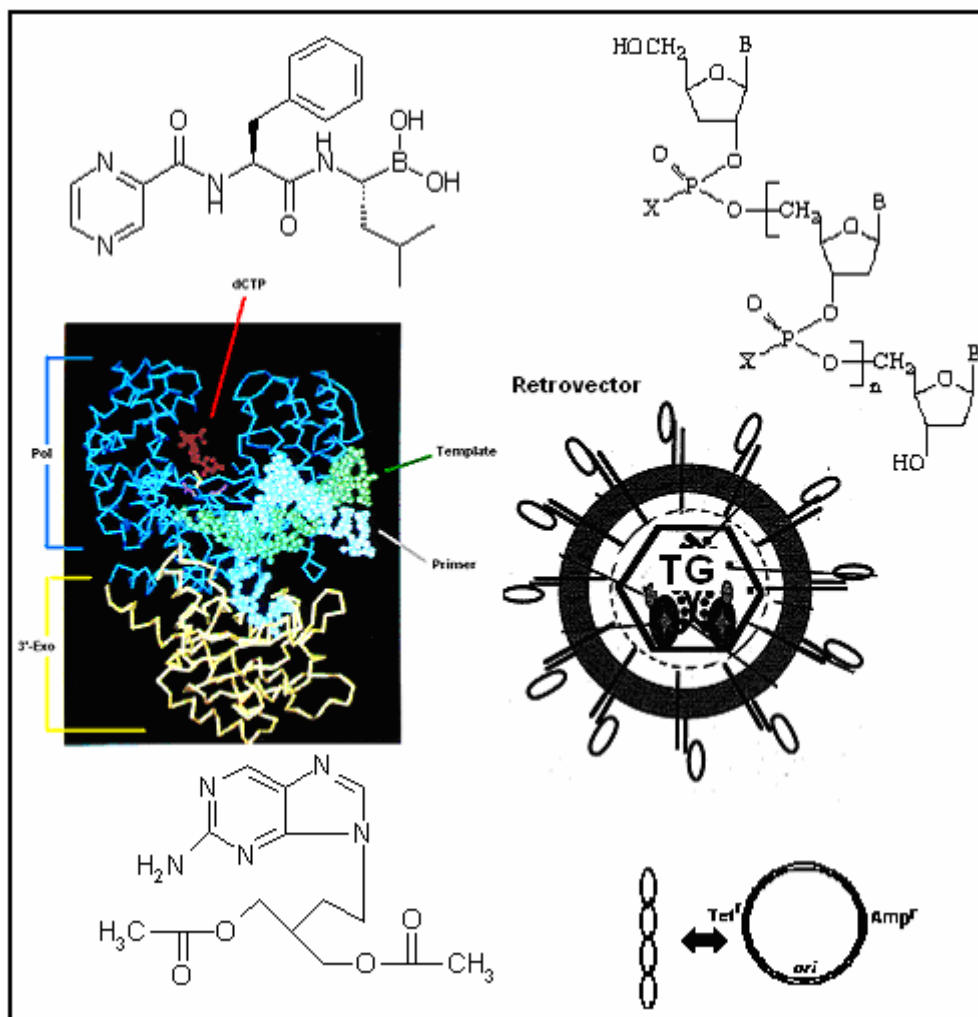


Course Outline
Medicinal Biochemistry II (PHCY 422/402R)
Spring, 2008



Dr. Ken Bastow: Course Coordinator (Room 322)

Drs. Ken Bastow & Rihe Liu: Instructors

Ken_Bastow@unc.edu; Tel: 6-7633

Rihe_Liu@unc.edu Tel: 3-3635

Honor Code:

It shall be the responsibility of every student at the University of North Carolina at Chapel Hill to obey and support the enforcement of the Honor Code, which prohibits lying, cheating and stealing when these actions involve academic processes or university, student or academic personnel acting in an official capacity

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PHCY 422 Lecture Schedule (Spring 2008)

