

PHM323H: Molecular Mechanisms of Drug Action **PHC300H: Molecular Pharmacology 1**

I. CONTACTS, TIMES, LOCATIONS

Instructors

<i>Name:</i>	<i>E-mail:</i>
Dr. Dasha Redka:	dasha.pylypenko@utoronto.ca
Dr. Ian Crandall:	ian.crandall@utoronto.ca
Dr. Mary Erclik:	mary.erclik@utoronto.ca
Dr. Tameshwar Ganesh:	tameshwar.ganesh@mail.utoronto.ca

Teaching Assistant

Siobhan O'Brien:	siobhan.obrien@mail.utoronto.ca
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Lecture Times, and Locations

Lectures will take place in person, unless otherwise announced. In person lectures will not be streamed live online, unless otherwise announced. Under special circumstances, including but not limited to changes in the regulations from the University of Toronto, or an illness of an instructor, lectures may temporarily take place online via Zoom. The University of Toronto no longer requires that the video recordings are available online, therefore availability of such recordings will be made solely up to the discretion of each individual instructor.

<i>Time:</i>	<i>Location:</i>
Mondays 2–3 pm EDT	MS 2173
Thursdays 2–4 pm EDT	2–3 pm: MS 4171, followed by 3–4 pm: MS 4279)

For important academic sessional dates, visit:

<https://www.artsci.utoronto.ca/current/dates-deadlines/academic-dates>

II. COURSE OVERVIEW

Course Description

Welcome to PHM323/PHC300. Are you curious about how drugs work? Most prescribed drugs target proteins and nucleic acids. These biological targets can be classified according to their structure and mechanism of action at the molecular level.

About 25% of all drugs marketed in North America act by affecting the catalytic activity of enzymes. The lectures in the first quarter of this course are intended to foster an understanding of the physical-chemical principles that underlie enzymatic catalysis and inhibition, including co-operative effects in the case of multimeric enzymes. Of particular interest will be mathematically formulated, mechanistic models that offer an explicit description of the system under consideration. Students will become familiar with the construction and use of such models and will gain an appreciation of how they are essential to the testing of hypotheses and the interpretation of data.

In the latter part of the course, major classes of therapeutic targets will be discussed with an emphasis on their normal biochemical roles and the exploitation of those roles for therapeutic

intervention. The mechanisms of action of drugs acting on enzymes (antiviral and antimicrobial agents), on nucleic acids and on the cytoskeleton (anti-cancer agents) will be of special interest. The concept of rational cancer therapy will be introduced with examples of drugs targeting growth factor signaling pathways that are dysregulated in cancers.

The goal of this course and that of PHM323H1/PHC300H1, taken together, is to provide an understanding of the molecular basis of pharmacology. Emphasis will be placed on pharmacodynamics in a variety of therapeutic areas, and the overall objective is multifaceted. The present course introduces the notion of enzymes as a class of drug targets. It then considers nucleic acids, specific enzymes and some receptors in various areas of therapeutic intervention. Receptors that mediate intra- and intercellular signaling are considered as a class in PHM323H1/PHC300H1 (Molecular Pharmacology 2), where they are grouped according to their structural and mechanistic properties.

This course is an elective for students in the Leslie Dan Faculty of Pharmacy (PHM323H1), and it will be taught assuming that you have a basic background in chemistry, biochemistry, mathematics, and pharmaceuticals.

Student Learning Outcomes

By the end of PHM323/PHC300, students will have acquired the following:

- An understanding of the physical-chemical principles that underlie enzymatic catalysis and inhibition, including co-operative effects in the case of multimeric enzymes.
- An ability to design and construct mathematically formulated, mechanistic models that offer an explicit description of the system under consideration.
- An appreciation of how mechanistic models are essential to the testing of hypotheses and the interpretation of data.
- A basic knowledge of different DNA structures and their physical properties *in vitro* and *in vivo*.
- An understanding of the molecular mechanisms of the interactions between low molecular weight molecules and DNA.
- An appreciation of the constraints on strategies for targeting DNA for therapeutic purposes.
- An understand the molecular mechanisms by which anti-infective agents either slow or prevent the replication of their target pathogen.
- An understanding of the issues involved in the effective use of anti-infective agents.
- A basic knowledge of the hallmarks of cancer.
- An understanding of the molecular mechanisms that drive the progression of cancer and how they can be targeted in therapy.
- An understanding of some of the different approaches used to target cancer and to stem its progression.
- An understanding of how discoveries in the basic sciences can drive the creation of novel cancer therapies.

