IMMUNOBIOLOGY

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http://immunobiology.yale.edu
M.S., M.Phil., Ph.D.

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FIELDS OF STUDY

Immunology is the study of the immune system that confers protection against infectious diseases. This complex system is also involved in the rejection of grafted tissues, in allergy, and in autoimmunity. The Department of Immunobiology is a multidisciplinary group of investigators committed to understanding the cellular, genetic, and molecular basis of these processes. The department is based on the understanding that the solution to complex biological problems requires the integration of individuals with a common goal but differing expertise. Research focuses on the molecular, cellular, and genetic underpinnings of immune system function and development, on host-pathogen interactions, and on a variety of autoimmune disorders. In addition to the growing need to apply basic science research toward human disease, we have developed a Human and Translational Immunology (HTI) section to improve our understanding and treatment of human immunological disorders. The general research interests of the Immunology track span almost all aspects of the immune system and its role in disease prevention.

RESEARCH AREAS

Fundamental Mechanisms of Immunity Research in the department examines the fundamentals of the immune system at multiple levels: development, activation, regulation, and evolution. Studies of lymphocyte and innate immune cell development examine the receptors and signals that control lineage commitment, cell maturation,

and cell death; the establishment of the proper environments for cellular development; and the mechanisms by which antibody and T cell receptor genes are assembled and diversified. A critical first step in an effective immune response is the activation of cells of the innate immune system, including monocytes, macrophages, dendritic cells, and neutrophils. Research examines the receptors and signaling molecules that control these processes, the mechanism by which cells process and present antigen, and the recognition of this antigen by T cell receptors on T lymphocytes. Upon activation, T and B cells differentiate and acquire critical effector functions including the production of cytotoxic anti-pathogen molecules and antibodies. Studies in the department examine the tissue spatial context and cellular interactions that influence effector lineage fate decisions, cytoplasmic signal transduction molecules, nuclear transcription factors, and mechanisms controlling gene expression during differentiation. Finally, resolution of the immune response (leading to scarring or healing) and the evolution of adaptive immunity are under study.

The Human Immune System The immune system has evolved to deal with many different challenges, some of which can vary widely among vertebrate species, and thus while many basic mechanisms may be shared between humans and various animal models, the human immune system has evolved to differ in important ways from that of commonly used experimental rodents. Furthermore, human diseases, especially chronic disorders, are also significantly more complex than commonly used disease models, and the approaches to studying human immunity, for ethical reasons, must often be fundamentally different from those used in experimental systems. New immunotherapies, especially those based on the use of biologicals, have created an opportunity to ethically investigate human immunology and improve the value of clinical trials. The Human and Translational Immunology (HTI) section of the Immunobiology department studies both the immune systems of healthy individuals and the roles that immunology plays in a variety of human disease and analyzes the alterations that therapies may have on the immune response. HTI investigators also develop new approaches for human investigation and create new experimental models that better replicate human immunity.

Immunology of Cancer The past several years have witnessed a revolution in cancer treatment based on the paradigm of activating a patient's own immune system to target their cancer. Cancer immunotherapy relies on the immune system's ability to not only recognize "non-self," but "altered self," detecting the remarkably subtle differences between cancer cells and healthy tissues. Moreover, many therapies rely on preexisting immune cells in the tumor microenvironment for efficacy, highlighting the potential of natural immunosurveillance mechanisms to destroy cancer. In close collaboration with the Yale Cancer Center, ongoing work in the Department of Immunobiology focuses on seeking to understand the basic mechanisms of how innate and adaptive immune responses are generated against tumors, how tumor clearance is achieved, and how the immune system can be manipulated to enhance immunotherapy.

Disorders of the Immune System Adaptive immune responses provide powerful long-lived protection from pathogens, but when misdirected, T and B cell responses can cause significant injury and disease. The mechanisms controlling inappropriate adaptive immunity to self-targets/autoantigens (autoimmunity), allergens (allergy), or transplanted tissues (alloimmunity) are being addressed by faculty in our department. Diabetes, multiple sclerosis, lupus, and rheumatoid arthritis are just some of the

autoimmune diseases under study. Why and how allergens are targeted by the immune system in diseases like food allergy and asthma are questions being actively studied. Vascular graft and red blood cell rejection are examples of alloimmune responses under investigation in our department.

Host-Microbe Interactions The immune system evolved to manage our constant exposure to diverse microbial stimuli, ranging from the smallest viruses to fifty-foot-long tapeworms. Researchers in the Department of Immunobiology investigate the full spectrum of possible host-microbe interactions, including antagonistic interactions with parasitic viruses, bacteria, and helminths, as well as mutualistic interactions with the trillions of microbes that live in and on us (our microbiota).

