3rd January 2023

PHM140H1/PHC301H1
MOLECULAR PHARMACOLOGY
Policies and Procedures for 2022-2023

EXAMINATIONS

The arrangements described below are essentially the same for students enrolled in the Leslie Dan Faculty of Pharmacy (PHM140H1) and for those enrolled in the Faculty of Arts and Science (PHC301H1) except for policies related to petitions and failed courses. The term "examination" can be read throughout as "assessment" by students in PHC301H1.

The grade for the year will be based upon two mid-term examinations and a final examination. Questions on the mid-term examination will be drawn exclusively from material covered during the periods shown below. The final examination is comprehensive and will be based upon material covered throughout the year, weighted as described below.

SCHEDULE OF EXAMINATIONS

1st Mid-term examination (2 hr)

material: 9th January to 7th February (15 lectures)
lecturer: D. S. Redka
date: 8:45-10:45 am, 28th February 2023
place: Examination Centre, EX-100
weight: Overall, 24%; *i.e.*, 60 x 15/38

2nd Mid-term examination (2 hr)

material: 8th February to 21st March (16 lectures)
lecturers: C. Cummins and R. P. Bonin
date: 8:45-10:45 am, 28th March 2023
place: Examination Centre, EX-100
weight: Overall, 25%; *i.e.*, 60 x 16/38

C. Cummins:	60 x 5 /38	= 8%	(31 %)
R. P. Bonin:	60 x 11/38	= 17%	(69 %)
Total:	60 x 16/38	= 25%	(100 %)

Final examination (3.0 hr)

material: All (9th January – April 5th, 2023)
lecturers: All lecturers
date: On or about 24th April 2023
weight: Overall, 51%; *i.e.*,

D. Redka (*part 1*):	40 x 15/38	= 15.7	(30.9%)
C. Cummins:	40 x 5/38	= 5.3	(10.3%)
R. P. Bonin:	40 x 11/38	= 11.6	(22.7%)
D. Redka (*part 2*):	(40 + 60) x7/38	= 18.4	(36.1%)
Total		51.0	(100.0%)

WEIGHTING

The weighting of marks is based upon the number of lecture-hours and the notion of a 60/40 split between the mid-term examinations and the final examination. There will be no mid-term examination on the last 7 lectures; rather, that material will be covered only on the final examination and weighted accordingly as shown above. The final examination therefore will account for 51% of the overall grade rather than 40%, with the extra 11% reflecting the mid-term component of the last 7 lectures.

INCOMPLETE EXAMINATIONS

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

Petitions

To receive consideration for any absence, a student must submit a petition and appropriate documentation as follows: for PHM140H1, to the Registrar of the Leslie Dan Faculty of Pharmacy (*i.e.*, Gustavo Luna, g.luna@utoronto.ca, 416-978-2931); for PHC 301H1, to the course-coordinator (*i.e.*, R. P. Bonin, rob.bonin@utoronto.ca, 416-978-2716). Please consult the calendar of the Leslie Dan Faculty of Pharmacy (PHM140H1) or the Faculty of Arts and Science (PHC301H1) for further details.

If a petition has not been filed and approved, the absentee will receive a grade of zero for the missed examination. If a petition has been filed and approved, the absentee's grade will be determined as described below.

Absence from Mid-term Examinations

Should a student miss one of the mid-term examinations, the mark on each section will be taken as that obtained on the corresponding section of the final examination. The effect therefore is to increase the overall weight of the final examination. If the first mid-term examination is missed, the final examination will account, in effect, for 75% of the overall grade for the year. If the second mid-term examination is missed, the final examination will account for 76% of the overall grade for the year.

Should a student miss both of the mid-term examinations, the mark on each section will be taken as that obtained on the corresponding section of a make-up (PHM140H1) or deferred (PCH301H1) examination to be held in the summer as described below. In the interim, the grade will be shown on ACORN as DNW (PHM140H1) or SDF (PHC301H1).

Absence from the Final Examination

A student who misses the final examination may apply to take a make-up or deferred examination to be held in the summer as described below. Eligibility will be deter-mined according to the policy of the Leslie Dan Faculty of Pharmacy or the Faculty of Arts and Science for missed examinations.

