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

## I. CONTACTS, TIMES, LOCATIONS

***Instructors***

| *Name:* | *E-mail:* |
|---|---|
| Dr. Dasha Redka: | dasha.pylypenko@utoronto.ca |
| Dr. Mary Erclik: | mary.erclik@utoronto.ca |
| Dr. Tameshwar Ganesh: | tameshwar.ganesh@mail.utoronto.ca |

***Teaching Assistant***
**Fatemeh Molaei**

***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 instruction, 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.

| *Time:* | *Location:* |
|---|---|
| Mondays 2–3 pm EDT | MS4279 |
| Thursdays 2–4 pm EDT | HA401 |

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 pharmaceutics.

***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.

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 — Tameshwar Ganesh (7h)*
Reverse Transcriptase
Proteases
HIV
DNA-dependent RNA polymerase
Cell wall biosynthesis
Protein biosynthesis
Membrane permeability

*Cancer Pharmacology — Mary Erclik (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 Ganesh (Antimicrobials): 50.0% (2:10 to 4:00 pm, Thursday October 17th 2023 (HA410)
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 Ganesh: 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 17th, 2024 HA401)
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 and for PHC 300H1, to the course-coordinator (*i.e.*, Dr. Erclik, mary.erclik@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.

***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 instructions 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 2024 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.viceprovoststudents.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://onesearch.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);
- 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.

**PHM 323H/PHC 300H: Molecular Pharmacology 1 / Molecular Mechanisms of Drug Action**
**Schedule of Lectures, Tutorials and Examination for 2024**

1st September 2024

**Lectures**

| Instructor | Monday 2-3 pm MS4279 | Thursday 2-3 pm HA401 | Thursday 3-4 pm HA401 |
|---|---|---|---|
| D.S. Redka | | 5th Sep 2024 | 5th Sep 2024 |
| | 9th Sep 2024 | 12th Sep 2024 | 12th Sep 2024 |
| | 16th Sep 2024 | | |
| T. Ganesh | | 19th Sep 2024 | 19th Sep 2024 |
| | 23rd Sep 2024 | 23rd Sep 2024 | 23rd Sep 2024 |
| | 30th Sept 2024 | 3rd Oct 2024 | 3rd Oct 2024 (tutorial) |
| M. Erclik | Oct 7th 2024 | 10th Oct 2024 | 10th Oct 2024 |
| | **October 14th Thanksgiving No Class** | **17th OCTOBER 2024 MIDTERM EXAM DURING CLASS** | |
| | 21st Oct 2024 | 24th Oct 2024 | 24th Oct 2024 |
| | **Reading week Oct 28th -Nov 1st** | | |
| M. Erclik | 4th Nov 2024 | 7th Nov 2024 | 7th Nov 2024 |
| T. Ganesh | 11th Nov 2024 | 14th Nov 2024 | 11th Nov 2024 |
| | 18th Nov 2024 | 21st Nov 2024 | 21st Nov 2024 |
| | 25th Nov 2024 | TBA | TBA |

**Examinations**

Midterm: Date: 2:10-4:00 pm, 17th October 2024
Lecturers: D.S. Redka and T. Ganesh
Material: 5th Sep to 3rd Oct 2024
HA410

Final Examination / Midterm 2: Date: TBD

Lecturers: M. Erclik and T. Ganesh
Material: 10th Oct to Nov 25th 2024
Place: TBD