MASTER OF SCIENCE BIOCHEMISTRY AND SPECIALIZATION HUMAN AND MOLECULAR GENETICS

Summary
• Degrees offered: Master of Science (MSc)
• Registration status option: Full-time
• Language of instruction: English
• Primary program: MSc in Biochemistry
• Collaborative specialization: Human and Molecular Genetics
• Program option (expected duration of the program):
  • with thesis (6 full-time terms; 24 consecutive months)
• Academic units: Faculty of Medicine (http://med.uottawa.ca/graduate-postdoctoral/), Department of Biochemistry, Microbiology and Immunology (http://med.uottawa.ca/bmi/).

Program Description
The programs prepare candidates for a variety of careers in teaching and research both within and outside of academia.

Graduate students are actively involved in laboratory research, coursework, and presentation of research seminars. Thus, they acquire autonomy in conducting research and in preparing publications.

The programs create a stimulating and challenging environment which will allow students to achieve excellence in research. Graduates of the programs must demonstrate research skills and credential as professionals in their area of research.

The Department is a participating unit in the Human and Molecular Genetics collaborative program.

Collaborative Program Description
The Faculty of Medicine offers a collaborative program in Human and Molecular Genetics at the master’s and doctoral levels. The primary graduate programs in Biochemistry (BCH), Cellular and Molecular Medicine (CMM) and Neuroscience (NSC) collaborate in offering the specialization. The degree awarded specifies the primary program and indicates “specialization in Human and Molecular Genetics.”

Members of the program include scientists with interest and expertise in the following areas: developmental genetics, neuromuscular disease, microbial genetics, host resistance, cancer biology, aging, development of novel molecular therapeutics, gene therapy, growth and development, autoimmune diseases, molecular biology of viruses, bacteria and parasites, genetic epidemiology, retinal development and disease, animal models of human disease, molecular aspects of signal transduction.

Main Areas of Research
• General biochemistry
• Molecular biology
• Nutrition and metabolism

Other Programs Offered Within the Same Discipline or in a Related Area
• Master of Science Biochemistry (MSc)
• Master of Science Biochemistry Specialization in Bioinformatics (MSc)
• Master of Science Biochemistry Specialization in Pathology and Experimental Medicine (MSc)
• Doctorate in Philosophy Biochemistry (PhD)
• Doctorate in Philosophy Biochemistry Specialization in Human and Molecular Genetics (PhD)
• Doctorate in Philosophy Biochemistry Specialization in Pathology and Experimental Medicine (PhD)
• Master of Science Cellular and Molecular Medicine Specialization in Human and Molecular Genetics (MSc)
• Master of Science Neuroscience Specialization in Human and Molecular Genetics (MSc)
• Doctorate in Philosophy Cellular and Molecular Medicine Specialization in Human and Molecular Genetics (PhD)
• Doctorate in Philosophy Neuroscience Specialization in Human and Molecular Genetics (PhD)

Fees and Funding
• Program fees:

  The estimated amount for university fees (https://www.uottawa.ca/university-fees/) associated with this program are available under the section Finance your studies (http://www.uottawa.ca/graduate-studies/programs-admission/finance-studies/).

  International students enrolled in a French-language program of study may be eligible for a differential tuition fee exemption (https://www.uottawa.ca/university-fees/differential-tuition-fee-exemption/).

  • To learn about possibilities for financing your graduate studies, consult the Awards and financial support (https://www.uottawa.ca/graduate-studies/students/awards/) section.

Notes
• Programs are governed by the general regulations (http://www.uottawa.ca/graduate-studies/students/general-regulations/) in effect for graduate studies.
• In accordance with the University of Ottawa regulation, students have the right to complete their assignments, examinations, research papers, and theses in French or in English.
**Program Contact Information**
Graduate Studies Office, Faculty of Medicine (https://med.uottawa.ca/graduate-postdoctoral/)
451 Smyth Road, Room RGN 2016
Ottawa, Ontario, Canada
K1N 6N5

Tel.: 613-562-5215
Email: grad.med@uottawa.ca

Twitter | Faculty of Medicine (https://twitter.com/uOttawaMed/)
Youtube | Faculty of Medicine (https://www.youtube.com/channel/UCP2nDlrjFEEtyfMi0mle2HA/)
Flickr | Faculty of Medicine (https://www.flickr.com/photos/uottawamed/)

**Admission Requirements**
For the most accurate and up to date information on application deadlines, language tests and other admission requirements, please visit the specific requirements (https://www.uottawa.ca/graduate-studies/programs-admission/apply/specific-requirements/) webpage.

