DOCTORATE IN PHILOSOPHY
CELLULAR AND MOLECULAR
MEDICINE SPECIALIZATION
IN HUMAN AND MOLECULAR
GENETICS

Summary

• Degree offered: Doctorate in Philosophy (PhD)
• Registration status option: Full-time
• Language of instruction:
  • French
  • English

  Note: Most of the courses in this program are offered in English.

• Primary program: PhD in Cellular and Molecular Medicine
• Collaborative specialization: Human and Molecular Genetics
• Program option (expected duration of the program):
  • with thesis (16 full-time terms; 64 consecutive months)
• Academic units: Faculty of Medicine (http://med.uottawa.ca/cellular-molecular/), Department of Cellular and Molecular Medicine (http://med.uottawa.ca/cellular-molecular/).

Program Description
The programs prepare candidates for a variety of careers in teaching and research both within and outside of academia. During training, the student will develop a critical approach to published work and to his own work. Graduates acquire an excellent knowledge of their chosen field and a general understanding of the areas related to their own particular research project. They must demonstrate research skills and credibility as professionals in their area of research.

The Department is a participating unit in the collaborative programs in Bioinformatics (at the master’s level), in Human and Molecular Genetics (at the master’s and doctoral levels), and in Pathology and Experimental Medicine (at the master’s and doctoral levels).

The doctoral program participates in the Combined MD / PhD Program, which allows students to graduate with both a PhD in Cellular and Molecular Medicine and an MD. For more information please see the website of the Faculty of Medicine (http://www.med.uottawa.ca/md-phd/eng/).

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, auto-immune 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
Most research groups in the Department are part of a research centre. These centres include the Centre for Neuromuscular Disease, the Kidney Research Centre, and the Centre for Research in Biopharmaceuticals. Members of the Department are involved in three main research fields:

• Growth and development
• Pharmacology
• Physiology

Other Programs Offered Within the Same Discipline or in a Related Area

• Master of Science Cellular and Molecular Medicine Specialization in Bioinformatics (MSc)
• Master of Science Cellular and Molecular Medicine Specialization in Human and Molecular Genetics (MSc)
• Master of Science Cellular and Molecular Medicine Specialization in Pathology and Experimental Medicine (MSc)
• Doctorate in Philosophy Cellular and Molecular Medicine (PhD)
• Doctorate in Philosophy Cellular and Molecular Medicine Specialization in Pathology and Experimental Medicine (PhD)
• Doctorate in Philosophy Neuroscience (PhD)
• Doctorate in Philosophy Neuroscience Specialization in Pathology and Experimental Medicine (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. 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 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 a master's degree in science (with a background in biology, biochemistry, human kinetics, pharmacology, physiology or biopharmaceutical sciences) with a minimum average of B+ (75%).

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.

• Demonstrate a good academic performance in previous studies as shown by official transcripts, research reports, abstracts or any other documents demonstrating research skills.

• 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 thesis director must be a member of the collaborative program.

Language Requirements
Applicants must be able to understand and fluently speak the language of instruction (French or English) in the program to which they are applying. Proof of linguistic proficiency may be required. Most of the courses in these programs are offered in English.

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.
• Candidates must apply to the primary program and indicate in their application for admission to the PhD program in Cellular and Molecular Medicine that they wish to be accepted into the collaborative-specialization in Human and Molecular Genetics. Students are normally informed about their acceptance into the collaborative program at the same time as being informed about their admission into the primary program. To be admitted to the collaborative program, candidates must also be accepted in the primary program.

Fast-Track from Master’s to PhD
Students enrolled in the master’s program in Cellular and Molecular Medicine at the University of Ottawa may be eligible to fast-track directly into the doctoral program without writing a master’s thesis, provided the following conditions are met:

• Successful completion of the seminar and all the core courses required for the master’s program.
• Satisfactory progress in the research program.
• Written recommendation by the supervisor and the advisory committee.
• Approval by the graduate studies committee.

Notes:
• The transfer must take place within sixteen months of initial enrollment in the master’s.
• The minimal admission average requirements for the doctoral program must also be met.
• Following transfer, all the requirements of the HMG doctoral program must be met: six units of courses including three HMG units, the
seminar in the primary program, comprehensive exam, presentation of one research seminar, and the thesis.

