of Yale University's most noted physician-scientists as enthusiastic participants in this undertaking. All students receive HIPAA training and appropriate training in infection control relating to patient contact. It should be noted that in addition to offering the students a multidimensional opportunity to explore human disease, the Mentored Clinical Experience class allows the students to form relationships with a superb cadre of physician-scientists. Through these relationships, the students are able to explore research opportunities, make additional connections with other physicians and scientists engaged in disease related research, and acquire mentors and role models who can continue to advise them as they progress through the program and graduate school.