W & F, 9.00-10.15 Kerr 1001/ECSU 101

Date	Lecture Topic/Event/Assignment	Readings
Jan.9	Course Intro: Nucleic Acids: Structure & Function (KB)	M vH Ch. 4
Jan.11	Nucleic Acids: Structure & Function (KB)	M vH Ch. 4
Jan.16	Nucleic Acids: Structure & Function (KB)	M vH Ch. 4
Jan.18	Nucleic Acids S & F /Intro: Nucleotide Metabolism (KB)	M vH Ch. 22
Jan.21	MLK Jr. HOLIDAY	
Jan.23	Nucleotide Metabolism (KB)	M vH Ch. 22
Jan.25	Nucleotide Metabolism / EXAM REVIEW (KB)	M vH Ch. 22
Jan. 30	EXAM I (KB)	
Feb.1	Nucleotide Metabolism (KB)	M vH Ch. 22
Feb.6	Nucleotide Metabolism/Intro:DNA Metabolism & Function (KB)	M vH Ch. 24, 25
Feb. 8	DNA Metabolism & Function (KB)	M vH Ch. 24, 25
Feb.13	DNA Metabolism & Function (KB)	M vH Ch. 24-25
Feb.15	DNA Metabolism & Function (KB)	M vH Ch. 24-25
Feb.20	Intro: RNA Metabolism & Function/ EXAM REVIEW (KB)	
Feb. 22	EXAM II (KB)	
Feb. 27	RNA Metabolism & Function (KB)	M vH Cht. 26, 28
Feb. 29	RNA Metabolism & Function (KB)	M vH Cht. 26, 28
Mar. 05	RNA Metabolism & Function (KB)	M vH Cht. 26, 28
Mar.07	RNA Metabolism & Function/ EXAM REVIEW (KB)	M vH Ch. 26, 28
Mar.07	Term Paper, due no later than 12:00 Noon	
Mar.10-15	SPRING BREAK	
Mar.19	EXAM Quick Q&A (KB) – Intro: Protein Synthesis (RL)	M vH Cht. 27, 28
Mar.21	HOLIDAY	
Mar.26	EXAM III (KB)	
Mar.28	Protein Synthesis (RL)	M vH Cht. 27, 28
April 02	Protein Synthesis (RL)	M vH Cht. 27, 28
April 04	Protein Synthesis (RL)	M vH Cht. 27, 28
April 09	Protein Synthesis / EXAM REVIEW (RL)	M vH Cht. 27, 28
April 11	EXAM IV (RL)	
April 16	Intro: Macromolecular Drugs/Mol. Medicine- Nucleic Acid Drugs(KB)	Sources TBA
April 18	Recombinant DNA Technology /Gene therapy(KB)	Sources TBA
April 23	Recombinant DNA Technology /Gene therapy(KB)	Sources TBA
April 25	Wrap-up: Course and FINAL EXAM REVIEW (KB/RL)	
April 28	CUMULATIVE FINAL: 9-11am Kerr 1001/2001/ECSU 101	

- The textbook is detailed and often covers material in more depth than is required –the key topics will be covered during lecture/recitation and the Chapter Readings can be best used to supplement this information.
- Recitation schedule TBA

KEY PERSONNEL & CONTACT INFORMATION

A. Faculty

Dr. Ken Bastow (KB), ken_bastow@unc.edu, 6-7633 (Coordinator, Instructor), 322 Beard

Dr. Rihe Liu (RL), rliu@email.unc.edu, 3-3635 (Instructor), 209-A Beard

Mrs Tammie Davis, Tammie_davis@unc.edu, 919-843-2538 (PHCY402R) 204-C Beard

Kassim Traore, ktraore@mail.ecsu.edu (ECSU Faculty Liaison)

KTL Vaughan, ktlv@email.unc.edu (UNC HSL Librarian)