Program Requirements
Doctorate with Collaborative Specialization

The Department may require students to take additional courses, depending on their backgrounds.

Students must meet the following requirements for the doctorate with collaborative specialization:

Compulsory Courses (CMM):
MED 8166  Professionalism and Professional Skills
3 optional course units in cellular and molecular medicine (CMM) at the graduate level 3 Units

Compulsory Course (HMG):
3 course units from:
HMG 8103 Advanced Topics in the Molecular Biology of Human Diseases I 1
HMG 8105 Advanced Topics in the Molecular Biology of Human Diseases II
HMG 8600 Special Topics in Human and Molecular Genetics

Seminar:
CMM 8325S  Seminars II 2 3 Units

Comprehensive Examination:
CMM 9998  Comprehensive Examination (PhD) 3

Thesis:
THD 9999  Doctoral Thesis 4, 5

Note(s)

1. Course selection is subject to the approval of the HMG program director.
2. The seminar course involves the presentation of a seminar and regular attendance at the approved departmental seminars.
3. Successful completion of a comprehensive examination in the form of a written research proposal followed by an oral examination.
4. Presentation and successful defence of a thesis in Human and Molecular Genetics based on original research carried out under the direct supervision of a member of the collaborative program.
5. 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 two courses (equivalent to 6 units), the thesis proposal, or the comprehensive exam or whose research progress is deemed unsatisfactory are required to withdraw.

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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 health care. 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 (http://www.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 (http://www.canadianstroke.ca/en/)
- 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

CMM 5001 The Pathological Basis of Disease (3 crédits / 3 units)
Introductory course for non-medical graduate students in Life Sciences. This course will consist of a brief introduction to pathology describing the manifestation of disease at the macroscopic and microscopic level. This will be followed by (i) a description of various types of microscopy and methodology; (ii) concepts in flow cytometry, tissue/cell fractionation; (iii) histo-/cytochemistry and immunohisto-/cytochemistry; (iv) normal cells and tissues; (v) organs; (vi) the general pathology of cells and tissues including hypertrophy, aplasia, atrophy, hyperplasia, metaplasia, dysplasia, neoplasia, storage diseases, extracellular space pathologies, necrosis and apoptosis. Blood vessel and cardiac pathologies will be covered as well as concepts in neuropathology, organ/system specific pathologies and genetic diseases.
Volet / Course Component: Cours magistral / Lecture

CMM 5105 Introduction to Cancer Biology (3 units)
An introduction to the biology of cancer. Major topics in cancer biology include the following: tumor suppression/oncogenes; apoptosis in cancer; cell immortalization and senescence; genomic instability; multistep tumorigenesis/inflammation in cancer; biology of angiogenesis; rational therapies.
Course Component: Lecture

CMM 5111 Computational Cell Biology (3 units)
Emphasis is on providing students with the background knowledge and the tools needed to develop and analyze models of cellular processes. Topics include modeling enzyme kinetics, signal transduction pathways, and gene regulatory networks, using differential equations, nonlinear dynamics, and stochastic processes.
Course Component: Lecture

CMM 5210 Mammalian Physiology (6 units)
Course Component: Lecture
Permission of the Department is required.

CMM 5301 Directed Studies (3 units)
A program of study designed for a given student according to the student's educational requirements.
Course Component: Seminar

CMM 5302 Comprehensive Pharmacology I (3 units)
Extensive coverage of pharmacodynamics, pharmacokinetics, and the pharmacology of the autonomic and central nervous system. Courses CMM 5301, CMM 5302 cannot be combined for units.
Course Component: Lecture

CMM 5303 Comprehensive Pharmacology II (3 units)
Extensive coverage of the pharmacology of antibiotic and anti-inflammatory drugs, of chemotherapeutic agents, and of the cardiovascular and gastro-intestinal systems. Courses CMM 5301, CMM 5303 cannot be combined for units.
Course Component: Lecture

