SYLLABUS - MCMP 690D "Biological Targets for Drug Discovery" - Spring 2006

RE-REVISED 1/18/06

Instructors: Dr. Gibbs (Course Coordinator: RHPH 406B); Dr. Barker; Dr. Cushman; Dr. Davisson; Dr. Geahlen; Dr. Hockerman; Dr. Nichols; Dr. Watts; and Dr. Weatherman

Text and Reading List: No assigned text; Goodman & Gilman's "The Pharmacological Basis of Therapeutics" may be used for background material. See attached list of primary literature. Each paper will either be available online, or will be copied and distributed to the class.

Evaluation Procedures:

Class Participation:	30%
Oral Presentations:	35%
Written Proposal:	35%

Class Participation: Students will be evaluated on the basis of their contribution to the group discussion. The instructor in charge of the module will be responsible for the evaluation. Each student is expected to read all assigned papers in advance, and be prepared to discuss them. Written submission of a question regarding the paper will be required. The grading will be done on a S/NS basis: 0 or 1 NS mark will result in a grade of A for class participation, 2-3 NS will result in a grade of B, and 4 -5 NS will result in a C, and 6 or more NS marks will result in a grade of F for this portion of the course.

Oral Presentation: Each instructor will administer the student oral presentations in their section. The course coordinator will assign the students to present specific papers. Each student will present two discussion sections (in two different modules of the course). The presentations and accompanying discussion will take 30 minutes to 1 hour. The presentation and discussion will follow, in a general sense, the format of an NIH study section. Each student will also be assigned as the "secondary" reviewer of two papers. In this case, the student will not present the paper, but will lead the group discussion of the paper, and will also prepare a written summary (~one-two paragraphs) of this discussion. Each instructor, in each of the modules, will evaluate the student on the basis of their performance in presenting the paper. The grading will be done on a S/NS basis: 0 NS mark will result in a grade of A for oral presentation, 1 NS will result in a grade of B, and 2 NS will result in a C. Failure to present one or both of the papers will result in a grade of F for this section. If the student is unable to attend the class period where they are scheduled to present for any reason, they must contact the course coordinator and make alternative arrangements.

Written Proposal: The proposal should be brief and concise in nature. It should be constructed to generate preliminary data to address the feasibility of a follow-up proposal. The experimental work proposed should be very limited – it should be able to be accomplished by a single student in 6 months to one year. A maximum length of five pages (single spaced, including figures but excluding references) is allowed. The paper must fit into a standard NIH format; more details on the exact format will be provided at the time of the distribution of the proposal topics. The proposal topic will be chosen by the student from a list of potential topics developed by the instructors and provided by the course coordinator. The paper should address many, if not all, of the common course themes listed below. The list of potential topics will be distributed to the students by Tuesday, Feburary 28, and the student will then have until Thursday, March 9 to choose the topic, which will be in an area distinct from their current research. The due date for the proposal will be Thursday, April 13. The proposal will be evaluated by the course coordinator and an additional instructor whose expertise is in the area of the proposal. The evaluations will be given to the student on Monday, April 24; at this point, the student will have the option of revising the proposal in response to the critiques. The revised proposal will be due by the end of the finals period.

Common Themes for MCMP 690D:

a. Historical context: how was the biological system recognized as a drug target?
b. Crosstalk in signaling pathways
c. Therapeutic (or potential therapeutic) agents
d. Signal transduction
e. Comparison of therapeutic approaches
f. Structures of targets

MCMP 690D - Spring 2006

MWTh, 5:30-6:30 PM; RHPH 162

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Class Schedule:

