

**Medicinal Agents III – Phar 6156**  
**CHEMOTHERAPEUTIC AGENTS**

Fall Semester, 2007 7-135 WDH 1:25-2:15 MWThF

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**Course Objectives:**

The ultimate goal of all pharmacy courses and experiences that relate to chemotherapy is to develop the student's ability to select the proper chemotherapeutic for a patient with cancer or infectious disease. This will require the student to integrate all aspects of their pharmacy education.

After successful completion of MChm 5350, student should be able to perform the following tasks:

1. Apply structure-activity relationships, mechanism of action, and modes of resistance for each chemotherapeutic agent or class covered to the care of patients with infectious disease or cancer. This will require a basic understanding of the underlying principles of biochemistry, immunology, and microbiology.
2. Retrieve and evaluate information on the cause, nature, and problems associated with cancer and infectious diseases and be able to correlate structure with function for each agent..

3. Describe the spectrum of activity and general uses for each chemotherapeutic and antiviral agent. Students should be able to select an agent for a given viral infection and explain the pharmacology and mechanism of action of anticancer agents.

4. Describe the antimicrobial spectrum of activity, side effects, drug interactions, and general uses for each antimicrobial agent. For the best understanding of this material, students should have a working knowledge of medical microbiology.

Note: Treatment of specific cancers will be covered in Oncology. Treatment of specific infectious diseases will be covered more in depth in Infectious Diseases section of Pharmacotherapy IV. Application to individual patients will be demonstrated during externships and clinical rotations.

5. Be familiar with the various products and formulations available for each drug and their relative costs, and be able to recommend a product that is most suitable for a given clinical infection, esp. community-acquired infections such as pneumonia, sinusitis, urinary tract infections, otitis media, pharyngitis, vaginal infections, and sexually transmitted infections

### **Course Policy:**

1. Shortly after the conclusion of a designated section, an examination will be given (Unit Exam). Unit examination typically take around 90 minutes (into the noon hour- so plan accordingly). Four examinations will be given over the designated sections. The minimum passing grade is normally considered to be 60%. Scores less than 60% **will count** in your final total (no make-up will be given).
2. An in-class treatment plan for a patient will be given to cover material presented on the Pharmacotherapy of various community acquired infections (otitis media, community acquired pneumonia, Pharyngitis, Sinusitis, community acquired urinary tract infections). This will be an open-note exam. You will be presented with a case when you arrive and will have 10 minutes to read the case. The class will be allowed 10 minutes (as a group) to ask questions or either the patient, caregiver, or prescriber. Thirty minutes will be allowed to complete a written treatment plan that will be given to the patient.
3. Make-up exams will only be given to those students who have legitimate excuses and who have prior permission. Legitimate excuses include verified illness, family emergencies, U.S. military service, and University sponsored events. Subsequent written verification of illness by a physician is required. Acceptability of excuses for other reasons will be determined by the unit examination director. In such cases, the student may take the makeup exam during finals week or by arrangement with the unit director. Students with a disability should contact the course director in the first week of class to arrange for any accommodations.
4. If a student wishes to have an examination re-graded, s/he must arrange for it within one week after the graded exam is returned.
5. The final letter grade given to a student who has passed all unit exams (90% of total) and completed a term paper (10% of total) will be based on the student's total score. Normally, a total score of 93% or more is needed in order to receive a grade of A, 90-92 for an A-, 87-89 for a B+, 83-86 for a B, 80-82 for a B-, 77-79 for a C+, 73-76 for a C, 70-72 for C-, and 60-69% is needed for a D.
6. Incidents of academic misconduct, such as cheating or plagiarism, will be reported to the Honor Council for disciplinary action.
7. The Term Paper is to consist of a three- page summary (not including references) of a specific problem in antimicrobial or antiviral resistance to be selected from a list of potential topics. The due date for submission of this paper will due in the next to the last week of the semester and represents 5% of your final grade (see accompanying instructions).

### **Content and Nature of Examinations:**

Examination questions may pertain to material presented in lectures, assigned readings, and handout material.