B. PHCY 422 Teaching Assistants

TBA: Note: Not Assigned as of 1-03-08

ACADEMIC RESOURCES

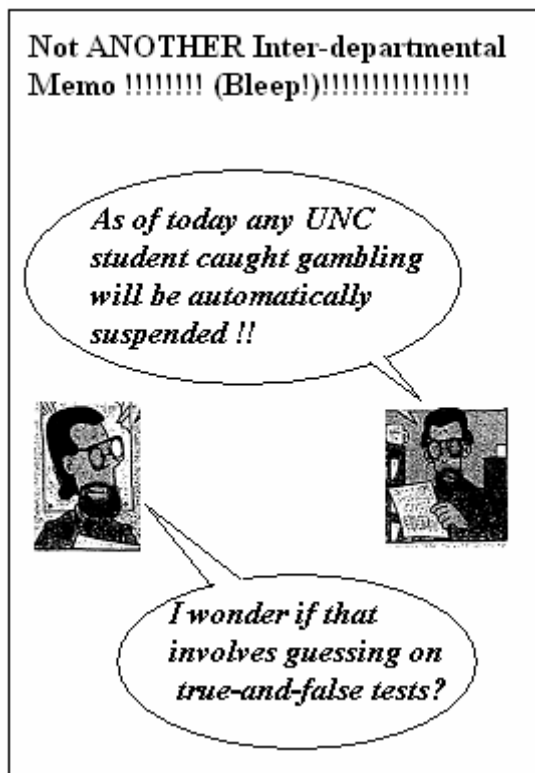
For course content issues and help with lecture material/concepts please contact the relevant instructors or TA's. Office hours will be scheduled and announced early in the semester as will TA recitation assignments. For performance issues/concerns, please contact Dr. Bastow or Kassim Traore (ECSU Cohort) **as early as possible during the semester** so that the need for remediation and tutorial help can be assessed and appropriate intervention can start early in order to maximize benefit.

BLACKBOARD

Key information including course outline, announcements, exam performance, assigned quizzes and lecture slides will be posted in a timely fashion on Blackboard. Announcements of new postings will be made during lecture or via E-mail but **it is ultimately your responsibility to check the site regularly for up-dates and course-sensitive information.**

Overall Learning Objective: To appreciate that biochemistry and allied disciplines are foundational for understanding traditional therapeutics and emerging molecular medicines.

Student Evaluation and Competencies:



(Thankfully!), there are more to the exams than T/F questions but there will likely be some on each exam; one thing is certain though - **you will be challenged continuously during this course to think and apply the information you have learned.**

The following guideline and educational outcomes are applicable to PHCY 422

Current ACPE Accreditation standards (guideline 13.1) states that: *"the system of student evaluation should foster self-initiated learning. Testing procedures should condition students for the integration and application of principles, critical thinking and problem-solving rather than for short-term retention or memorization of specific details or isolated facts"*.

A minimal listing of general Chemistry- and Biochemistry-related competencies can be viewed at the AACP web-site (<http://www.aacp.org>)

Textbook:

The text for PHCY 62 is "Biochemistry" (3rd edition by C.K. Mathews and K.E. van Holde (Benjamin/Cummings Publishing co., 2000). Relevant chapters (assigned on page 3) are supplemental reading that will complement your class notes, recitation handouts (previous mid-term exams and keys if available).

On-Line Resources:

- Electronic Study Guide (M vH).- A great companion to the Textbook for Chapter-related terminology, Outlines, Quizzes etc.
- Molecular Models from Biochemistry at CMU [<http://info.bio.cmu.edu/Courses/BiochemMols/>]. A great site for looking at tRNA structure, Polynucleotide structure, Ribosomes, Elongation factors, restriction enzymes etc., and there are quizzes on identifying nucleotides from structures. Check it out!.
- Multimedia Educational Resource for Learning and Teaching Online: MERLOT. This is a searchable and rich resource that has peer-reviewed course materials and is worth a visit if you are having difficulties or just are looking for a different perspective on PHCY062 subject material or any other for that matter. It is worth a look -go to [<http://www.merlot.org/>]

Quizzes: Several quizzes will be assigned throughout the semester and will be available to you via Blackboard™ once the relevant topics are covered in lecture. You are expected to complete the Quizzes by yourself. Quiz questions are designed to test and supplement your knowledge of course material and although you get no credit for trying them, it will prove to be a useful exercise in preparation for the exams. See the instructor if you have difficulty completing these quizzes or still have difficulty after checking your answers against the postings on Blackboard™ (time will be found to go over more difficult questions during lecture or exam review).

Course Requirements:

(1) Recitation.