To obtain an overall grade for the course, the mark from the make-up or deferred examination will be used in lieu of that from the final examination and combined with the mid-term marks in the manner described above.

Pending the outcome of the make-up or deferred examination, the grade will be shown on ACORN as DNW (PHM140H1) or SDF (PHC301H1).

Passing Grade

PHM140H1

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. The supplemental examination will be held in the summer as described below. A student who fails to obtain a grade of at least 60% on the supplemental examination is deemed to have failed the course.

PHC301H1

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.

Supplemental, Make-up & Deferred Examinations

A single examination will serve as the supplemental examination in PHM140H1, the make-up examination in PHM140H1 and the deferred examination in PHC301H1. It 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 co-ordinator 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 among the different sections is described below. Note that it differs from that on the final examination.

Supplemental Examination in PHM140H1

Students will answer all sections of the supplemental examination. Marks will be allocated among the different sections in direct proportion to the number of lecture-hours (*i.e.*, D. Redka (*part 2*), 18.4%; R. P. Bonin, 28.9%; C. Cummins, 13.2%; D. Redka (*part 1)*, 39.5%).

Make-up Examination in PHM140H and Deferred Examination in PHC301H

Students who were absent from the final examination will answer all sections of the make-up or deferred examination. Marks will be allocated among the different sections in direct proportion to the number of lecture-hours (*i.e.*, D. Redka (*part 2*), 18.4%; R. P. Bonin, 28.9%; C. Cummins, 13.2%; D. Redka (*part 1)*, 39.5%), and the grade will be used in lieu of that from the final examination to determine the overall grade for the year as described above.

Students who were absent from both of the mid-term examinations will answer only the corresponding sections of the make-up or deferred examination. The marks will be incorporated into the grade for the year as described above.

There will be only one make-up or deferred examination. Should a student miss that examination, the next opportunity will be the final examination at the end of the next academic year. In that event, the student will be held responsible for any changes in the content of the course during the intervening year. Eligibility to write such an examination will be determined according to the policies of the Leslie Dan Faculty of Pharmacy for missed examinations.

Students enrolled in PHC301H1 are asked to note that the deferred examination will be administered by the Leslie Dan Faculty of Pharmacy. It therefore will be held during the period selected for supplemental and make-up examinations in the Leslie Dan Faculty of Pharmacy, which will be in the summer as described above. This is not necessarily the same as the period for deferred examinations in the Faculty of Arts and Science. Students in the last year of their programme ought to note that a deferred examination in PHC301H1 may delay their graduation.

Reviewing Examinations

Mid-term Examinations

Students may review what they wrote on the first mid-term 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

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 PHM140H1 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 PHC301H1 are conducted as described in the calendar of the Faculty of Arts and Science.

Turnitin

Assessments in PHM140H1/PHC301H1 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.

TUTORIALS

Questions from previous examinations and issues related to the lectures presented by D. Redka from January 9 – February 7 will be discussed at weekly tutorials scheduled for 9:10 am on Tuesdays between 17th January and February 7th. That period otherwise will be available for unscheduled tutorials or used for lectures, as shown in the schedule of lectures. The class will be divided into five sections, which are expected to meet in person in PB150. Tutorials may also be held via Quercus and / or Zoom as determined by the appropriate Teaching Assistant. You must attend tutorials in the session to which you have been assigned.

DELIVERY OF LECTURES AND TUTORIALS

Lectures and tutorials will be delivered in-person unless directed otherwise by the University of Toronto or the Leslie Dan of Pharmacy for reasons of public health, pandemic-related restrictions, *etc*.

Recordings

This course, including any questions or comments from students, will be recorded on video. The recordings will be available for remote viewing within Quercus after each session.

Course videos and materials belong to your instructor, the University, and/or other source depending on the specific facts of each situation, and they are protected by copyright. Sessional videos and other materials in this course are provided for your own academic use. You must not copy, share or use them for any other purpose without the explicit permission of the instructor.

For questions about recording and use of videos in which you appear please contact your instructor.