Examination questions normally consist of short answer/essay questions in a case-study format mixed with

some matching and fill-in-the-blank questions. Old exams are not available and use of fraudulent copies or compilations is considered a violation of the honor code.

### **Course Grades:**

In determining the final course grade, five unit exams (one during finals week) and a term paper will be valued as follows:

Examination I (Antivirals)	20%
Examination II (Anticancer- Xing)	10%
Examination III (Anticancer –Xing)	15%
Treatment Plan	5%
Examination IV (Antimicrobials I)	20%
Term Paper	5%
Final Exam (Antimicrobials II)	<u>25%</u>
	100%

**Note: All exams (except Examination II and the Treatment Plan) are 2 hour exams starting at 12:15!**

### **Assumed Entry Knowledge:**

In order to take MChm 5350 the student is assumed to have:

- A. Completed a college-level course in physiology/pathology (Phsl 6061)
- B. Completed Biochemistry of Medicinals I and II (Phar 6151) or equivalent.
- C. Completed a college-level course in Immunology (Phar 6153) or equivalent.
- D. Completed a college-level course in microbiology and Phar 6141 (Medical Microbiology and Immunizations) or an equivalent course in Medical Microbiology. **Note: An exam on Medical Microbiology and Virology will be given during the first week of class to insure competency of this material.**

### **Course Material:**

Course handouts for the Chemotherapeutic Agents and the Antimicrobial agents will be available through the College Board and are required. Selected required readings from: The Medical Letter and other sources will also be available.

It is highly recommended that the students have access to an up-to-date text on Medical Microbiology. One alternative is to use an on-line Medical Microbiology text by Samuel Baron. The web-site for the table of contents with access to the subsequent chapters is <http://www.md.huji.ac.il/microbiology/book>. The book is arranged by organisms and each chapter begins with a short summary entitled General Concepts followed by a much more detailed section. For this class, the general concepts will suffice. You can purchase the book on-line as well. A relatively inexpensive (~\$40) recommended paperback text is Medical Microbiology & Immunology, 8th edition by Warren Levinson, Lange Medical Books/McGraw Hill, New York, 2004. This book is widely used by medical students for board review, is clearly written, and has a succinct 42 page summary of medically important organisms along with case studies and review questions. Students will be assigned general readings on various organisms throughout the quarter.

In addition to the notes, student may wish to consult a general text in pharmacology: "The Pharmacological Basis of Therapeutics." 11th Edition, Eds. A. Gilman, L. Goodman, T. Rall and F. Murad, 2005 has good information. Pharmacotherapy, may also be consulted for lectures dealing with disease states.

Phar 6156 Medicinal Agents III CLASS SCHEDULE  
 Fall Semester, 2007 7-135 WDH 1:25 -2:15 MWThF

<b>Lecture</b>	<b>Date</b>	<b>Topic</b>	<b>Instructor</b>
1	9/5 (W)	Orientation/Medical Microbiology	Rommel
2	9/6 (Th)	Medical Microbiology	Rommel
	9/7 (F)	DULUTH CELEBRATION	
3	9/10 (M)	Intro to Antiviral Chemotherapy/COMPETENCY EXAM	Rommel
4	9/7 makeup	Antiviral Agents for Herpes viruses	Rommel
5	9/12 (W)	Anti-Herpes/Anti-HIV nucleosides	Rommel
6	9/13 (Th)	Anti-HIV Nucleosides/ Anti-hepatitis Nucleosides	Rommel
7	9/14 (F)	Non-nucleoside RTIs/HIV Protease Inhibitors	Wynn Vezina
8	9/17 (M)	Fusion Inhibitors/Integrase inhibitors	Rommel
9	9/19 (W)	Anti-influenza agents/Neuraminidase inhibitors	Rommel
10	9/20 (Th)	Etiology of Cancer	Xing
11	9/21 (F)	Side Effects of Antiretroviral Therapy	Wynn Vezina
12	9/24 (M)	Molecular Biology of Cancer	Xing
13	9/26 (W)	Molecular Biology of Cancer	Xing
14	9/27 (Th)	DNA-Interactive Agents	Xing
15	9/28 (F)	<b>EXAMINATION I (12:20-2:15PM)</b>	Vezina/Rommel
16	10/1 (M)	DNA-Interactive Agents	Xing
17	10/3 (W)	Antimetabolites	Xing
18	10/4 (Th)	Antimetabolites	Xing
19	10/5 (F)	Tubulin Binding Agents	Xing
20	10/8 (M)	Hormonal Therapy	Xing
21	10/10 (W)	Hormonal Therapy	Xing
22	10/11 (Th)	Differentiation Agents	Xing