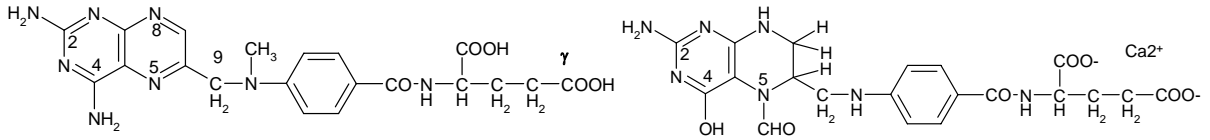
The PHCY 422 recitation sessions are coupled with the PCL course sequence (PHCY 402R: Tammie Davis, Coordinator)-**Recitation is scheduled for Tuesday afternoon 12.30-3.30 p in 3 Lab sections in Kerr 1001/ECSU 101 – Groups will be assigned during the first month of the semester via Skills Lab and will begin sometime in February (TBA).** Presentations assignments are designed to build-on biochemical principles and processes discussed and, or introduced in class. This requirement affords students with a self-directed learning opportunity, strengthens presentation skills and fosters peer-instruction and peer-interaction. Students will learn to apply and integrate biochemical information with therapeutic problems and to communicate with, teach and learn from their peers about drug use and mechanism. Students will present information (about 20 min. duration) and answer questions about an assigned drug, covering both mechanism of action and clinical use. Each student will, with one or two partners, lead one discussion during the course of the semester. Presentations will be graded as **a team-effort** relative to the other teams presenting the same week, therefore **it is very important that students do not attend presentations in other sections without prior permission from Dr. Bastow. TA's will be primarily responsible for grading biochemical aspects of the recitation presentations.** The performance criteria for the PHCY 422 evaluation will include organization, integration, accuracy, clarity, originality and completeness of the information presented *about biochemical mechanism of action* and the ability **of teams** to answer questions. Specific feedback on performance can be obtained from the assigned TA's and/or Drs. Bastow and Liu upon request once the graded evaluation is posted. Tammie Davis and/or a "Skills-Lab" TA will evaluate and examine the team on clinical aspects of the presentation and assess general presentation skills. Feedback on these aspects is typically given immediately or shortly after each session. **Students who are not presenting will be expected to actively participate in the discussions during recitation.** Although a grade for this participation will not be assigned, students who actively participate throughout the semester will be noted and their efforts will be taken into account when considering borderline final grade assignments. Recitation schedule, student pairings and drug topics will be coordinated through PCL and will be finalized as soon as possible once the semester begins. Student presentations typically commence early in February and run throughout the rest of the semester.

The assigned drugs scheduled for Spring 2008 as well as general guidelines for the PHCY 422 portion are covered below followed by the grading/evaluation sheet used.

► Recitation Drugs:

Student presentation of mechanism of action for some or all of the drugs shown below will complement and supplement the biochemical principles introduced during lecture. **Each presentation should cover drug structure as it pertains to biochemical mechanism of action as well as key aspects of clinical use.** Listed under each drug topic are key points that must either be covered during the presentation or the group must understand and be prepared to answer questions about. The Course Textbook as well as on-line resources like Clinical Pharmacology, Facts and Comparisons and Drug Information Handbook are useful resources for places to start your research but **you will also need to read the primary (scientific) literature to get a fuller understanding and gain the level of competency we expect of you for this course.**

Methotrexate (MTX) - Folic acid analog



Folate coenzymes ([overview](#) of 1-carbon transfer RXN's)

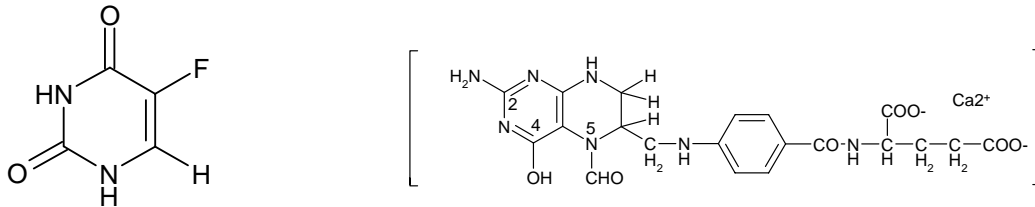
The folate cycle

De novo Thymidylate synthesis and oxidation of folate

Mechanism of action (MOA)

Polyglutamoylation-significance? /High dose therapy (HDMTX) and basis for Leucovorin rescue

5-Fluorouracil (FU) - Base analog



Anabolism of FU ([overview](#) of pathways)

Active [metabolites](#) (brief overview of RNA and DNA-directed activities)

Thymidylate synthase and primary MOA (“ternary complex”)

Modulation by Leucovorin

Catabolism of FU ([brief](#) overview of clinical significance)