Inflammation Biology Inflammation is a protective response including infection and injury as well as other causes of loss of tissue homeostasis. Although primarily orchestrated by the immune system, the inflammatory response can affect virtually any physiological process, from cardiovascular and digestive functions to growth, reproduction, and behavior. However, because inflammation operates at the expense of some normal physiological processes, it can also be a source of a variety of pathological sequela. Indeed, most human diseases are now known to be associated with inflammation. Research in our department addresses multiple aspects of inflammation biology, ranging from detailed molecular mechanisms underlying the response, to human diseases.

Computational Immunology Computational immunology (or systems immunology) involves the development and application of bioinformatics methods, mathematical models, and statistical techniques for the study of immune system biology. The immune system is composed of dozens of different cell types and hundreds of intersecting molecular pathways and signals. Systems approaches can be used to predict how the immune system will respond to a particular infection or vaccination. Or it can help understand how best to design an immunotherapy: will it help ease disease, and what might the side effects be? In addition, computational approaches are increasingly vital to understanding the implications of the wealth of gene expression and epigenomics data being gathered from immune cells. Yale has a diverse research program in computational immunology that brings together expertise from a variety of scientific disciplines to bear on research projects in vaccine response, host-pathogen dynamics, cell-fate choices, immune genomics, informatics, and many other topics. Students interested in computational immunology can be co-mentored by faculty from the Immunology track and the Computational Biology and Bioinformatics tracks.

FACILITIES

More than thirty laboratories are actively involved in research in immunology. Many share adjoining or nearby laboratory space in the Anlyan Center (TAC) and include faculty who are funded by the Howard Hughes Medical Institute. The Department of Immunobiology provides one of the largest integrated training programs in immunology in the country, led by a faculty with a reputation for excellence in research. The department maintains a wide variety of major equipment. In addition, investigators have access to a wide variety of cutting-edge equipment on campus in open-access core facilities for flow cytometry, mass cytometry, EM, and imaging including light-sheet microscopy and intravital two-photon LSM.

PROGRAM ENTRY

Most students enter the Immunobiology graduate program through the Immunology track of the interdepartmental graduate program in Biological and Biomedical Sciences (BBS), http://bbs.yale.edu. Other types of students enter from the M.D./Ph.D. program (see below), the MRSP (see below), or another BBS track, with approval of the Immunobiology director of graduate studies (DGS) and the faculty adviser.

The faculty and students of the BBS program are organized into interest-based tracks. Immunology, being one of eight tracks, encourages individualized attention to maximize scientific interactions. There is complete freedom to work with any of the 350 faculty members affiliated within any of the tracks and to take courses offered by any of the BBS departments or programs. Students are encouraged to supplement core courses in molecular and cellular immunology with additional courses selected from the wide range available in cell biology, molecular biology, developmental biology, biochemistry, genetics, pharmacology, molecular medicine, neuroscience, and bioinformatics. Research seminars and informal interactions with other graduate students, postdoctoral fellows, and faculty also form an important part of graduate education.

The Section of Human and Translational Immunology (HTI) is a component of the Immunobiology department and is located at 10 Amistad Street and 300 George Street. Its mission is to accelerate the application of new developments in the field of immunology to the treatment of human diseases. HTI faculty study the immunologic aspects of a very broad range of human diseases, encompassing investigations in the fields of cancer; transplantation of solid organs and stem cells; autoimmune diseases; and neurologic disease.

The Medical Research Scholars Program (MRSP) is open to students who have already been accepted into the BBS program. A separate application is also required, and is to be submitted to the BBS. A total of eight students each year (four first-years and four second-years) will be enrolled as Medical Research Scholars. They remain in their BBS tracks or departments but participate in the additional MRSP curriculum. The program bridges barriers between traditional predoctoral and medical training by providing Yale Ph.D. students with both medically oriented course work and a mentored clinical experience. This combination of medical knowledge and face-to-face interaction with patients and their doctors provides a new perspective to Ph.D. students and enhances the rigorous training in basic science already provided.

SPECIAL REQUIREMENTS FOR THE PH.D. DEGREE

Students are required to take six courses for a grade in the graduate school.