Instructor	Date	Day		Topic
Gibbs	Jan. 9	M		Introduction to course – organizational meeting
Watts	Jan. 11	W	**Module 1**	G-protein Coupled Receptors – intracellular aspects
Watts	Jan. 12	Th		G-protein Coupled Receptors – intracellular aspects
	Jan. 16	M		NO CLASS – Martin Luther King Day
Watts	Jan. 18	W		G-protein Coupled Receptors – intracellular aspects
Nichols	Jan. 19	Th	**Module 2**	G-protein Coupled Receptors – extracellular aspects
Nichols	Jan. 23	M		G-protein Coupled Receptors – extracellular aspects
Nichols	Jan. 25	W		G-protein Coupled Receptors – extracellular aspects
Hockerman	Jan. 26	Th	**Module 3**	Ion Channels
Hockerman	Jan. 30	M		Ion Channels
Hockerman	Feb. 1	W		Ion Channels
Hockerman	Feb. 2	Th		Ion Channels
Barker	Feb. 6	M	**Module 4**	Transporters
Barker	Feb. 8	W		Transporters
Barker	Feb. 9	Th		Transporters
Barker	Feb. 13	M		Transporters
Weatherman	Feb. 15	W	**Module 5**	Nuclear Receptors
Weatherman	Feb. 16	Th		Nuclear Receptors
Weatherman	Feb. 20	M		Nuclear Receptors
Weatherman	Feb. 22	W		Nuclear Receptors
Gibbs	Feb. 23	Th	**Module 6**	Introduction to cancer targets
Gibbs	Feb. 27	M		Kinases
	Feb.28	**Tu**		***Proposal Ideas Distributed***
Gibbs	Mar. 1	W		Kinases
Gibbs	Mar. 2	Th		Kinases
Gibbs	Mar. 6	M		Kinases
Gibbs	Mar. 8	W	**Module 7**	Prenyltransferases
Gibbs	Mar. 9	Th		Prenyltransferases
	Mar. 9	**Th**		***Proposal Topic Chosen***
	Mar. 13, 15, 16			SPRING BREAK
Gibbs	Mar. 20	M		Prenyltransferases
Davisson	Mar. 22	W	**Module 8**	Apoptosis
Davisson	Mar. 23	Th		Apoptosis
Davisson	Mar. 27	M		Apoptosis
Davisson	Mar. 29	W		Apoptosis
Gibbs	Mar. 30	Th	**Module 9**	Proteases
Gibbs	Apr. 3	M		Proteases
Gibbs	Apr. 5	W		Proteases
Geahlen	Apr. 6	Th	**Module 10**	PI_3 Kinase Pathway
Geahlen	Apr. 10	M		PI_3 Kinase Pathway
Geahlen	Apr. 12	W		PI_3 Kinase Pathway
	Apr. 13	**Th**		***Proposals Due***
Cushman	Apr. 13	Th	**Module 11**	Topoisomerases
Cushman	Apr. 17	M		Topoisomerases
Cushman	Apr. 19	W		Topoisomerases
Gibbs/TBA	Apr. 20	Th	**Module 12**	Crosstalk/Integration
Gibbs/TBA	Apr. 24	M		Crosstalk/Integration
Gibbs/TBA	Apr. 26	W		Crosstalk/Integration
Gibbs/TBA	Apr. 27	Th		Crosstalk/Integration

Description of Topics and Assigned Reading List

Module 1 – GPCRs: Intracellular Aspects (Watts)

Neurotransmitters, hormones, and peptides act on G protein coupled receptors (GPCRs) to activate a variety of second messenger signaling cascades. It is estimated that over 50% of the prescription drugs available today target GPCRs making them an extremely important therapeutic moiety. Modulation of GPCR signaling has traditionally involved the design and synthesis of small molecules that could be used to activate (agonists) or block (antagonists) receptor activation of heterotrimeric G proteins. These chemical entities were designed to have high affinity interactions with the extracellular accessible binding domains on individual GPCRs. On the other hand, a number of recent discoveries have suggested that intracellular sites may provide an alternative drug target for modulating GPCR signaling. Such a hypothesis is based on the ability of novel biochemical reagents and newly discovered proteins to alter the G protein signaling. This section of the course will use the receptor-G protein activation cycle as a basis to discuss sites of receptor-G protein interactions as intracellular therapeutic targets. The didactic portion of this section will include a review of basic G protein pharmacology as well as an introduction of many techniques that are used to measure receptor-G protein interactions. We will also introduce novel reagents and describe the discovery of novel modulators of G protein signaling. The remainder of the class time will be used for the active discussion of relevant primary literature articles describing potential therapeutic targets capable of modulating G protein signaling.

Literature for discussion

(1/12) Ulrich Rümenapp, Melanie Asmus, Helge Schablowski, Markus Woznicki, Li Han, Karl H. Jakobs, Mercedeh Fahimi-Vahid, Christina Michalek, Thomas Wieland, and Martina Schmidt, "The M3 Muscarinic Acetylcholine Receptor Expressed in HEK-293 Cells Signals to Phospholipase D via G12 but Not Gq-type G Proteins: REGULATORS OF G PROTEINS AS TOOLS TO DISSECT PERTUSSIS TOXIN-RESISTANT G PROTEINS IN RECEPTOR-EFFECTOR COUPLING*" J. Biol. Chem., **276:** 2474-2479, 2001
Online acces to full text
http://www.jbc.org/cgi/content/full/276/4/2474