To be eligible, candidates must:
- Have one of the following:
  - A bachelor’s degree with a specialization or a major (or equivalent) in science with a minimum average of 75% (B+).
  - An MD (Doctor of Medicine) degree with a minimum average of 75% (B+).
  - A DVM (Doctor of Veterinary Medicine) degree with a minimum average of 75% (B+).
- Identify at least one professor who is willing to supervise your research and thesis.
- We recommend that you contact potential thesis supervisors as soon as possible.
- To register, you need to have been accepted by a thesis supervisor.
- The supervisor’s name is required at the time of application.
- The thesis director must be a member of the collaborative program.
- Demonstrate a good academic performance in previous studies as shown by official transcripts, research reports, abstracts or any other documents demonstrating research skills.
- Note: International candidates must check the admission equivalencies (https://www.uottawa.ca/graduate-studies/international/study-uottawa/admission-equivalencies/) for the diploma they received in their country of origin.
- Accounts and capabilities can be conducted either in English, French or both, depending on the language used by the professor and the members of his or her research group.

**Language Requirements**
Applicants must be able to understand and fluently speak the language of instruction in the program to which they are applying. Proof of linguistic proficiency may be required.

Applicants whose first language is neither French nor English must provide proof of proficiency in the language of instruction.

Note: Candidates are responsible for any fees associated with the language tests.

**Notes**
- The admission requirements listed above are minimum requirements and do not guarantee admission to the program.
- Admissions are governed by the general regulations (http://www.uottawa.ca/graduate-studies/students/general-regulations/) in effect for graduate studies.
- Students must indicate in their initial application for admission to the master's program in Biochemistry that they wish to be accepted into the collaborative program in Human and Molecular Genetics. Students must be admitted in one of the primary programs participating in the collaborative program. Students will normally be informed about their acceptance into the collaborative program at the same time as being informed about their admission into the primary program.
- Research activities can be conducted either in English, French or both, depending on the language used by the professor and the members of his or her research group.

**Program Requirements**

**Master’s with Collaborative Specialization**
The Department may require students to take additional courses, depending on their backgrounds. Students wishing to take a course in a related discipline must obtain prior approval from the Department.

Students must meet the following requirements for the master's with collaborative specialization:

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<tr>
<th>Compulsory Courses (BCH):</th>
<th>SEMINAR:</th>
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<tbody>
<tr>
<td>MED 8166</td>
<td>BCH 5366</td>
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<tr>
<td>Professionalism and Professional Skills</td>
<td>MSc Seminar</td>
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<tr>
<td>3 optional course units from the list of approved biochemistry (BCH) courses at the 8000 or 9000 level</td>
<td>3 Units</td>
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<td>3 Units</td>
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<tr>
<td>3 course units from:</td>
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<tr>
<td>HMG 8103 Advanced Topics in the Molecular Biology of Human Diseases I</td>
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3 Units
HMG 8105 Advanced Topics in the Molecular Biology of Human Diseases II

HMG 8600 Special Topics in Human and Molecular Genetics

Thesis:
THM 7999 Master’s Thesis 3,4

Note(s)
1. This requirement involves the presentation of a seminar and regular attendance at the departmental seminars until permission to write the thesis is granted.
2. Course selection is subject to the approval of the HMG program director.
3. Successful presentation and defence of a thesis on a topic in human and molecular genetics based on original research carried out under the direct supervision of a member of the collaborative program.
4. Students are responsible for ensuring they have met all of the thesis requirements (http://www.uottawa.ca/graduate-studies/students/theses/).

Minimum Requirements
The passing grade in all courses is C+.

Students who fail 6 units must withdraw from the program.

Fast-Track from Master’s to PhD
Students enrolled in the master’s program in Biochemistry at the University of Ottawa may be eligible to fast-track directly into the doctoral program without writing a master’s thesis. For additional information, please consult the “Admission Requirements” section of the PhD program.