Technological Requirements for Online Learning

Minimum technical requirements for participation in courses delivered online have been identified by the Office of the Vice-Provost, University of Toronto. Details can be found at:
https://www.viceprovoststudents.utoronto.ca/covid-19/tech-requirements-online-learning/

This document lists several recommended accessories, including headphones, speakers, webcams, microphones, scanners and cameras. Headphones or speakers are essential for the lectures and tutorials in PHM 140H1/PHC 301H1. Other peripheral devices are not required, but that does not preclude their use should a student choose to do so. A microphone may be helpful, for example, when asking a question during a lecture or participating in a tutorial. The use of a webcam is similarly at the student's discretion. We appreciate that students may experience a range of circumstances that shape their ability or their decision to participate in course-related activities using video.

Troubleshooting

For general questions regarding technological issues, contact the Information Commons Help Desk (416-978-4357, help.desk@utoronto.ca). They are open evenings and weekends (https://onesearch.library.utoronto.ca/ic-faq-categories/about-and-hours-service).

Technological issues related specifically to the course in molecular pharmacology may be directed to individual lecturers or the co-ordinator, as appropriate. Please provide as much information as possible, including a description of the problem, the time and date, the web browser and the device which you were using (*e.g.*, laptop or tablet etc.) and screen-shots of messages that identify the error.

EQUITY, DIVERSITY, INCLUSION & 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.

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.

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).

PHM 140H1/PHC 301H1
MOLECULAR PHARMACOLOGY
Syllabus for 2022-2023

DESCRIPTION

Many drugs act via the receptors and other proteins that mediate signalling within and between cells. Although there are more than 1,000 such proteins, they can be grouped into a handful of families on the basis of their structural and functional similarities. Each family will be examined at the molecular level from a pharmacological, biochemical and biophysical point of view with specific members taken as representative examples. Of particular interest will be their structure, their mechanism of action, their modulation by drugs and the underlying dysfunctions toward which the drugs are directed. Basic principles of molecular pharmacology are introduced as a tool for decoding the relationship between dose and response, with an emphasis on the nature of concepts such as affinity, allostery, intrinsic activity and efficacy.

OBJECTIVES

The course will emphasise principles and understanding. Concepts and broad themes are described in molecular terms and presented in the context of key observations taken from the scientific literature. The intent is not only to introduce the "facts", such as they are, but also to impart an appreciation of the scientific process and the nature of the information that constitutes the basis of present knowledge. Limits to current understanding, uncertainty over the interpretation of data, and alternative hypotheses are pointed out from time to time in an effort to encourage a critical approach to the subject. A primary aim is to foster a conceptual grasp that will outlive the specific and perhaps transient details of today and assist in understanding those of tomorrow.

RATIONALE

Informed therapeutic intervention is based upon a knowledge of structure and mechanism at the molecular level. That in turn derives from advances in biophysics, biochemistry, immunology, molecular genetics and related sciences as they pertain to fields such as neuroscience and pharmacology. The course therefore builds on the student's knowledge in the basic sciences, particularly with regard to the structure and function of proteins, to provide an understanding of how drugs act at the molecular level.

The material complements that in disciplines focussed on other aspects of therapeutic intervention, such as pharmacokinetics and pharmaceutics, and it provides a unifying framework for courses in which therapeutic agents are discussed in terms of their physiological, pharmacological or toxicological effects.

SUGGESTED READING

Material presented in the course is drawn from a variety of sources at the discretion of each lecturer, and the handouts are the best guide to content, nature and scope. For further reading, students are directed to sources recommended by the lecturers and to the monographs listed below. All of the latter are available in printed form from the University of Toronto Library. Those identified by an asterisk (*) also are available on-line. Those without an asterisk may be available on-line in an earlier edition.

The books identified as textbooks are comprehensive in nature and contain at least some material on most of the topics covered in the course. The others are more focussed and can be very enlightening in particular areas.

TEXTBOOKS

Berg, J. M., Tymoczko, J. L, Gatto, G. L. and Stryer, L., *Biochemistry, 9th Edition*, W. H. Freeman and Company, New York, 2019.

Brunton, L. L., Knollman, B. C. and Hilal-Dandan, R. (editors), *Goodman and Gilman's The Pharmacological Basis of Therapeutics, 13th Edition*, McGraw-Hill, New York, 2018. (*)

Kalant, H., Grant, D. M. and Mitchell, J. A. (editors), *Principles of Medical Pharmacology, 7th Edition*, Saunders Elsevier, Toronto, 2007.