(1/18) David S. Feldman, A. Musa Zamah, Kristen L. Pierce, William E. Miller, Francine Kelly, Antonio Rapacciuolo, Howard A. Rockman, Walter J. Koch, and Louis M. Luttrell, "Selective Inhibition of Heterotrimeric Gs Signaling: TARGETING THE RECEPTOR-G PROTEIN INTERFACE USING A PEPTIDE MINIGENE ENCODING THE Gs CARBOXYL TERMINUS*" J. Biol. Chem., **277:** 28631-28640, 2002
Online acces to full text
http://www.jbc.org/cgi/content/full/277/32/28631

Module 2 – GPCRs: Extracellular Aspects (Nichols)

G-Protein-coupled receptors (GPCRs) are one of the largest superfamilies of cell surface receptors, and mediate responses to a wide variety of signaling molecules. It is estimated that GPCR genes represent about 3% of the total human genome so it is perhaps not surprising that an estimated 50% of all new drugs are targeted to GPCRs.

GPCRs are classified into three families. Family A receptors are similar to rhodopsin and the adrenergic receptors. Family B receptors include the glucagon and secretin receptor-like family, and family C receptors comprise the metabotropic glutamate receptor-like family. In this series of discussions we shall focus on the Type A family of GPCRs.

Conventional wisdom had been that an agonist ligand bound to its receptor, after which the "activated" receptor coupled to a specific heterotrimeric G protein, leading to a cascade of signaling

events. Now, however, we know that GPCRs can bind to different G proteins, with agonist interaction therefore leading to activation of multiple intracellular signaling pathways.

In this section of the course we shall briefly consider some key structural elements of the receptor, and likely mechanisms that are involved in agonist activation of the receptor. We shall then consider whether the conventional view of receptor signaling is correct by examining some key papers that describe receptor coupling to multiple G proteins. This phenomenon has been referred to as "agonist-directed trafficking," "differential engagement of G proteins," and "functional selectivity."

Literature for Discussion

First discussion paper (1/23):

Kurrasch-Orbaugh DM, Watts VJ, Barker EL, and Nichols DE (2003) Serotonin 5-Hydroxytryptamine(2A) Receptor-Coupled Phospholipase C and Phospholipase A(2) Signaling Pathways Have Different Receptor Reserves. *J.Pharmacol.Exp.Ther.* **304**:229-237.

Online access to full text:
http://jpet.aspetjournals.org/cgi/reprint/304/1/229.pdf

Second discussion paper (1/25):

Gay EA, Urban JD, Nichols DE, Oxford GS, and Mailman RB (2004) Functional selectivity of D_2 receptor ligands in a Chinese Hamster Ovary hD_{2L} cell line: evidence for induction of ligand-specific receptor states. *Mol. Pharmacol.*, **66**, 97-105.

Online access to full text:
http://molpharm.aspetjournals.org/cgi/reprint/66/1/97

Module 3
Molecular Pharmacology of Ion Channels (Hockerman)
Following the pioneering experiments of Coleman and Katz, and Hodgkin and Huxley, the central role of ion channels in neurotransmission, muscle contraction, and hormone secretion was soon appreciated. Electrophysiological studies revealed that membrane permeabilities and modes of channel gating varied widely between cell types. During the genomic era, distinct membrane permeabilities were ascribed to specific transmembrane proteins, and functional domains within these proteins responsible for specific electrophysiological characteristics were identified. Ion channels are important targets for small molecule drugs, which act primarily by inhibiting ion flux through specific channels. However, drug modulation often involves modulation of channel states, rather that simple pore occlusion. In the post-genomic era, the role of protein-protein interactions that couple ion flux to specific cell signaling events is a major focus of research. Small molecule drugs able to uncouple such channel-protein interactions are potentially tissue-specific modulators of channel function.

Reading List

(2/1) Young, K., Lin, S., Sun, L., Lee, E., Modi, M., Hellings, S., Husbands, M. Ozenberger, B., and Franco, R. Identification of a calcium channel modulator using a high throughput yeast two-hybrid screen. Nature Biotechnology **16**:946-950 (1998).

(2/2) Macianskiene, R., Viappinai, S., Sipidio, K.R., and Mubagwa, K. Slowing of the inactivation of cardiac voltage-gated sodium channels by the amiodarone derivative 2-methyl-3-(3,5-diiodo-4-carboxymethoxybenzyl)benzofuran (KB130015) *J. Pharmacol. Exp. Ther.* **304**:130-138 (2003).