23	10/12 (F)	<b>EXAMINATION II/</b> Angiogenesis Inhibitors <b>(12:20-2:15)</b>	Xing
24	10/15 (M)	Protein Processing Inhibitors	Xing
25	10/17 (W)	Protein Processing Inhibitors	Xing
26	10/18 & 19	BREAK	
27	10/22 (M)	Miscellaneous Anticancer Agents	Xing
28	10/24 (W)	Introduction to Antimicrobial Therapy	Rommel
29	10/25 (Th)	Mechanisms of Action	Rommel
30	10/26 (F)	<b>EXAMINATION III (12:20-2:15PM)</b>	Xing
31	10/29 (M)	Mechanisms of Resistance/Host Factors	Rommel
32	10/31 (W)	Penicillins/Pencillinase-Resistant Penicillins	Rommel
33	11/1 (Th)	Aminopenicillins/Extended- Spectrum Penicillins	Rommel
34	11/2 (F)	Cephalosporins	Rommel
35	11/5 (M)	2 <sup>nd</sup> & 3 <sup>rd</sup> Generation Cephalosporins	Rommel
35	11/7 (W)	Beta-Lactam Hypersensitivity Reactions	Rommel
34	11/8 (Th)	Other Beta-Lactam Antibiotics	Rommel
35	11/9 (F)	Macrolides and Ketolides	Rommel
36	11/12 (M)	Quinolones	Rommel
37	11/14 (W)	Sulfonamides/Trimethoprim/Nitrofurantoin	Sturla
38	11/15 (Th)	Other Urinary Tract Antiinfectives	Sturla
39	11/16 (F)	<b>EXAMINATION IV (12:20-2:15PM)</b>	Rommel
40	11/19 (M)	Tetracyclines – <i>Breeze on STDs</i>	Sturla
41	11/21 (W)	Sinusitis – <i>Breeze on Pharyngitis</i>	Rommel
42	11/26 (M)	Vancomycin/Synercid/Linezolid/Daptomycin	Peterson
43	11/28 (W)	Community-Acquired Urinary Tract Infections	Rommel
44	11/29 (Th)	Otitis Media	Peterson
45	11/30 (F)	Aminoglycosides/Colistin	Sturla
46	12/3 (M)	Clindamycin/Bacitracin/Metronidazole – <i>Breeze on Vaginosis</i>	Sturla
47	12/5 (W)	Community-Acquired Pneumonia	Guay

48	12/6 (Th)	Antiprotozoal Agents	Sturla
49	12/7 (F)	IN-CLASS TREATMENT PLAN/Anthelmintics (12:20-2:15)	Remmel/Sturla
50	12/10 (M)	Antimycobacterials/Tuberculosis	Sturla
51	12/12 (W)	Antimalarials	Sturla
52	12/13 (Th)	Systemic Antifungal Agents/Amphotericin/Echinocandins	Peterson
53	12/14 (F)	Azoles//Topical Antifungals – <i>Breeze on Candidal vaginitis</i>	Peterson

Finals Week            FINAL EXAMINATION  
 Remmel/Sturla

### Required Breeze Presentations

There are several required breeze presentations (viewable in Web CT) on common ambulatory infections. These should be viewed prior to the in-class treatment plan on December 8<sup>th</sup>. The required modules are as follows:

- 1) Pharyngitis (Strep throat)
- 2) Sexually Transmitted Infections (STDs)
- 3) Vaginal Yeast Infections (Candidiasis)
- 4) Bacterial Vaginosis

These modules are designed to augment your knowledge of common conditions that are encountered in community practice.