Prerequisite Courses

This course requires a basic understanding of biochemistry and chemistry.
The following courses are pre-requisites for PHC300:

Prerequisite: ([CHM135H1](#), [CHM136H1](#))/([CHM138H1](#), [CHM139H1](#))/[CHM151Y1](#);
[CHM220H1](#)/[CHM222H1](#)

Exclusion: [PCL302H1](#)

Distribution Requirements: Science

Breadth Requirements: Living Things and Their Environment (4)

Readings and Lectures Content

Required Text - None

Course Resources

Lecture materials will be provided online, through [Quercus](#). These notes will serve as the best guide to course content and scope. Further materials and information also will be made available through the University of Toronto [Quercus](#) system.

III. COURSE SYLLABUS

The course comprises four sections. The first section deals with enzymes as a major class of targets for therapeutic intervention. It begins with a brief review of the thermodynamic, molecular and mechanistic determinants of enzymatic catalysis. The focus then settles on mechanism and mathematically formulated models of catalysis and inhibition, beginning with monomeric enzymes (*e.g.*, the Michaelis—Menten equation) and proceeding to multimeric systems and co-operative effects (*e.g.*, the Adair equation). Topics to be covered include traditional assumptions and approximations, systems that violate those assumptions, the construction of mechanistic models, assessing the viability of a model and computational challenges that attend more complex systems.

The second section will focus on Antivirals and Antimicrobials with an emphasis on bacterial cell wall synthesis inhibitors, bacterial protein synthesis inhibitors, other antibacterial agents, antifungal agents, antiviral agents and antiparasitic agents.

The third section of the course will cover cancer biology (discovery of tumor suppressors, process of metastasis and oncogenes), cancer treatment regimens (conventional and targeted) and how discoveries in basic sciences can drive the discoveries of new cancer targets (Hedgehog signaling – Development of Vismodegib)

The fourth and final section of the course will focus on Nucleic Acids. Topics covered in this section will include the structure and properties of nucleic acids such as the different types of DNA and factors that modulate DNA structure. There also will be an introduction to the different classes of drugs that target nucleic acids including alkylating agents and drugs that form non-covalent interactions. Emphasis will be placed on the utility of these agents in oncological and neurological therapies.

Syllabus

Basic Concepts of Enzyme Action — Dasha Redka (6h)

Structure and mechanism
Nature and determinants of catalysis
 Thermodynamic
 Molecular
 Mechanistic
Mechanisms of catalysis and inhibition
 Mechanistic models
 Michaelis-Menten
 Haldane
 Cooperative systems
Formulation of mechanistic models
 Saturable processes
 Pre-equilibrium approximation
 Steady-state approximation
 Analytic and numerical solutions
 Graphical representations
Allosteric effects and cooperativity
 Adair
 Hill
 Monod, Wyman, Changeux
 Koshland, Nemethy, Filmer
 Eigen
 Haemoglobin
 Aspartate transcarbamoylase

Antivirals & Antimicrobials — Ian Crandall (7h)

Reverse Transcriptase
Proteases
HIV
DNA-dependent RNA polymerase
Cell wall biosynthesis
Protein biosynthesis
Membrane permeability

Cancer Pharmacology — Mary Erlick (6h)

Introduction to Cancer
Microtubule inhibitors
 Stabilizing
 Destabilizing
Growth Factor
Cell cycle
Oncogenes
Tumour suppressor

Endocrine Therapy
Targeted Therapy
Tyrosine kinase inhibitors
Gleevec in CML
Mechanisms of resistance

Nucleic Acids — Tameshwar Ganesh (6h)

Structure

Properties

Therapy

Non-covalent agents

Covalent Agents

IV. COURSE EVALUATION

The final grade will be based on two midterm examinations. Questions will be drawn from the lecture handouts provided in class and material discussed in the lectures.