Research
Research Fields & Facilities
Located in the heart of Canada’s capital, a few steps away from Parliament Hill, the University of Ottawa is among Canada’s top 10 research universities.

uOttawa focuses research strengths and efforts in four Strategic Areas of Development in Research (SADRs):

- Canada and the World
- Health
- e-Society
- Molecular and Environmental Sciences

With cutting-edge research, our graduate students, researchers and educators strongly influence national and international priorities.

Research at the Faculty of Medicine
“The Faculty of Medicine has a long history of conducting both basic and clinical research of the highest quality. Many of our high profile research projects are conducted in partnership with affiliated-teaching hospitals and research institutes. These partnerships lead to biomedical discoveries that have a significant impact on healthcare. In the process they educate the next generation of Canadian scientists. Our research activity also attracts significant investment, which stimulates the Ottawa economy.”

- Dr. Bernard Jasmin, Vice-Dean, Research

Facilities, Research Centres and Institutes at the Faculty of Medicine

- Centre for Neural Dynamics (https://neurodynamic.uottawa.ca/)
- University of Ottawa Centre for Neuromuscular Disease (http://med.uottawa.ca/neuromuscular/)
- Centre for Research in Biopharmaceuticals and Biotechnology (http://www.med.uottawa.ca/crbb/eng/),
- Canadian Partnership for Stroke Recovery (https://canadianstroke.ca/),
- Kidney Research Centre (http://www.ohri.ca/centres/KRC/default.asp),
- University of Ottawa Skills and Simulation Centre (http://uossc.ca/),
- Medical Devices Innovation Institute,
- Ottawa Institute of Systems Biology (http://med.uottawa.ca/oisb/)
- University of Ottawa Brain and Mind Research Institute (http://www.uottawa.ca/brain/).

For more information, refer to the list of faculty members and their research fields on Uniweb.

IMPORTANT: Candidates and students looking for professors to supervise their thesis or research project can also consult the website of the faculty or department (https://www.uottawa.ca/graduate-studies/students/academic-unit-contact-information/) of their program of choice. Uniweb does not list all professors authorized to supervise research projects at the University of Ottawa.

Courses
BCH 5101 Analysis of -Omics Data (3 units)
Theoretical and practical aspects of various methods currently used to analyze the plethora mountain of omics data. Methods: sequence alignment and database searches; sequence analysis and bioinformatics of gene regulation; DNA microarray and sequencing technologies to identify transcription factor binding sites; analysis of proteomics data; statistical analysis of preprocessed gene expression and protein/metabolite abundance data; epidemiology applications. Critical reading of the literature and strategies for making informed choices of methods for the analysis of students’ own data.
Course Component: Lecture

BCH 5102 Principles of Biomanufacturing (3 units)
This course will cover the fundamental biological principles impacting the development and efficacy of biotherapeutics. The course will also include topics such as the steps related to biomanufacturing processes, analytical development, quality control and assurance.
Course Component: Lecture

BCH 5103 Seminar in Biomanufacturing and Commercialization (3 units)
Seminars on topics of current interest in biomanufacturing and related subjects. Seminars will consist of visiting lectures from entrepreneurs and speakers from industry, regulatory agencies and patient advocate organizations with real-life experience, who will share their stories on the path to production, clinical implementation and commercialization of biological therapeutics.
Course Component: Seminar

BCH 5366 MSc Seminar (3 units)
Attendance and participation in the annual BMI Student Symposium and BMI Poster Day, attendance at BMI seminars relevant to Biochemistry. Students must present at least one poster and one oral presentation during the course of their program. Graded S (Satisfactory) / NS (Not Satisfactory).
Course Component: Seminar

BCH 5501 Analyse des données omiques (3 crédits)
Les aspects théoriques et pratiques des méthodes actuellement utilisées pour l'analyse des données omiques. Méthodes: alignement des séquences et recherche dans les bases de données; analyse des séquences et bioinformatique de l'expression génique; micro puces d'ADN et technologies de séquençage utilisées pour l'identification des sites de liaison des facteurs de transcription; l'analyse des données protéomiques; l'analyse statistique de l'expression génique prétraitée; et applications aux données protéine/abondance de métabolites, épidémiologie. Lecture critique de la littérature et stratégies pour faire des choix informés quant à la sélection des méthodes pour l'analyse des données.
Volet : Cours magistral

BCH 8101 Physical and Chemical Methods in Biochemistry (3 units)
Current applications of physical and chemical methods to the study of macromolecule structure-function relationships.
Course Component: Lecture