### PROCEDURE FOR WRITING THE PAPER ON ANTIMICROBIAL or ANTITUMOR RESISTANCE

1. Select a topic of mutual interest to you or your partner. Do this as early as possible!

e.g. Resistance to Vancomycin in Methicillin-resistant *Staphylococcus aureus*

2. Do a computer search. It is the fastest and easiest way to get references on your topic. A standard search on Ovid MedLine at [www.biomedsearch.lib.umn.edu/ovidweb/ovidweb.cgi](http://www.biomedsearch.lib.umn.edu/ovidweb/ovidweb.cgi) from 2000 to the present is a good way to start. You will need to combine terms to search successfully with Ovid/Medline searches through the library.
3. You may also use PubMed at <http://www4.ncbi.nlm.nih.gov/PubMed/> which allows you to retrieve related articles. PubMed has a very useful feature that will allow you to select “Related Articles” that can expand your search (both forward and backward in time). Many articles are now retrievable electronically, but you may have to go to the library for other articles.
4. Meet with your partner and outline a plan of action for the paper. For this assignment, your group (2 students per group) will be writing a three page paper on a specific problem in antimicrobial resistance OR resistance to anti-cancer chemotherapy. Assume that the audience for your paper is a physician with a good working knowledge of infectious disease or cancer. In the paper you should provide a succinct summary of the problem (including epidemiological data), the mechanism(s) of

the resistance, and a simple guideline as to how to treat patients harboring resistant organisms or tumors and how to prevent the spread of the resistance. The information should be up-to-date and directly relevant to therapy. **A web-based paper is unacceptable. Only peer reviewed literature or information from the CDC & Minn. Dept. of Health will be accepted.**

5. Obtain a complete list of references. Your charge is to find the most recent information for your specific topic on antimicrobial or antitumor resistance. This may include papers on both humans and animals or in vitro studies. Note: references before 1998 regarding epidemiology and treatment will be of little use since the levels of resistance change so rapidly. Several techniques for compiling a complete list of references on your topic are:
  - i. Computer search (Minnesota Medline, OVID, or PubMed - see above)
  - ii. Search of recent or upcoming references (Current Contents or PreMedline)
  - iii. References cited in secondary references (Books, review articles)
  - iv. CDC and Minnesota Department of Health (for survey data)

On-line computer searches with either Medline or PubMed are the most effective means of obtaining key primary references. **It is expected that for each topic, you should be able to reference a minimum of 10 primary or secondary references. Papers missing key articles or having insufficient references will receive a low score.**

6. COPY and read the primary references. You must read the articles completely and not just use the abstracts, because you will need to critically evaluate the data. Review articles will be valuable in this subject area, but the most current information will be in the primary references. (Most reviews are at least one or two years behind the current literature.) Most of your articles will be in the journals listed below.

To find the most recent information, you can use the index in the journals at the end of each volume, usually the December issue or browse the table of contents on-line. Computer searches of Current Contents or PreMedline are also useful to obtain very recent references.

The most important journals for information on resistance to cancer chemotherapy are the following:

*Annals of Oncology*  
*Anticancer Research*  
*British Journal of Cancer*  
*Cancer*  
*Cancer Cell*  
*Cancer Chemotherapy and Pharmacology*  
*Cancer Research*  
*Cancer Treatment Reports*  
*Clinical Cancer Research*  
*European Journal of Cancer*  
*International Journal of Cancer*  
*Journal of the National Cancer Institute*  
*Journal of Cancer Research and Clinical Oncology*  
*Journal of Clinical Oncology*  
*Lancet Oncology*  
*Nature Reviews of Cancer*  
*Oncology*