Required graded courses for first- and second-year students are:

1. IBIO 530, Biology of the Immune System (Students have the option of passing out of IBIO 530 by taking the final exam from the previous year.)
2. IBIO 531, Advanced Immunology
3. Two Immunobiology seminar courses taken from this series: IBIO 532, IBIO 536, IBIO 537, IBIO 538, IBIO 539 (The second seminar course can be audited if a student has grades in six other science courses and has already taken one seminar course for credit.)

Required credit-only, nongraded courses for first-year students are:

1. IBIO 600, Introduction to Research (Immunology-track first years only)
2. IBIO 611, IBIO 612, IBIO 613, Research Rotations (short research projects are taken under the guidance of three Yale professors) (Immunology-track first years only)
3. IBIO 601, Fundamentals of Research: Responsible Conduct of Research

Fourth-year students are required to take IBIO 503, a refresher training course in the responsible conduct of research.

Additional courses are determined based on the individual needs of the student, and include courses in biochemistry, cell biology, genetics, molecular biology of prokaryotes, molecular biology of eukaryotes, animal viruses, the structure of nucleic acids and proteins, microbiology, and disease mechanisms. Students choose courses after consulting the DGS and the thesis adviser.

Honors The graduate school uses grades of Honors, High Pass, Pass, or Fail. Students are required to earn a grade of Honors in at least two courses in the first two years, and are expected to maintain a High Pass average. There is no foreign language requirement.

Teaching Students are required to serve as a science TA (teaching assistant) for two terms before the end of their sixth term. Teaching protocol and rules are as follows:

1. Teaching two term-long science courses is required as a fulfillment of the Ph.D.
2. First-year students do not teach.
3. Teaching opportunities are first given to students who need teaching credit.
4. Teaching for additional income is available when openings exist after those selected for credit are hired; approval signatures from the adviser and DGS are required.
5. The maximum teaching allowed is one course per term.

A one-day seminar entitled "Teaching at Yale" is offered by the Yale Poorvu Center for Teaching and Learning at the start of each term. Attending this seminar is recommended prior to teaching.

Prospectus and Qualifying Exam In the second year, early in the fourth term, or in certain circumstances, in the third term, students make a thirty-minute presentation to the department of their proposed research and initial results. Thereafter, they meet with their prospectus committee, which assigns four or five broad areas of biology and immunology that are of particular relevance to the proposed research and on which the student will be examined in the qualifying exam. During the next several weeks, students prepare a formal research proposal (in NIH grant format) concerning the proposed thesis research and study for the exam. The exam is held within three months. It is an oral exam covering all aspects of immunology generally, with a focus on the assigned areas mentioned above. The student is questioned on aspects of the thesis proposal.

Admission to Candidacy Requirements for admission to candidacy, which usually takes place after six terms of residence, are: completion of course requirements, one of the two teaching requirements, the qualifying exam, and the third-year committee meeting—at the one year anniversary of the qualifying exam—with a signed

certification form from the adviser and committee members verifying that the student has made good progress.

Progress in thesis research in the third and later years is monitored carefully by the student's thesis committee (composed of the adviser and three or four other faculty). See below.

REQUIREMENTS FOR M.D.-PH.D. STUDENTS MAJORING IN IMMUNOBIOLOGY

Six courses for a grade. Out of the six courses the following are mandatory:

1. IBIO 530, Biology of the Immune System (Students have the option of passing out of IBIO 530 by taking the final exam from the previous year.)
2. IBIO 531, Advanced Immunology
3. Two Immunobiology seminar courses taken from this series: IBIO 532, IBIO 536, IBIO 537, IBIO 538, IBIO 539 (The second seminar course can be audited if a student has grades in six other courses and has already taken one seminar course for credit.)

Two grades of Honors: Yale University graduate courses taken for a grade at the School of Medicine may be counted toward the Honors fulfillment and the six total required courses. Verification must be provided to the DGS.

One term of teaching: Previously taught courses in the School of Medicine may count toward this requirement. To request credit for previous teaching experience, a note from the course director describing the teaching experience (duration of the teaching experience, frequency of class meetings, number of students taught, materials covered, dates, and for whom) should be provided to the Immunobiology DGS.

Responsible Conduct of Research, Refresher Course: Fourth-year students are required to take a refresher training course in the responsible conduct of research. M.D.-Ph.D. students can fulfill this NIH requirement through Immunobiology (IBIO 503) or through the M.D.-Ph.D. program.

Annual thesis committee meetings: Each student is required to have a thesis committee meeting at least every twelve months, and more frequently if the student or committee feels that it would be appropriate or helpful. The thesis supervisor (the student's PI) then submits a thesis committee report form to the DGS summarizing the student's progress.