BCH 8102 Selected Topics in Protein Structure and Function (3 units)
An advanced study of recent literature dealing with structure-function relationships in selected proteins.
Course Component: Lecture

BCH 8103 Advanced Topics in Gene Expression and Protein Synthesis (3 units)
An advanced study of the recent literature dealing with the chemistry, metabolism and function of nucleic acids, the biosynthesis of proteins, biochemical and genetic control mechanisms, genetic engineering and the control of gene expression. Offered every second year in alternation with BCH 8105.
Course Component: Lecture

BCH 8104 Advanced Topics in Cell Regulation (3 units)
An advanced study of recent literature dealing with signal transduction processes and the regulation of metabolism, cell proliferation and differentiation.
Course Component: Lecture
Offered in alternate years.

BCH 8105 Advanced Topics in Molecular Biology of Human Diseases (3 units)
Topics will be selected and representative of current developments in the field. The course consists of a repeated series of a 3 hour lecture by an expert in the field one week, followed by student presentations, discussions and critique of assigned papers on that topic the following week. Topics on selected diseases will focus on various aspects of cancer, apoptosis, disease gene identification and gene therapy. In the past these topics have included the molecular aspects of various cancers, spinal muscular atrophy, tissue regeneration, the discovery of disease genes, infectious disease (HIV) and gene therapy. Students will write a grant proposal and participate in mock grant review panels. Depending on enrolment, the course may be limited to HMG students only.
Course Component: Lecture

BCH 8106 Mitochondrial Medicine: Theory and Approaches (3 units)
An advanced study of the recent literature dealing with metabolism, nutrition and metabolic control theory, with emphasis on both whole body and cell metabolism in metabolic and nutritional disorders such as obesity and non-insulin-dependent diabetes mellitus (NIDDM).
Course Component: Lecture

BCH 8107 Advanced Topics in Lipid Metabolism and Disease (3 units)
An advanced study of the recent literature dealing with the role of lipids in both normal physiology and pathophysiology, with a focus on the mechanisms underlying the regulation of both lipid signaling and lipid metabolism in disease processes.
Course Component: Lecture

BCH 8108 Advanced Methods of Macro-Molecular Structure Determination (3 units)
A detailed examination of modern methods used to determine the structures of proteins, nucleic acids, and carbohydrates. May include X-ray crystallography, electron diffraction, nuclear magnetic resonance, and other spectroscopic methods.
Course Component: Lecture

BCH 8109 Advanced Topics in Cell Death (3 units)
Molecular mechanisms of cell death. Particular attention to be paid to role of aberrant cell death in human disease. Offered in the Fall of odd numbered years.
Course Component: Lecture

BCH 8110 Advanced Topics in Systems Biology (3 units)
Recent advances in genomics, proteomics, bioinformatics, and neuroinformatics including functional and chemical genomics, RNA analyses, microarrays, mass spectrometry, and neural imaging. Course requirements include student presentations and writing a mock research proposal based on Canadian Institutes of Health Research (CIHR) guidelines. Limited enrollment. Offered in alternate years with BCH 8101 Physical and Chemical Methods in Biochemistry.
Course Component: Lecture
Permission of the Department is required.

BCH 8111 Chromosome and Chromatin Biology (3 units)
Higher order chromosome structure and chromatin remodeling and their impact on regulation of gene expression, DNA replication, repair and recombination, and chromosome segregation. Histone modifications and nucleosome positioning and their influence on higher order chromosome structure. Importance of chromosome and chromatin in the context of the cell cycle, development, and disease. Critical reading of the literature on chromosome and chromatin biology.
Course Component: Seminar

BCH 8114 Advanced Topics in the Cell Cycle (3 units)
Mechanisms of cell cycle regulation. Model systems critical to deciphering the cell cycle in eukaryotes: budding and fission yeast, Xenopus laevis egg extracts, Aspergillus nidulans, Drosophila melanogaster, sea urchin and mouse oocytes and cultured vertebrate cells. Overview of the prokaryotic cell cycle.
Course Component: Lecture