The website, [www.clinicaltrials.gov](http://www.clinicaltrials.gov) and [www.cancer.gov](http://www.cancer.gov), can be useful to find information about ongoing Phase I and II clinical trials in cancer. To limit PubMed searches to a cancer subset, go to <http://www.cancer.gov/search/pubmed/>

The most important journals for information on antiviral and antimicrobial resistance are the following:

*AIDS*  
*Antimicrobial Agents and Chemotherapy*  
*Chemotherapy*  
*Clinical Infectious Disease (formerly Reviews in Infectious Disease)*  
*Clinical Microbiological Reviews*  
*Emerging Infectious Diseases (on CDC Website)*  
*Infection and Immunity*  
*Journal of Antimicrobial Chemotherapy*  
*Journal of Infectious Diseases*  
*Microbial Drug Resistance*  
*Morbidity and Mortality Weekly Report (on CDC web site)*  
*Pediatric Infectious Diseases*  
*Sexually Transmitted Diseases*

Some specialty journals describing resistance to parasites, e.g., *Plasmodium falciparum* (the causative agent of malaria) are listed below:

*Annals of Tropical Medicine and Parasitology*  
*Journal of Tropical Medicine and Hygiene*  
*Parasitology*  
*Transactions of the Royal Society of Tropical Medicine and Hygiene*  
*Tropical Medicine and Parasitology*

This method of searching will give you the 2002/2003 references and the most recent information, but is time-consuming.

6. Obtain information on the pharmacology of the drug. This can be found in standard reference books or your class notes. Several examples are listed below. There is no need to be overly detailed. You may need to find some information on the basic disposition and pharmacokinetics of your drug in order to treat resistant infections or cancers appropriately.

*Facts and Comparisons*

*American Hospital Formulary Service*

*The Pharmacological Basis of Therapeutics, Goodman and Gilman, eds.*

7. Follow the outline below in preparing your initial draft. Be sure to include a list of references in numerical order as presented in the paper.
  - I. Introduction and Statement of the Problem
    - A. Introduction on the pathogenic organism or cancer and its importance
    - B. Current data on rates of resistance
    - C. Problems caused by resistance
  - II. Mechanism of Resistance
  - III. Treatment Strategies in Patients with Resistance
  - IV. Methods to Prevent Resistance
  - V. Bibliography

The paper should be no longer than three pages (single spaced) excluding references.

8. Use the format for references found in Clinical Pharmacology and Therapeutics. You should follow the “Uniform Requirements for Manuscripts Submitted in Biomedical Journals” (Ann. Int. Med. 1997; 126;36-47). An example of this Vancouver reference style for journal articles is:

1. Lam K. Tsang OT. Yung RW. Lau KK. Japanese encephalitis in Hong Kong. *Hong Kong Med. J.* 11(3):182-8, 2005.

2. An example of the reference style for chapters in books is:

Romero JR and Newland JG, “Enteroviruses”. In: Antimicrobial Therapy and Vaccines. Volume I: Microbes, 2<sup>nd</sup> ed.. Yu VL, Weer R, Raoult D, eds; Apple Trees Productions, LLC, New York, 2005; pp. 1167-1176

3. For website citations an example from the CDC would be:

Centers for Disease Control and Prevention. Division for Vector-Borne Infectious Diseases. “Japanese Encephalitis Fact Sheet” Nov. 10, 2003 <http://www.cdc.gov/ncidod/dvbid/jencephalitis/facts.htm> (Accessed 10/24/06).

For some websites, there may be an author and a posting date.

Note: **Use of et al. is unacceptable.** If there are six or fewer authors, list all of them. If there are more than seven authors, list the names of the first six authors followed by et al. References are numbered in the order of appearance. Reference numbers may used more than once (do not use Ibid.)

9. Prepare an initial draft, make revisions, and carefully proofread the final copy. Proper grammar and spelling are part of the grading criteria. Complete your initial draft one week before the due date.
10. Plagiarism will not be tolerated. Examples of plagiarism include: copying sentences or sections “word-for-word” from a paper or website without the use of quotations, lack of an accompanying citation (reference number) for a stated fact, use of a previous student’s paper on the same topic, and placing reference numbers only at the end of paragraphs or at the end of the paper. Incidences of blatant plagiarism will be reported to the Honor Council.