CMM 5304 Introduction to Developmental Biology (3 units)
Concepts in development and signalling pathways during development including formation of the germ layers; establishment of the body axis and principles of segmentation; patterning and homeobox genes; neurogenesis; axonal and neuronal guidance; stem cell concepts; germ cells; animal models in developmental biology.
Course Component: Lecture

CMM 5305 Neurogenesis and Axonal and Neuronal Guidance (3 units)
Topics will include the major cell signaling pathways and the action of steroid and non-steroid hormones. These signaling pathways will be discussed in the context of biological function and pharmacology.
Course Component: Lecture

CMM 5311 Physiology and Pathophysiology of Energy Metabolism and Muscle Functions (3 units)
Advanced comprehensive training in mammalian and human physiology with emphasis on pathophysiology. Topics include: neural and endocrine control of the hypothalamus-hypophysis axis; role of pancreas, adipose tissue and skeletal muscle in carbohydrate and lipid metabolism; cellular and molecular aspects of muscle contraction and fatigue in cardiac and skeletal muscle.
Course Component: Lecture

CMM 5313 Physiology and Pathophysiology of the Reproductive, Renal and Gastrointestinal Systems (3 units)
Advanced comprehensive training in mammalian and human physiology with emphasis on pathophysiology. Topics covered include reproductive physiology, molecular and bulk transport processes in the renal system, enteric control of the gastrointestinal tract.
Course Component: Lecture

CMM 5315 Cellular and Molecular Basis of Cardiovascular Function/Dysfunction (3 units)
Mechanism of failing heart and cardiovascular system, its associated functions and associated conditions. Therapies for restoring function. Topics include: regulation of heart development, cell signaling, cellular and molecular mechanisms of atherosclerosis and heart disease , hormonal regulation, hypertension, bioenergetics, cardiovascular genomics and genetics, cell therapy, and regenerative medicine.
Course Component: Lecture

CMM 5316 Introductory Cell Biology (3 units)
Volet / Course Component: Lecture
Introductory course for non-medical graduate students in Life Sciences.

CMM 5317 Biostatistics (3 units)
Course Component: Lecture
An introduction to biostatistics for students in Life Sciences.

CMM 5326 Experimental Preparations and Animal Models (3 units)
Applied and theoretical course intended to give the potential researcher basic surgical skills. Lectures followed by demonstrations and/or practical exercises.
Course Component: Lecture

CMM 5341 Stem Cells (3 units)
Topics in stem cell biology which will include an in-depth look at the properties of embryonic and adult stem cell populations, tissue-specific stem cells (muscle, skin, neural, etc.), differentiation and reprogramming, the stem cell niche, induced pluripotent stem cells, and therapeutic advances using stem cell therapy.
Course Component: Lecture

CMM 5360 Imaging in Cell Biology (3 units)
Microscopy, biological imaging, and image generation. Overviews of common transmitted light, electron microscopic and epifluorescent techniques. Discussion of enhanced fluorescence microscopy and live cell imaging techniques, including image acquisition, processing and analysis with focus on quantitative and ethical issues.
Course Component: Lecture

CMM 5372 Cell Signalling and Hormone Action (3 units)
Topics will include the major cell signaling pathways and the action of steroid and non-steroid hormones. These signaling pathways will be discussed in the context of biological function and pharmacology.
Course Component: Lecture

CMM 7301 Directed Studies (3 units)
A program of study designed for a given student according to the student's educational requirements.
Course Component: Seminar
CMM 8103 Epithelial Cell Polarity (3 units)
Cell polarity with emphasis on tight junctions and Claudins (tight junction molecules). Topics include: the molecular basis of cell polarity and permeability barrier during development, organogenesis and disease including inflammatory disease and cancer.

Course Component: Lecture

CMM 8105 Advanced Topics in Cancer Biology (3 units)
Advanced study of recent developments in the field of cancer biology with emphasis on cellular and molecular aspects. Specific topics to be covered include: angiogenesis, apoptosis, cancer genetics, cell signaling, genetic instability, oncogenes and tumour suppressors.