BCH 8116 Model Organisms and Systems Biology (3 units)
Utilization of model organisms in the development and advancement of the systems biology field. Particular attention will be paid to the use of organisms such as Saccharomyces cerevisiae as a model platform for cell cycle progression/cancer. Other models may also be included. The basics of the technology will be discussed along with the application of technology to complex biological questions, in particular relating to the cell cycle. Course offered in alternate years.
Course Component: Lecture

BCH 8117 Advanced Topics Relating to the Cell Cytoskeleton and Membranes (3 units)
Advanced study of recent literature dealing with the mammalian cellular cytoskeleton and membrane with an emphasis on the regulation of cell motility, adhesion and cell division.
Course Component: Lecture

BCH 8120 ADVANCED TOPICS IN IMMUNOMETABOLISM (3 units)
An advanced study of the recent literature dealing with the field of immunometabolism, with a focus on both immunometabolic pathways and the specialized techniques that allow for understanding chronic inflammatory/metabolic diseases, such as cancer, type 2 diabetes, obesity, atherosclerosis, neurodegeneration, etc.
Course Component: Lecture

BCH 8134 Structure and Expression of Eukaryotic and Prokaryotic Genomes (3 units)
Sequencing of eukaryote and prokaryote genomes with emphasis on recent technologies, sequence alignments and databases and assembly of genomes from massively parallel sequencing data. Focus on mapping studies, including linkage disequilibrium-based genome-wide association study (GWAS), to characterize functional variants associated with complex traits. Analysis and structure of microbial metagenomes from environmental and human habitats, including structure-function analysis of microbial communities, microbiota-human disease correlations, and molecular phylogeny. Genome expression, including measures of RNA transcripts and proteins and statistical analysis of data. Combination of various -omics data to understand gene-environment interactions.
Course Component: Lecture

BCH 8165 Special Topics in Biochemistry (3 units)
A survey of recent advances in selected areas of biochemistry.
Course Component: Lecture

BCH 8166 Special Topics in Biochemistry II (3 units)
A survey of recent advances in selected areas of biochemistry.
Course Component: Lecture

BCH 8213S Seminars (2 crédits / 2 units)
Compulsory for second-year graduate students.
Volet / Course Component: Cours magistral / Lecture

BCH 8214S Seminars (2 crédits / 2 units)
Compulsory for third-year graduate students.
Volet / Course Component: Cours magistral / Lecture

BCH 8310 Current Topics in RNA Molecular Biology (3 units)
Properties, mechanisms associated with regulation and the functions of RNAs and Ribonucleoprotein (RNPs) as well as RNA organisms. Current knowledge on RNA expression (synthesis, processing, transport and localization), the structure-function relationship and molecular mechanisms associated with RNAs and RNA genomes, RNA in evolution and in the origin of life, and RNA as therapeutic agents.
Course Component: Lecture
Courses CMM 8310, BCH 8310 cannot be combined for units.

BCH 8366 PhD Seminar (3 units)
Attendance and participation in the annual BMI Student Symposium and BMI Poster Day, attendance at BMI seminars relevant to Biochemistry. Students will present a poster in their first and every alternate year, and an oral presentation the second and every alternate year until they have permission to write their thesis. Graded S (Satisfactory) / NS (Not satisfactory).
Course Component: Seminar

BCH 8511 Biologie des chromosomes et de la chromatine (3 crédits)
Organisation de la structure des chromosomes et le remodelage de la chromatine ainsi que l’impact de ceux-ci sur la régulation de l’expression génique, la réplication, la réparation et la recombinaison de l’ADN ainsi que sur la ségrégation des chromosomes. Les modifications histoépigeniques et le positionnement des nucléosomes ainsi que leur influence sur la structure organisée des chromosomes. Importance des chromosomes et de la chromatine dans le contexte du cycle cellulaire, du développement et des maladies. Lecture critique de la littérature portant sur la biologie des chromosomes et de la chromatine.
Volet : Cours magistral

BCH 8534 Structure et expression des génomes procaryotes et eucaryotes (3 crédits)
Le séquençage des génomes eucaryotes et procaryotes, avec un accent particulier sur les technologies récentes, l’alignement des séquences et les bases de données, et l’assemblage des génomes à partir de données générées par séquençage haut débit. Les études de cartographie comparée incluant les études d’associations pangénomiques basées sur le déséquilibre de liaison pour caractériser les variantes fonctionnelles associées aux traits complexes. L’analyse et la structure de métagénomiques microbiens issus d’habitats humains et environnementaux incluant l’analyse structure-fonction des communautés microbiennes, les corrélations entre les maladies humaines et le microbiome ainsi que la phylogénie moléculaire. L’expression génique incluant les mesures de transcriptomes et de protéomes ainsi que l’analyse statistique des données. La combinaison des différentes données omiques pour comprendre les interactions génée-environnement.
Volet : Cours magistral