M.D.-Ph.D. students are *not* required to take:

1. IBIO 600, Introduction to Research
2. IBIO 611, IBIO 612, IBIO 613, Research Rotations
3. IBIO 601, Fundamentals of Research: Responsible Conduct of Research. A note from the DGS of the M.D.-Ph.D. program must be forwarded to the Immunobiology DGS stating that the student has taken a course in Research Conduct and Ethics, or its equivalent in the School of Medicine. *Include dates, titles, and faculty*. If the student has not taken this course, then registration in this class is required.

MASTER'S DEGREES

M.Phil. A student is entitled to the M.Phil. degree once all academic and prospectus requirements, and one of the two teaching requirements, have been met. Also required is a third-year committee meeting at which the members sign an approval form stating that the student is making good progress toward the student's research.

M.S. Students who withdraw from the Ph.D. program may be eligible to receive the M.S. degree if they have met the requirements and have not already received the M.Phil. degree. For the M.S., students must successfully complete at least one year of resident graduate study at Yale with the quality of work judged satisfactory by the Department of Immunobiology faculty, as well as ten courses with an average grade of High Pass.

For additional information on the Program in Biological and Biomedical Sciences see http://bbs.yale.edu.

COURSES

For a complete listing of immunology-related courses, https://medicine.yale.edu/immuno/graduate-program/curriculum/

IBIO 530a / MBIO 530a / MCDB 530a, Biology of the Immune System Grace Chen, Ann Haberman, Carla Rothlin, Kevin O'Connor, Carrie Lucas, Ellen Foxman, Markus Müschen, Andrew Wang, Peter Cresswell, Jordan Pober, Joao Pereira, Craig Roy, Joseph Craft, Paula Kavathas, Noah Palm, Craig Wilen, Jeffrey Ishizuka, Daniel Jane-Wit, and David Schatz
The development of the immune system. Cellular and molecular mechanisms of immune recognition. Effector responses against pathogens. Immunologic memory and vaccines. Human diseases including allergy, autoimmunity, cancer, immunodeficiency, HIV/AIDS.

IBIO 600a, Introduction to Research: Faculty Research Presentations Carla Rothlin
Introduction to the research interests of the faculty. Required of all first-year Immunology/BBS students. Pass/Fail.

IBIO 601b / MBIO 601b, Fundamentals of Research: Responsible Conduct of Research Staff
A weekly seminar presented by faculty trainers on topics relating to proper conduct of research. Required of first-year Immunobiology students, first-year CB&B students, and training grant-funded postdocs. Pass/Fail.

IBIO 611a, Research Rotation 1 Carla Rothlin
Intensive experience in the design and execution of experiments in immunology or other areas of biology. Students design a focused research project in consultation with a faculty mentor and execute the designed experiments in the mentor's laboratory. Students are expected to read relevant background papers from the literature, design and perform experiments, interpret the resulting data, and propose follow-up experiments. Students are also expected to attend the mentor's weekly lab meeting(s) as well as weekly Immunobiology departmental seminars and Research in Progress seminars. The course concludes with the student giving a brief presentation of the work performed at Rotation Talks, attended by other first-year immunology-track graduate students. Evaluation is by the mentor; students also evaluate the rotation experience.

Students must turn in a prioritized list of four possible mentors to the office of the DGS at least one week prior to the beginning of the course. Mentors are assigned by the DGS. Graded Satisfactory/Unsatisfactory. Minimum of 20 hours/week. Required of all first-year Immunology/BBS students.

IBIO 612a, Research Rotation 2 Carla Rothlin
Intensive experience in the design and execution of experiments in immunology or other areas of biology. Students design a focused research project in consultation with a faculty mentor and execute the designed experiments in the mentor's laboratory. Students are expected to read relevant background papers from the literature, design and perform experiments, interpret the resulting data, and propose follow-up experiments. Students are also expected to attend the mentor's weekly lab meeting(s) as well as weekly Immunobiology departmental seminars and Research in Progress seminars. The course concludes with the student giving a brief presentation of the work performed at Rotation Talks, attended by other first-year immunology-track graduate students. Evaluation is by the mentor; students also evaluate the rotation experience. Students must turn in a prioritized list of four possible mentors to Barbara Cotton in the office of the director of graduate studies at least one week prior to the beginning of the course. Mentors are assigned by the DGS. Graded Pass/Fail. 1 course credit; minimum of 20 hours/week. Required of all first-year Immunology/BBS students.