Lodish, H., Berk, A., Kaiser, C. A., Krieger, M., Bretscher, A, Ploegh, H., Amon, A. and Martin, K. C., *Molecular Cell Biology, 8th Edition*, W. H. Freeman and Company, New York, 2016.

OTHER SOURCES

Ehlert, F. J., *Affinity and Efficacy. The Components of DrugBReceptor Interactions*, World Scientific, Hackensack, 2015. (*)

Foreman, J. C., Johansen, T. and Gibb A. J. (editors), *Textbook of Receptor Pharmacology*, *3rd Edition*, CRC Press, Boca Raton, 2011.

Kenakin, T., *Molecular Pharmacology. A Short Course*, Blackwell, Oxford, 1997.

Kenakin, T. P., *Pharmacologic Analysis of Drug-Receptor Interaction, 3rd Edition*, Lippincott-Raven, Philadelphia, 1997.

Kenakin, T., *A Pharmacology Primer: Theory, Application, and Methods*, Elsevier Academic Press, Amsterdam, 2004. (*)

Zheng, J. and Trudeau, M. C. (editors) *Handbook of Ion Channels*, CRC Press, Boca Raton, 2015. (*)

Molleman, A., *Patch Clamping: An Introductory Guide to Patch Clamp Electrophysiology*, Wiley, Chichester, 2003. (*)

Weinberg, R. A., *The Biology of Cancer*, Garland Science, New York, 2006.

OUTLINE

INTRODUCTION TO SIGNALLING D.S. Redka (7 h)

Classification according to initiating signal
Classification according to molecular mechanism

- contribution of molecular biology and genetics
- structure of membrane proteins
- comparative summary of transducing systems
  - G protein-coupled receptors
  - ligand- and voltage-gated ion channels
  - tyrosine kinases
  - guanylate cyclases
  - transcriptional enhancers
  - transporters

Pharmacological properties
- dose and response
- full and partial agonists
- antagonists
- specificity
- affinity and potency
- intrinsic activity and efficacy
- allosteric modulators
- assays

FAMILIES OF SIGNALLING SYSTEMS

G protein-coupled receptors D. S. Redka (8 h)

Introduction to G protein-coupled receptors

Effectors
- adenylate cyclase
- cyclic GMP phosphodiesterase
- phospholipase C
- potassium channels

G proteins
- primary, secondary, tertiary and quaternary structure
- post-translational modifications
- relationship between structure and function
- subtypes
- ADP-ribosylating toxins
- binding of guanyl nucleotides and GTPase activity
- RGS proteins and GAPs
- mechanism of action
- dysfunction in disease

Receptors
- primary, secondary and tertiary structure
- post- and co-translational modifications
- relationship between structure and function
- ligand-binding site
- subtypes and subtype-specific ligands
- pharmacological specificity
- recognition and characterisation of heterogeneity
- the Hill equation
- dysfunction in disease

Mechanism of action
- binding of agonists and antagonists
- allosteric effects between agonists and guanyl nucleotides
- relationship between binding and response
- mobile receptor hypothesis
- dysfunction in disease
- desensitisation and trafficking
- detection and role of oligomers

  - cloning and primary sequence
  - molecular family of ion pumps
  - subtypes of Na pumps

Nuclear Receptors C. Cummins (5 h)

Discovery and early detection

Comparison with membrane-bound receptors

Structure
- functional domains

Mechanisms of action
- ligand-dependent transcription
- regulation of gene expression

Therapeutic importance
- thyroid hormone and corticoid replacement therapy
- gonadal steroids and fertility control
- anabolic steroids
- vitamin D
- vitamin A and related retinoids
- antagonists
  - Tamoxifen (anti-estrogen in cancer therapy)
  - RU486 (anti-progestin)

Orphan receptors

Ion Fluxes R. P. Bonin (11 h)

Biophysical characterisation of ion flux
- significance of electrophysiological assays
- ion gradients and conductance
- conventional *vs.* patch recording of ion currents
- voltage-clamp
- voltage-activation curve
- current-voltage relation
- single channel analysis
- kinetics of state transitions
- activation and inactivation