BCH 9998 Examen de synthèse (doctorat) / Comprehensive-Examination (PhD)
À l’intention des étudiants inscrits au programme de Ph.D. L’inscription à ce cours est limitée à trois sessions consécutives. / For students enrolled in the doctoral program. Enrolment in this course is limited to three consecutive academic sessions.
Volet / Course Component: Recherche / Research

HMG 8103 Advanced Topics in the Molecular Biology of Human Diseases I (3 units)
Topics will be selected and representative of current developments in the field. The course consists of a repeated series of a 3 hour lecture by an expert in the field one week, followed by student presentations, discussions and critique of assigned papers on that topic the following week. Topics on selected diseases will focus on various aspects of cancer, apoptosis, disease gene identification and gene therapy. In the past these topics have included the molecular aspects of various cancers, spinal muscular atrophy, tissue regeneration, the discovery of disease genes, infectious disease (HIV) and gene therapy. Students will write a grant proposal and participate in mock grant review panels. Depending on enrolment, the course may be limited to HMG students only.
Course Component: Lecture
Prerequisite: Permission of the HMG program director.
HMG 8105 Advanced Topics in the Molecular Biology of Human Diseases II (3 units)
Topics will be selected and representative of current developments in the field. The course consists of a repeated series of a 3 hour lecture by an expert in the field one week, followed by student presentations, discussions and critique of assigned papers on that topic the following week. Topics on selected diseases will focus on various aspects of cancer, apoptosis, disease gene identification and gene therapy. In the past these topics have included the molecular aspects of various cancers, spinal muscular atrophy, tissue regeneration, the discovery of disease genes, infectious disease (HIV) and gene therapy. Students will write a grant proposal and participate in mock grant review panels. Depending on enrolment, the course may be limited to HMG students only.
Course Component: Lecture
Prerequisite: Permission of the HMG program director.

HMG 8106 Clinical Cytogenomics (3 units)
Comprehensive review of the basic principles and technologies in cytogenomics and their clinical application for diagnostic and prognostic purposes. Registrations may be limited depending on enrolment.
Course Component: Lecture
Prerequisite: Permission of the course coordinator.

HMG 8107 Clinical Biochemical Genetics (3 units)
Presentation of the biomechanical and molecular bases of inborn errors of metabolism. The course consists of a series of lectures followed by student discussion of a related paper assigned the previous week. Registrations may be limited depending on enrolment.
Course Component: Lecture
Prerequisite: Permission of the course coordinator.

HMG 8108 Clinical Molecular Genetics (3 units)
Comprehensive review of all aspects of clinical molecular genetics acquainting students with clinical applications of various molecular technologies. Registrations may be limited depending on enrolment.
Course Component: Lecture
Prerequisite: Permission of the course coordinator.

HMG 8506 Cytogénomique clinique (3 crédits)
Revue exhaustive des principes de base et des techniques en cytogénomique et de leur application clinique à des fins diagnostiques et pronostiques. Les inscriptions peuvent être limitées selon la participation.
Volet : Cours magistral

HMG 8507 Génétique biochimique clinique (3 crédits)
Présentation des bases biochimiques et moléculaires des maladies innées du métabolisme. Les inscriptions peuvent être limitées selon la participation.
Volet : Cours magistral

HMG 8508 Génétique moléculaire clinique (3 crédits)
Revue exhaustive de tous les aspects de la génétique moléculaire clinique donnant aux étudiants des exemples des applications cliniques des différentes techniques en génétique moléculaire. Les inscriptions peuvent être limitées selon la participation.
Volet : Cours magistral

HMG 8600 Special Topics in Human and Molecular Genetics (3 crédits)
Current topics in molecular genetics, developmental genetics, cancer genetics, neurogenetics, population genetics, clinical genetics and other areas depending on available expertise and interest expressed. Offered alternate years subject to sufficient demand.
Volet : Cours magistral
Permission of the Department is required.