Etoposide (VP-16) -analog of podophyllotoxin, plant alkaloid

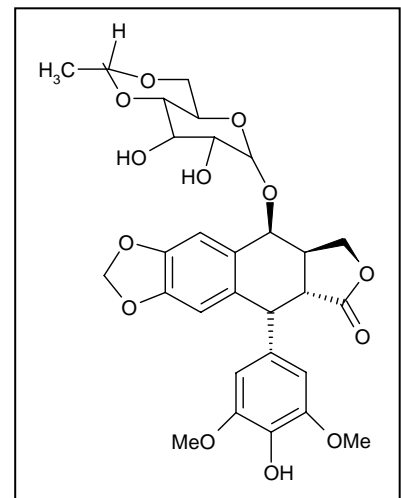
Epipodophyllotoxins (source and important structural features)

Overview of (human) DNA topology

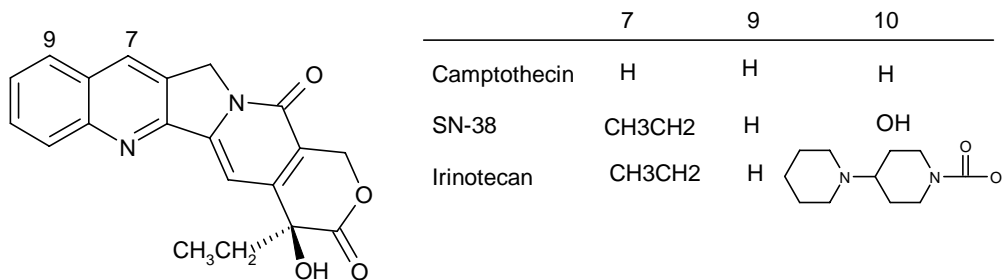
Human DNA topoisomerase II alpha (general structure and function)

MOA (“cleavable complex” / enzyme poisoning).

Mechanisms of resistance

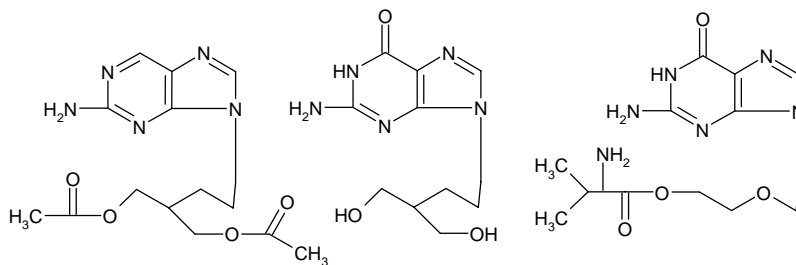


Irinotecan - Analog of Camptothecin, plant alkaloid



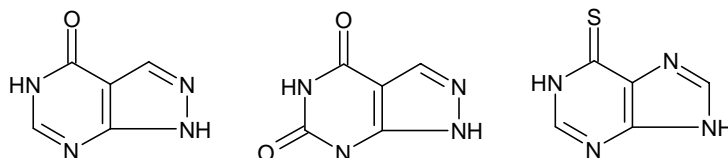
Camptothecins (source and important structural features)
 Human DNA topoisomerase I (general structure and function)
 Prodrug-activation
 MOA (“cleavable complex”, enzyme poisoning).
 S-phase specificity -“fork-collision” model

Famciclovir (FCV) - Acyclic nucleoside analog



Overview of of herpesvirus replication (relevant aspects)
 Penciclovir (PCV)
 Prodrug concept
 Activation of FCV to PCV
 Active metabolite and mechanism of action
 Valaciclovir (briefly compare and contrast).

Allopurinol - Base analog



Overview of purine metabolism

Importance in diseases (hyperuricemia/Gout) and cancer chemotherapy

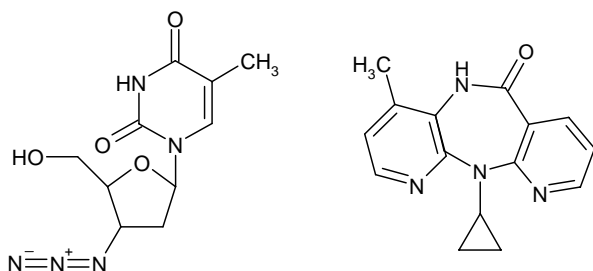
Biochemical and nutritional basis of hyperuricemia

Allopurinol/Alloxanthine (Oxypurinol)-MOA

6-Mercaptopurine (brief overview)

Allopurinol in ALL maintenance therapy and drug interaction with 6-MP.