Assessment Dates and Weights

For **PHM323** students, the schedule and weighting of the evaluative components of the course are as follows:

- 1) *First midterm*
 - Redka and Crandall: 50.0% (2:10 to 4:00 pm, Thursday October 13th, 2022 EX320)
- 2) *Final Exam/Second midterm*
 - Erclik and Ganesh: 50.0% (during the December exam period, location and time TBD)

For **PHC300** students, the schedule and weighting of the evaluative components of the course are as follows:

- 3) *First midterm*
 - Redka and Crandall: 40.0% (if grade lower than that for Midterm 2) or 60.0% (if grade higher than that for Midterm 2) (2:10 to 4:00 pm, Thursday October 13th, 2022 EX320)
- 4) *Final Exam/Second midterm*
 - Erclik and Ganesh: 40.0% (if grade lower than that for Midterm 1) or 60.0% (if grade higher than that for Midterm 1) (during the December exam period, location and time TBD)

V. COURSE POLICIES

Each member of this course is expected to maintain a:

- (i) professional and respectful attitude during all course activities, including classes and online activity.

- (ii) personal calendar/schedule/organizer to ensure that all course activities are completed, and due dates are met.
- (iii) collection of notes recorded independently based on concepts covered in course activities (students registered with Accessibility Services requiring a class note-taker will have access to this accommodation)
- (iv) familiarity with the university policy on Academic Integrity (overleaf)

Incomplete Examinations and Midterms

A student who begins but does not complete an examination will be deemed to have been present. The examination will be graded, and the mark will contribute to the final grade in the manner described above. There will be no opportunity to re-write the examination. It is each student's responsibility to make appropriate decisions regarding his or her fitness to attend and to complete an examination.

Absence from Examinations and Midterms

To receive consideration for absence from an examination, a student must submit a petition and appropriate documentation as follows: for PHM323H1, to the Registrar of the Leslie Dan Faculty of Pharmacy (*i.e.*, Brenda Thrush, brenda.thrush@utoronto.ca, 416-978-2873); for PHC 300H1, to the course-coordinator (*i.e.*, D. Redka, dasha.pylypenko@utoronto.ca). Please consult the calendar of the Leslie Dan Faculty of Pharmacy (PHM323H1) or the Faculty of Arts and Science (PHC300H1) for further details.

If a petition has been filed and approved, the absentee will be given the opportunity to write a make-up examination.

If a petition has not been filed and approved, the absentee will receive a grade of zero for the missed examination.

Students must also report their absence through the online absence declaration. The declaration is available on ACORN under the Profile and Settings menu.

Online Examinations

As needed, it is expected that examinations could be conducted online via Quercus in a timed and synchronous manner. More detailed information regarding the nature and format of the examination will be provided prior to the date. Invigilation by ProctorU One or more of the examinations may use invigilation provided by ProctorU, a fully online proctoring service that allows completion of the assessment from an off-campus location. Proctoring may be automated, or it may be performed by a highly trained human proctor. The decision to use ProctorU and related details will depend upon divisional policies and the requirements of the course. Students will be advised of the specific procedure prior to the examination. The proctoring service includes the use of a webcam. ProctorU will record the session, and the recordings will be held for a limited period of time in order to ensure that academic integrity is maintained. The University of Toronto has an institutionally endorsed agreement with ProctorU that protects the privacy of the recordings and other personal information.

Students taking their examinations online must agree to be proctored by ProctorU, should it be deployed, throughout the duration of the examination. Students in PHC300H1 will be required to

show their T-Card prior to beginning to write the examination. Students in PHM323H1 will be required to show their T-Card or valid government identification (e.g., driver's licence, passport) prior to beginning to write the examination.