## **Cancer Drug Resistance**

### **Suggested Topics for Phar 6156 Paper**

1. Resistance to Gleevec<sup>®</sup> (imatinib, STI571)
2. Multidrug-resistance P-glycoprotein (MDR Pgp) and resistance to *Vinca* alkaloids or paclitaxel
3. Increased thymidylate synthase activity and resistance to 5-FU.
4. O<sup>6</sup>-alkylguanine-alkyltransferase (O<sup>6</sup>-AT) and resistance towards alkylating agents.
5. Glutathione (GSH) and GSH S-transferases in resistance towards alkylating agents.
6. An investigational nitrogen mustard called TLK286 (TER286) was briefly mentioned in class. Explain why its unique bioactivation makes TLK286 potentially of great value in treating cancers resistant to other alkylating agents.
7. Mismatch repair (MMR) system and cisplatin resistance.
8. Tamoxifen-resistant breast cancer
8. Decreased topoisomerase I expression and resistance to camptothecin analogs (irinotecan/topotecan)
9. Doxorubicin (Adriamycin resistance) in prostate cancer
10. Resistance to Herceptin<sup>®</sup> (trastuzumab)

### **Suggested Topics for Term Paper on Antimicrobial Resistance**

Resistance to vancomycin in Methicillin-resistant *Staphylococcus aureus*

Linezolid Resistance in Methicillin-resistant *Staphylococcus aureus*

Trimethoprim/sulfamethoxazole resistance to community-acquired Methicillin-Resistant *Staphylococcus aureus* (CA-MRSA)

Resistance to clindamycin in community-acquired methicillin-resistat *Staph. aureus* (CA-MRSA)

Clindamycin resistance in Group B streptococci

Erythromycin resistance in Group B streptococci

*Neisseria gonorrhoeae* resistance to Ciprofloxacin (fluoroquinolones)

*Neisseria gonorrhoeae* resistance to Ceftriaxone or Cefixime

Ampicillin/Amoxicillin resistance to beta-lactamase negative *Haemophilus influenzae* (BLNAR)

Mefloquine resistance in *Plasmodium falciparum*

Resistance of *Mycobacterium tuberculosis* to pyrazinamide

Resistance of *Mycobacterium tuberculosis* to ethambutol

Resistance of *Mycobacterium avium* complex (MAC) to clarithromycin

Resistance of *Enterobacter* to third-generation cephalosporins and imipenem

Aminoglycoside resistance in *Enterococcus* sp.

Linezolid Resistance in *Enterococcus* sp.

Resistance of *Helicobacter pylori* to clarithromycin

Resistance of HIV to abacavir (carbovir triphosphate)

Resistance of HIV to atazanavir

Resistance of HIV to lopinavir/ritonavir

Resistance of HIV to efavirenz

Resistance of HIV to enfuvirtide (Fuzeon)

Resistance of CMV to ganciclovir

Resistance of *Haemophilus influenzae* to cefuroxime

Resistance of *Pseudomonas* sp. to piperacillin

Resistance of *Pseudomonas* sp. to ceftazidime

Resistance of *Pseudomonas* sp. to carbapenems (imipenem and meropenem)

Resistance of *Acinetobacter* to 3rd generation cephalosporins

Resistance of *Streptococcus pneumoniae* to macrolides (azithromycin, clarithromycin)

Resistance of *Streptococcus pneumoniae* to levofloxacin

Clindamycin resistance in *Streptococcus pneumoniae*

Resistance of *Candida albicans* to fluconazole

Resistance of *Aspergillus* sp. to itraconazole

Resistance of cytomegalovirus to ganciclovir

Resistance of Hepatitis B virus to lamivudine (3TC)

If you wish to choose another topic not listed above, please consult Professors Remmel or Xing