AZT - Nucleoside analog and Nevirapine (NNRTI)



Overview of HIV replication (relevant aspects)

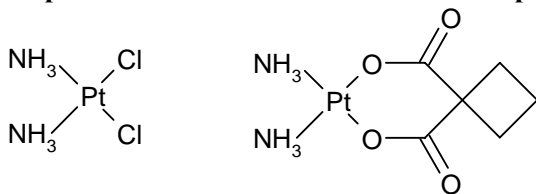
Activation of AZT

Active metabolite and MOA

Nevirapine (NNRTI; compare and contrast)

HAART (Principle successes and failures)

Cisplatin - Platinum II coordination complex, DNA-binding drug



Importance of *Cis* vs. *Trans*

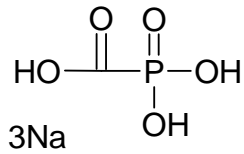
Intracellular activation via aquation

Displacement reactions with nucleophiles (focus on DNA-related adducts)

Biological consequences of DNA modification (overview)

Carboplatin (briefly compare & contrast)

Foscavir –Pyrophosphate (PPi) Analog



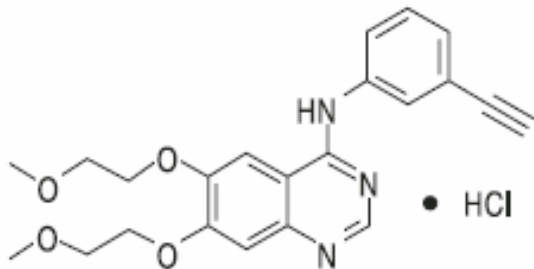
Overview of viral replication (focus on herpesviruses)

Role of PPi during polynucleotide biosynthesis

Mechanism of action – non-competitive inhibition with respect to dNTP's

Compare and contrast to nucleoside analogs

Tarceva –Inhibitor of receptor tyrosine kinase



What is NSCLC?

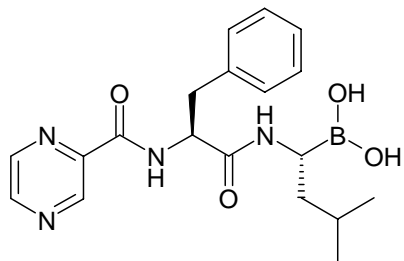
EFG, EGFR and receptor activation mechanism

Mechanism and consequences of inhibition

Other related drugs

Current Status and developments

Velcade – Proteasome Inhibitor

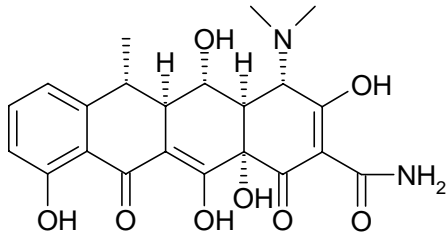


What is Multiple myeloma?

The Proteasome –ubiquitination pathway

Mechanism and consequences of proteasome inhibition (focus on NF-kappaB)

Doxycycline – Antibiotic (Ribosome inhibitor)

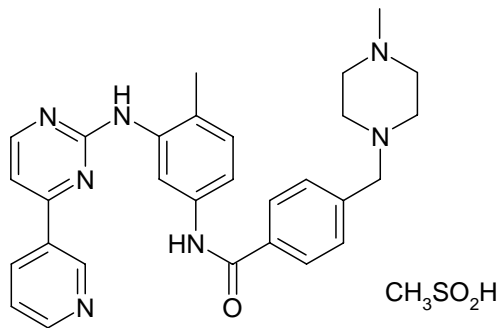


Bacterial ribosome and protein synthesis overview

Target and mode/mechanism of inhibition

Mechanisms of resistance

Gleevec – PTK Inhibitor



What is CML and GIST?

The formation of BCR-Abl oncoprotein and role in abnormal signal transduction

Mechanisms of inhibition and resistance.

Vitravine –PS-ODN Antiviral

What is an antisense drug?