Course Component: Lecture

CMM 8300 Special Topics in Reproductive and Developmental Biology (3 units)
In-depth study of current topics in reproductive and developmental biology, with emphasis on state-of-the art molecular and cell biology techniques as well as their applications to reproductive diseases. Topics may include assisted reproductive technologies, embryonic stem cells, contraception, endocrine disruptors, reproductive toxicology, and transgenics.

Course Component: Lecture

CMM 8310 Current Topics in RNA Molecular Biology (3 units)
Properties, mechanisms associated with regulation and the function 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. Courses BCH 8310 and CMM 8310 cannot be combined for units.

Course Component: Lecture

CMM 8311 Current Topics in Transcriptional Regulation (3 units)
Topics will include chromatin structure and its impact on gene expression, protein: DNA interactions, the assembly of transcriptional complexes, and the control of gene expression in mammalian systems.

Course Component: Lecture

CMM 83241 Seminars I (Part 1 of 2)
Compulsory for one year for all students enrolled in the master’s program. Presentation of two seminars or one seminar and one poster required during the year as well as regular attendance at the departmental seminar series. (Part 1 of 2)

Course Component: Seminar

CMM 83242 Seminars I (Part 2 of 2) (3 units)
Compulsory for one year for all students enrolled in the master’s program. Presentation of two seminars or one seminar and one poster required during the year as well as regular attendance at the departmental seminar series. (Part 2 of 2)

Course Component: Seminar

Prerequisite: CMM 83241

CMM 8324S Seminars I (3 crédits / 3 units)
Compulsory for one year for all students enrolled in the master’s program. Presentation of two seminars or one seminar and one poster required during the year as well as regular attendance at the departmental seminar series.

Volet / Course Component: Séminaire / Seminar

CMM 83251 Seminars II (Part 1 of 2)
Compulsory for all students enrolled in the doctorate program. Presentation of two seminars or one seminar and one poster required during the year as well as regular attendance at the departmental seminar series. (Part 1 of 2)

Course Component: Seminar

CMM 83252 Seminars II (Part 2 of 2) (3 units)
Compulsory for all students enrolled in the doctorate program. Presentation of two seminars or one seminar and one poster required during the year as well as regular attendance at the departmental seminar series. (Part 2 of 2)

Course Component: Seminar

Prerequisite: CMM 83251

CMM 8325S Seminars II (3 crédits / 3 units)
Compulsory for all students enrolled in the doctorate program. Presentation of two seminars or one seminar and one poster required during the year as well as regular attendance at the departmental seminar series.

Volet / Course Component: Séminaire / Seminar

CMM 8340 Neuromuscular Function and Dysfunction (3 units)
Topics to be covered include factors controlling muscle and synapse-specific gene expression, regulation of myogenesis and muscle cell growth, formation of the neuromuscular junction, motor neuron - muscle interactions, the role of the cytoskeleton in organization of post-synaptic domains, functional role of ion channels in muscle, molecular genetics of neuromuscular disease.

Course Component: Lecture

CMM 8341 Cell Stress (3 units)
Topics will include cellular responses to cell stress and will include hypoxia, oxidative stress, ER stress, autophagy, apoptosis and aging.

Course Component: Lecture

CMM 8345 Special Topics in Gastroenterology (3 units)
Lectures, tutorials and seminar-discussion sessions, designed to provide advanced training in gastrointestinal function. Emphasis on pathophysiological mechanisms.

Course Component: Lecture

CMM 8350 Ion Channels: Cellular and Molecular Aspects of Membrane Functions (3 units)
A study of the diversity, molecular structure, structure-function relationship, electrophysiological characteristics and physiological roles of different ion channels in excitable and non-excitable cells. The channels that are studied include the sodium, potassium, calcium and chloride channels.

Course Component: Lecture

CMM 8355 Renal Physiology (3 units)
Lecture and seminar course with emphasis on electrolyte transport. Topics to include: detailed structure and function of nephron segments, localization of primary and secondary active transport carriers, theories of autoregulation, hormone action in the kidney, drug action in the kidney, and regulation of renal vascular resistance.

Course Component: Lecture

CMM 9998 Examen de synthèse (doctorat) / Comprehensive Examination (PhD)

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.