Technical requirements

Access to a computer that can support remote recording is your responsibility as a student. You will need to ensure that you can complete the examination using a reliable computer equipped with a webcam and a microphone, as well as a reliable, high-speed internet connection. To that end, you are required to test your equipment no later than one week before the examination. The test can be performed at

<https://go.proctoru.com/users/4287473/system-metrics/new>. Access to the site requires that you hold an account with ProctorU. Further details regarding the equipment can be found at <https://support.proctoru.com/hc/en-us/articles/115011772748>

Equipment Requirements.

If you believe that you do not have the minimum requirements with respect to a computer and accessories, please contact either the Registrar of the Leslie Dan Faculty of Pharmacy (PHM323, brenda.thrush@utoronto.ca, 416-978-2873) or the course coordinator (PHC300, dasha.pylypenko@utoronto.ca, 416-910-9906) as appropriate. General process Students first must confirm their identity by means of photo ID with the proctor, either automated or human. The proctor then closely monitors students and their immediate environment throughout the entire examination using webcams and remote desktop monitoring through high-speed internet connection. All components of the proctoring must be maintained for the duration of the examination. Should any component be lost during the examination, such as would occur if the view from the camera became obstructed or if the remote desktop were to fail, the subsequent procedure will depend upon the nature of the proctor. A human proctor may contact the student during the examination through a pop-up message, voice or a loud beep, and the student is expected to respond. Failure to respond to the proctor and to allow the resumption of full proctoring threatens the integrity of the examination. An automated proctor will record the time and nature of the event for subsequent review but will not contact the student, who is expected to continue with the examination. Non-compliance with examination protocols flagged by the proctor will be investigated to determine whether an academic offence has been committed as per the Code of Behaviour on Academic Matters promulgated by the Governing Council of the University of Toronto. At the completion of the examination, a report of student exam-taking behaviours is generated and reviewed by the instructor and IT staff. Grades will not be released to students until the integrity of the examination has been verified through ProctorU, the instructor(s) and other divisional staff as appropriate. Privacy and security of information The University of Toronto has an institutionally endorsed agreement with ProctorU that protects the privacy of the recordings and other personal information. However, because you will be video-recorded while writing the examination, please consider preparing the background to avoid displaying personal details which you would not want to be visible. Pictures or other items might be removed, for example, or you might move to a room which you are comfortable showing on camera. It is recommended that students using the services of ProctorU remove the Chrome or Firefox extension after completion of the examination.

Retention of video content

Recordings captured via the ProctorU system are available to the University and the instructor for sixty days after a recording is made. Recordings flagged for review will be archived for twelve months. After these time periods have passed, recordings will be purged.

Turnitin

Assessments in PHM323H1/PHC300H1 do not normally require extended prose such might be found in reports or essays. Should such forms of assessment be employed, however, students normally will be required to submit their essays or other material to Turnitin.com for a review of textual similarity and detection of possible plagiarism. In doing so, students will allow their material to be included as source documents in the Turnitin.com reference database, where they will be used solely for the purpose of detecting plagiarism. The terms that apply to the University's use of the Turnitin.com service are described on the Turnitin.com web site.

All suspected cases of academic dishonesty will be investigated following procedures outlined in the Code of Behaviour on Academic Matters. If you have questions or concerns about what constitutes appropriate academic behavior or appropriate research and citation methods, you are expected to seek out additional information on academic integrity from your instructor or from other institutional resources (see <https://www.academicintegrity.utoronto.ca/>).

Passing Grade and Supplemental Examinations

PHC300H1

A student is required to obtain an overall grade of at least 50% to pass the course. Students who do not pass are required to repeat the course.

PHM323H1

A student is required to obtain an overall grade of at least 60% to pass the course. Students who do not pass may be eligible to take a supplemental examination, as determined according to the policies of the Leslie Dan Faculty of Pharmacy. A student who fails to obtain a grade of at least 60% on the supplemental examination is deemed to have failed the course.