HCMV Retinitis

Chemical structure and target

Proposed mechanism of action

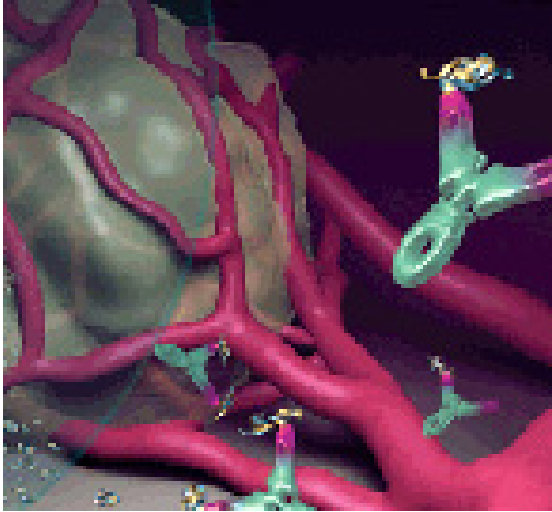
Pulmozyme –Recombinant hu DN^{ase} I - Mucolytic

What is cystic fibrosis?

Mode of action of pulmozyme.

Focus on development and key principles of cloning strategy (see Dr Bastow).

Avastin –Recombinant humanized monoclonal VEGF antibody



Angiogenic factors and tumor angiogenesis
Colorectal cancer, NSCLC, and anti-angiogenic therapy
Mechanism of action
Antibody technology: advantages and challenges

Filgrastim – Recombinant GCMSE -Cytokine

What is neutropenia?
Myeloid differentiation -overview
Cytokines and basic signaling mechanism.
Focus on key principles of cloning strategy (see Dr Bastow).

PHCY 422 (402R) Spring 2008
Student Seminar Evaluation and Comments Sheet

Student Presenters:

Date:

Seminar Title (Assigned Drug):

You are Faculty____, TA____

Please rate and add comments (5 = excellent, 4 = good, 3 = average, 2 = inadequate, 1 = poor).

I. Visual and other materials

II-1. The quality of slides	5	4	3	2	1
II-2. The clarity of slides	5	4	3	2	1
II-3. The clarity of the handout	5	4	3	2	1

II. Knowledge of the material presented

III-1. The ability to understand questions	5	4	3	2	1
III-2. The ability to answer questions	5	4	3	2	1
III-3. The ability to explain clearly new concepts and approaches	5	4	3	2	1
III-4. The ability to integrate drug mechanism with lecture material	5	4	3	2	1
III-5. Interest stimulated by the presentation	5	4	3	2	1

III. Presentation Style

IV-1. The confidence of the speakers	5	4	3	2	1
IV-2. The excitement of the speakers	5	4	3	2	1
IV-3. The pace of the talk	5	4	3	2	1
IV-4. The length of the talk	5	4	3	2	1
IV-5. Contact with the audience during the presentation	5	4	3	2	1
IV-6. The overall organization of the presentation	5	4	3	2	1

VII. Specific Comments: Please elaborate on any item under Section II

Circle your opinion for the most appropriate grade for this presentation

High pass (≥ 4.5)

Pass (≥ 3.5)

Low pass (≥ 2.5)

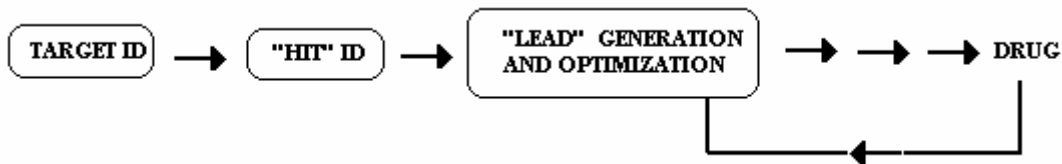
Deficient (< 2.5)

Course Requirements, cont.

(2) Paper Assignment:

The written requirement affords students a self-initiated learning opportunity and examines abilities to research scientific/technical information, understand the information and present it in a clear, accurate and concise fashion. The paper, covering an aspect of **modern antiviral drug development will be no more than three typewritten pages in length (12-pitch typeface, double spaced, on 8.5- by 11- inch paper with margins on all sides no less than one-half inch), is due by March 7th, 12.00 Noon., and should be given directly to Dr. Bastow, unless instructed otherwise.** Diagrams are permitted and will not be included in the page limit requirement. Students are expected to submit an original paper that is a product of their individual effort. There is no specific format required for the paper however **complete references, including authors, title and citation should be included but kept to a minimum. Papers will be graded on the basis of content, originality and clarity.** Specific feedback will be provided in writing and can be elaborated verbally and discussed upon request. An outline of the general topic of the paper and guidelines to help get you started follow:

PAPER ASSIGNMENT for PHCY 422, Spring 2008



Tasks:

1. Identify a modern antiviral drug **either a candidate undergoing development or an agent in clinical use.**
2. Research it's development and mechanism of action
3. Write paper to illustrate aspects of the discovery and development process [remember, you must follow the editorial requirements provided in the first paragraph of this subsection].