Module 4 – Transporters (Barker)
How do biologically active molecules and ions move across membranes? How do cells control movement of such molecules across membranes allowing substances to be concentrated within a cell or to be actively removed from the cytoplasm? In many instances, transporter proteins are present in cellular membranes and are responsible for facilitating the movement of substrates across the membrane lipid bilayer. These integral membrane proteins may be active (i.e., require energy) or passive transport systems. For example, neurotransmitters are removed from the extracellular space by Na^+-dependent transporters. In addition, neurotransmitters are sequestered into synaptic vesicles by specific H^+-dependent vesicular transporters. Various nutrients such as glucose are transported into cells via both Na^+-dependent as well as passive or facilitative transporters. Toxins and various drugs, on the other hand, are actively transported out of cells by a family of ATP-dependent transporters (P-glycoproteins) that function to protect cells from exogenous substances. This section of the course will discuss the identification, analysis, and application of transporter proteins as potential drug targets.

Discussion 1 (2/8):
Yamashita A, Singh SK, Kawate T, Jin Y, Gouaux E., **Crystal structure of a bacterial homologue of Na+/Cl--dependent neurotransmitter transporters.** Nature. 2005 Sep 8;437(7056):215-23

Discussion 2 (2/9):
Zhu CB, Carneiro AM, Dostmann WR, Hewlett WA, Blakely RD. **p38 MAPK activation elevates serotonin transport activity via a trafficking-independent, protein phosphatase 2A-dependent process.** J Biol Chem. 2005 Apr 22;280(16):15649-58.

Discussion 3 (2/13):
Annereau JP, Szakacs G, Tucker CJ, Arciello A, Cardarelli C, Collins J, Grissom S, Zeeberg BR, Reinhold W, Weinstein JN, Pommier Y, Paules RS, Gottesman MM. **Analysis of ATP-binding cassette transporter expression in drug-selected cell lines by a microarray dedicated to multidrug resistance.** Mol Pharmacol. 2004 Dec;66(6):1397-405.

Module 5 – Nuclear Receptors (Weatherman; Feb. 15 – Feb. 22)
The nuclear receptor family is a large group of ligand-dependent transcription factors that play key regulatory endocrine roles in almost every physiological process. Their ligands include the steroid hormones, non-steroidal hormones such as the retinoids and thyroid hormone, and a number of fatty acid-derived natural products. Almost every nuclear receptor is a validated therapeutic target in areas such as cancer treatment and prevention, anti-inflammation, contraception, and lipid homeostasis. One of the key areas of research in the development of drugs targeting nuclear receptors is the discovery of selective nuclear receptor modulation that allows for desirable effects in some tissues while avoiding undesirable effects in other tissues. This section of the class will focus on the development and mechanism of action of selective nuclear receptor modulators. The pedagogical sessions (the first two section of the class) will first introduce the nuclear receptors, their ligands and methods to study their function and then focus on a case study on the discovery and use of one selective modulator. The discussion sessions (the second two sections) will focus on the discovery of other selective modulators and studies trying to understand mechanisms of selective action.

Literature for discussion
Weatherman A: Gao, W., Reiser, P. J., Coss, C. C., Phelps, M. A., Kearbey, J. D., Miller, D. D., and Dalton, J. T. (2005). Selective androgen receptor modulator treatment improves muscle strength and body composition and prevents bone loss in orchidectomized rats. Endocrinology 146, 4887-4897.

Weatherman B: Lu, N. Z., and Cidlowski, J. A. (2005). Translational regulatory mechanisms generate N-terminal glucocorticoid receptor isoforms with unique transcriptional target genes. Mol Cell 18, 331-342.

Weatherman C: Metivier, R., Penot, G., Hubner, M. R., Reid, G., Brand, H., Kos, M., and Gannon, F. (2003). Estrogen receptor-alpha directs ordered, cyclical, and combinatorial recruitment of cofactors on a natural target promoter. Cell 115, 751-763.

Module 6 – Introduction to cancer targets; Kinases (Gibbs; February 23 – March 6)

We have entered a golden period in cancer drug discovery, with much emphasis being placed on the development of targeted agents. The first class period (February 23) will consist of a lecture on the biology of cancer and of tumor cells. The lecture will focus on topics discussed in the following paper: Hanahan, D., and R.A. Weinberg, "The Hallmarks of Cancer." *Cell* **100**: 57- 70 (2000). This lecture will set the stage for the subsequent material in both the kinase section and in the prenyltransferase section.