The examination will be held during the period selected for supplemental examinations in the Leslie Dan Faculty of Pharmacy, typically in mid-summer. The questions will be drawn from all sections of the course. Individual sections of the examination may be written or oral, as determined by the course coordinator in consultation with the individual lecturers. Decisions regarding the format will be made during the month or so preceding the examination.

The allocation of marks within each of the midterms will be equally distributed between the two instructors for the respective midterm (*e.g.*, in the case of PHM323 students, D. S. Redka, 25%; I. Crandall, 25%; M. Erclik 25%; T. Ganesh, 25%).

Privacy Policy

- Parts of this course, including your participation, may be recorded on video and may be available to students in the course for viewing remotely and after each session.

- Course videos and materials belong to your instructor, the University, and/or other sources depending on the specific facts of each situation and are protected by copyright. Do not download, copy, or share any course or student materials or videos without the explicit permission of the instructor.
- At times, you may be required to share your desktop, and turn on your webcam to share your completed (working) activity. This will be required in order to assess your participation mark, and help you troubleshoot your practical activities.

Reviewing Examinations

Mid-term Examinations

Students may review what they wrote on the first midterm examination by contacting the teaching assistant for their tutorial section. Students may review what they wrote on the second mid-term examination by contacting the teaching assistant who graded the papers. Requests for reviews must be made within a period of four months from the date of the examination. Changes to the grade will be considered according to a procedure that will depend upon whether the request for a change takes place before or after the time of the final examination. Requests for changes that are made prior to the final examination may be directed to the relevant teaching assistant, who will discuss the matter with the student and make appropriate adjustments to the grade. Disagreements that cannot be resolved between the two parties will be decided by the lecturer at his or her sole discretion. Requests for changes that are made after the final examination are directed either to the teaching assistant or to 6th January 2023 the course-coordinator, depending upon the nature of the change. Requests related to technical errors such as an unmarked answer or an error of addition may be directed to the teaching assistant, who will adjust the grade as required. No other change will be considered at that time; rather, the student may contact the course-coordinator and request that the entire examination be re-graded. In that event, the mark on any question may increase, decrease or remain the same.

Final Examination

Reviews of the final examination in PHM323H1 are conducted as described in the calendar of the Leslie Dan Faculty of Pharmacy. Corrections of technical errors such as an unmarked answer or an error of addition will be made as required. For any other change, the student may request that the entire examination be re-graded, and the mark on any question may increase, decrease or remain the same. Reviews of the final examination in PHC300H1 are conducted as described in the calendar of the Faculty of Arts and Science.

VI. TECHNOLOGY REQUIREMENTS

Required Equipment

- ***A laptop or desktop computer*** is required for this course.

Specific guidance from the U of T Vice-Provost, Students regarding student technology requirements is available here:

<https://www.vicereprovoststudents.utoronto.ca/covid-19/tech-requirements-online-learning/>

Advice for students more broadly regarding online learning is available here:

<https://onlinelearning.utoronto.ca/getting-ready-for-online.>

This course requires the use of computers, and technical issues are possible. When working on an assignment, students are responsible for scheduling enough time to allow for reasonable delays due to technical difficulties to be overcome, so such issues will not be acceptable grounds for deadline extension. Particularly, maintaining an up-to-date independent backup copy of your work is strongly recommended to guard against *e.g.* hard-drive failures, corrupted files, lost computers, etc.

We appreciate that students may experience a range of circumstances that shape their ability and/or decision to participate in course activities using video. We are committed to creating equitable and inclusive learning and teaching spaces. In support of this commitment we feel it is important to give participants the choice to turn their video on/off.

For General technology concerns, please contact the Information Commons Help Desk via (416) 978-HELP (4357) OR by e-mailing help.desk@utoronto.ca. They are open evenings and weekends. <https://onereach.library.utoronto.ca/ic-faq-categories/about-and-hours-service>

Please contact the course coordinator with course-specific technology concerns. Please be as detailed as possible with your question by including the time/date, detailed description of the problem, web browser and device you were using (*e.g.* laptop/tablet etc.) and include screenshots/error message etc.