Depending on the drug you choose, here are some general questions you might want to address:

What is the target and **why** is it appropriate for antiviral drug development?

How was the "hit" (a non-optimized drug candidate) identified? (ie. screening, structure-based design, other computational methods, historical precedent etc).

Did the lead/drug have acceptable pharmaceutical properties? If not, how was it changed and what was the rationale (ie. optimization, prod-drug development etc)?

You should also include:

Information about the virus infection your drug is used to treat or is being developed for by reviewing the viral replication cycle and the importance of the target.

Mechanism of action (knowledge about this is implicit in the discovery process).

Clinical trial data (only if it is directly relevant to the development process).

Some useful starting resources for you are:

1. Information from the manufacturer (not always).
2. Reviews in such Journals as: *Antiviral Chemistry and Chemotherapy*, *Antimicrobial Agents and Chemotherapy*, *Antiviral Research*, *Current Drug Targets (Infectious Diseases)*; *Nature Drug Discovery* etc.

Note: Some antiviral drugs are better than others to illustrate the modern approach to antiviral drug. If you are unsure about whether the drug you ultimately select is suitable, please check with Dr. Bastow before proceeding.

Advice and help with search strategies: contact KTL Vaughan, Librarian for Bioinformatics & Pharmacy Adjunct Clinical Asst Prof of Pharmacy UNC-CH Health Sciences Library, ktlv@email.unc.edu

Note: A specific example will be covered in class

Exam Policy & Grade Assignment:

The final grade in the course will be determined according to the system below. The final exam will be cumulative. No makeup exams will be given. If a student misses one of the mid-semester exams, the weight of the final exam in determining the final grade will be increased accordingly. This adjustment will be allowed only in the case of students having a valid written excuse for absence from a midterm exam.

Mid-semester exams (4 total)	600 pts
Recitation Presentation	150 pts
Term Paper	100 pts
Cumulative Final Exam	150 pts
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Total	1000 pts.

Grades will be assigned based on how many points you earn according to the following distribution:

900-1000	A
800-899	B
700-799	C
<699	F

Other Important Information

► **Inclement Weather:** late Winter/early Spring at UNC has been known to bring freezing rain, downed power-lines etc, and your instructors neighborhood sometimes becomes impassible or UNC may even close (less likely though!). In the case of inclement weather, you should call the University's adverse weather hotline at 919-843-1234 to determine the operating status of the University. During adverse weather incidents, status updates will also be communicated on the University's homepage at <http://www.unc.edu>. If UNC is open but the class will have to be cancelled, you will be notified via Blackboard™ as soon as possible. You should also call UNC student services (966-9429) to listen to voice mail message about the status of PHCY 422. In either event, you are expected to use the time wisely for self-study of the scheduled lecture material/topics using the power point slides, assigned quizzes and textbook as study guides. Depending on the circumstances, a make-up class will be scheduled and/or additional homework may be assigned

► **Keyword Lists:** part of the challenge to learning a lot of the course material is becoming familiar with the nomenclature and terminology used. To help you with this task, lists of key words/terminology's will be provided and reviewed as appropriate.

► **Students re-taking the Course:** These individuals can opt to place out of recitation and paper course requirements and have performance on examinations weighted more for the final grade. Those who choose this option must inform Dr. Bastow of their intent before the first exam is administered.

► **Course & Instructor Evaluation:** You will be given the opportunity to comment on your experiences in class and your perceptions of the course at the end of the semester and before the final exam. Standardized instruments for evaluation will be used and you are encouraged to elaborate on any aspect in writing. Student input is welcomed and is oftentimes a positive force in course development.

► **Honor Code Violations:** If you suspect individuals of honor code violations, please bring your concerns to the course Coordinator first. If your concerns are not dealt with in a satisfactory manner, you should contact the Pharmacy attorney general at voicemail: 843-4699 or email: PharmacyAttorneyGeneral@unc.edu.

Honor Code:

It shall be the responsibility of every student at the University of North Carolina at Chapel Hill to obey and support the enforcement of the Honor Code, which prohibits lying, cheating and stealing when these actions involve academic processes or university, student or academic personnel acting in an official capacity