Voltage-gated ion channels

- Na^+-channels
  - structure
  - voltage sensor
  - subtypes
- Ca^{2+}-channels
  - similarities with the Na^+-channel
  - modulation by phosphorylation
  - role as a sensor of membrane potential
  - subtypes
- K^+-channels
  - multiple subtypes
  - delayed rectifier
  - A-current
  - inward rectifier
  - calcium-activated K^+-channels
  - ATP-sensitive channels
  - molecular biology of K^+-channels
  - ATP channels as targets of oral hypoglycemic agents

Ion-gated transporters

- Na pump (Na, K-ATPase)
  - biochemical properties
- Ca pump (Ca, Mg-ATPase)
  - site-directed mutagenesis
  - peristaltic pump model

Ligand-gated Ion Channels

- Families of ligand-gated channels
- Nicotinic cholinergic receptor
  - prototype
  - subunit structure
  - channel structure
  - gating by acetylcholine
    - dynamic considerations
    - co-operativity
    - desensitisation
  - subtypes
- $GABA_A$ receptor
  - similarities with the nicotinic receptor
  - subunits
  - potentiation by barbiturates and benzodiazepines
  - subtypes
- Glutamate receptors
  - pharmacological and structural classification
    - NMDA receptors
    - kainate receptors
    - AMPA receptors
  - subtypes of receptors
  - functional properties
    - allosteric modulation (NMDA receptors)
    - desensitisation (kainate and AMPA receptors)
    - homomeric *vs* heteromeric receptors
  - excitotoxicity
  - therapeutic potential of glutamatergic agents
    - anti-epileptics
    - neuroprotectants
    - cognition and memory

Wnt Signalling D. S. Redka (2 h)

- Signalling in growth and development
  - morphogens
  - principle of cell-cell interactions
  - cell proliferation
  - determination of cell fate
  - mechanism of signalling
- Malfunction in cancers and other diseases
  - stem cells
  - therapeutic manipulation of progenitor cells

Intrinsic Tyrosine Kinases D. S. Redka (5 h)

- Growth factors
  - structure
  - cellular sources
  - mechanisms of release
  - regulation of secretion
- Tyrosine kinase receptors
  - classification of receptor types
  - subunit structure
  - primary amino acid sequence homology
  - functional domains
  - detailed structure of the insulin receptor
- Signal transduction
  - proteins that interact with receptor tyrosine kinases
  - regulation of cellular growth
  - regulation of cellular metabolic pathways
- Cell transformation and cancer
  - growth factors as oncoproteins
  - alterations to receptor tyrosine kinases
  - development of targeted therapeutic agents

PHM 140H/PHC 301H: MOLECULAR PHARMACOLOGY

Schedule of Lectures, Tutorials and Examinations for 2022–2023

3rd January 2023

Lectures and Scheduled Tutorials

	Mon. (1–2) PB B150	*Tue*. (9–10) PB B150	*Tue*. (10–11) PB B150	*Wed*. (12–1) PB B150	
D. S. Redka	09	10	10	11	January
	16	17 [a]	17	18	January
	23	24 [a]	24	25	January
	30	31 [a]	31		January
				01	February
	06	07 [a]	07		February
C. L. Cummins				08	February
	13	14	14	15	February
		Reading Week			February
R. P. Bonin	27	28: 1st Mid-Term Exam			February
				01	March
	06	07	07	08	March
	13		14	15	March
	20		21		March
D. S. Redka				22	March
	27	28: 2nd Mid-Term Exam		29	March
	03	04	04	05	April

[a] Tutorials held in conjunction with the lectures. The class is divided into five sections that meet separately, as described elsewhere. One additional tutorial, not shown above, will take place at a time yet to be determined.

Examinations

1st mid-term examination	Date:	8:45–10:45 am, 28th February 2022
	Lecturer:	D. S. Redka
	Material:	9th January to 7th February 2022
	Place:	Examination Centre, EX 100
2nd mid-term examination	Date:	8:45 to 10:45 am, 28th March 2022
	Lecturers:	C. L. Cummins and R. P. Bonin
	Material:	8th February to 21st March 2022
	Place:	Examination Centre, EX 100
Final examination	Date:	On or about 24th April 2022
	Lecturers:	all
	Material:	all
	Place:	T.B.A.