VII. INSTITUTIONAL POLICIES AND SUPPORT

Academic Integrity

Academic integrity is a fundamental value of learning and scholarship at the University of Toronto. Participating honestly, respectfully, responsibly and fairly in this academic community ensures that your University of Toronto degree is valued and respected as a true signifier of your individual academic achievement. All suspected cases of academic dishonesty will be investigated following procedures outlined in the Code of Behaviour on Academic Matters. You are expected to be familiar with the contents of that document and to seek out additional information on academic integrity from other institutional resources such as the University of Toronto website on Academic Integrity. The Code of Behaviour on Academic Matters outlines the behaviours that constitute academic misconduct, the processes for addressing academic offences and the penalties that may be imposed. Potential offences include, but are not limited to:

- Looking at someone else's answers, or working together to answer questions;
- Letting someone else look at your answers;
- Asking for or soliciting help, in any manner whatsoever, from people other than the instructor (*e.g.*, through online tutoring platforms such as [chegg.com](https://www.chegg.com));
- Having synchronous or asynchronous discussions about the examination material through any means during the entire time-window of the examination (*e.g.*, phone, text messaging, discussion boards, etc);
- Misrepresenting your identity or having someone else complete your test or examination. - Representing as your own any idea or expression of an idea or work of another (*i.e.*, plagiarism).

Verification of Academic Originality

Normally, students will be required to submit their course essays to the University's plagiarism detection tool for a review of textual similarity and detection of possible plagiarism. In doing so, students will allow their essays to be included as source documents in the tool's reference database, where they will be used solely for the purpose of detecting plagiarism. The terms that apply to the University's use of this tool are described on the Centre for Teaching Support & Innovation web site (<https://uoft.me/pdt-faq>).

Copyright

Students with diverse learning styles and needs are welcome in this course. The University of Toronto is committed to accessibility: if you require accommodations for a disability, or have any other accessibility concerns about the course, please contact [Accessibility Services](#) as soon as possible.

Accommodations for Religious Observances

Following the University's policies, reasonable accommodations will be made for students who observe religious holy days that coincide with the due date/time of an assignment, tutorial, class or laboratory session. Students must inform the instructor **before** the session/assignment date to arrange accommodations.

Accessibility Needs

Students with diverse needs are welcome in this course. The University of Toronto is committed to accessibility: if you require accommodations for a disability, or have any other accessibility concerns about the course, please contact Accessibility Services as soon as possible.

Additional Services and Support

The following are some important links to help you with academic and/or technical service and support:

- General student services and resources at [Student Life](#)
- Full library service through [University of Toronto Libraries](#)
- Resources on conducting online research through [University Libraries Research](#)
- Resources on academic support from the [Academic Success Centre](#)
- Learner support at the [Writing Centre](#)
- Information for [Technical Support/Quercus Support](#)

Equity, Diversity, Inclusion and Accommodation

The University of Toronto is committed to equity, human rights and respect for diversity. All members of the learning environment in this course should strive to create an atmosphere of mutual respect where all members of our community can express themselves, engage with each other and respect one another's differences. The University of Toronto does not condone discrimination or harassment against any persons or communities. The University provides academic accommodations for students with disabilities, in accordance with the terms of the Ontario Human Rights Code. This occurs through a collaborative process that acknowledges a collective obligation to develop an

accessible learning environment that both meets the needs of students and preserves the essential academic requirements of the University's courses and programs. 6th January 2022 Page 5 of 5
Students with diverse learning styles and needs are welcome in this course. If you require accommodations for a disability, or if you have any concerns about accessibility as it relates to the course, the classroom or the course materials, please contact Accessibility Services as soon as possible: accessibility.services@utoronto.ca, or <http://studentlife.utoronto.ca/as>.