Protein phosphorylation is perhaps the most important mechanism for the regulation of the activity of cellular proteins. Thus, the kinase enzymes that carry out this process are of crucial importance in cellular activity, and are thus natural potential targets for drug discovery in a variety of different diseases. The first kinase lecture (February 27) will provide an overview of certain key, well-studied kinase-mediated signaling events, with an emphasis on those processes important in cancer cell growth. In addition, a brief discussion of the catalytic mechanism employed by kinases will also be presented. (For a detailed review of this area, see J. A. Adams "Kinetic and Catalytic Mechanisms of Protein Kinases" *Chem. Rev.* **2001***, 101,* 2271-2290.) The second lecture (March 1) will present a general overview of the opportunities and challenges presented by kinases as potential drug targets (For a detailed review of this area, see A. J. Bridges "Chemical Inhibitors of Protein Kinases" *Chem. Rev.* **2001***, 101,* 2541-2571.) In the first discussion section, two students will present data from the two listed papers on the synthesis and mechanism of action of Iressa (gefitinib), the first approved EGFR kinase inhibitor. In the second discussion period, one student will present a paper on the development of an inhibitor of the MAP kinase pathway member MEK as a potential anti-cancer agent.

Discussion Section 1 (3/2A):

A. J. Barker et al. "Studies Leading to the Identification of ZD1839 (Iressa^{TM}): An Orally Active, Selective Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Targeted to the Treatment of Cancer" *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1911-1914.

Discussion Section 2 (3/2B):

J. G. Paez et al. EGFR Mutations in Lung Cancer: Correlation with Clinical Response to Gefitinib Therapy" *Science* **2004**, *304,* 1497-1500.

Discussion Section 3 (3/6):

J. S. Sebolt-Leopold et al. "Blockade of the MAP kinase pathway suppresses growth of colon tumors *in vivo. Nature Medicine* **1999**, *5,* 810-816.

Module 7 - Prenyltransferases (Gibbs; March 8 - March 20)

The development of farnesyltransferase inhibitors (FTIs) has been one of the most active areas of anticancer drug development for the past ten years. The historical background, discovery, and evolution of this field will be presented. Numerous potent FTIs have been developed and extensively evaluated in preclinical model biological systems. The discovery of new, more potent FTIs, and in particular the

results seen with agents currently being evaluated in clinical trials will be emphasized. The emerging, surprising differences between the proposed and actual anticancer mechanisms of the FTIs will also be discussed. In the first two discussion sections, two different routes to the development of FTIs will be discussed. In the third and fourth discussion section, two alternative approaches to the development of "anti-Ras" agents related to FTIs will be discussed.

Discussion Section 1 (3/9A).
C. L Strickland et al. "Tricyclic Farnesyl Protein Transferase Inhibitors: Crystallographic and Calorimetric Studies of Structure-Activity Relationships" *J. Med.Chem.* **1999**, *42,* 2125-2135.

Discussion Section 2 (3/9B).
D. J. Augeri et al. "Potent and Selective Non-Cysteine-Containing Inhibitors of Protein Farnesyltransferase" *J. Med.Chem.* **1998**, *41,* 4288-4300.
K. J. Henry, Jr. et al. "Discovery of a Series of Cyclohexylethylamine-Containing Protein Farnesyltransferase Inhibitors Exhibiting Potent Cellular Activity" *J. Med.Chem.* **1999**, *42,* 4844-4852.

Discussion Section 3 (3/20A).
S. J. deSolms et al. "Dual Protein Farnesyltransferase-Geranylgeranyltransferase-I Inhibitors as Potential Cancer Chemotherapeutic Agents" *J. Med. Chem.* **2003,** *46,* 2973-2984.

Discussion Section 4 (3/20B).
A. M. Winter-Vann et al. "A small-molecule inhibitor of isoprenylcysteine carboxyl methyltransferase with antitumor activity in cancer cells" *PNAS* **2005**, *102,* 4336-4341.

Module 8 – Regulation of Apoptosis as a Target for Drug Discovery – (Davisson; March 22 – March 29)
Section Content: TBA
Reading Assignments:
3/27 – TBA
3/29 – TBA

Module 9 – Proteases (Gibbs; Mar. 30, Apr. 3, Apr. 5)
Proteases play a wide variety of regulatory roles in cellular and extracellular regulation. As advances in genomics and other areas of cellular biology have led to identification of and a more detailed knowledge about the important regulatory proteases implicated in disease states, these proteins have become important new targets for drug discovery. The first lecture in this section will present a brief overview of the different mechanistic classes of proteases, and some of the important strategies used to rationally design protease inhibitors. This will then be followed in the second lecture by a presentation highlighting recent developments in the biology and targeting caspases, which are key regulators of apoptosis. In the third class period, a student will present two papers on the development of inhibitors of beta-secretase , which appears to play an important role in the progression of Alzheimer's disease.
<u>Background Reading List:</u>
F. Lecaille et al. "Human and Parasitic Papain-Like Cysteine Proteases: Their Role in Physiology and Pathology and Recent Developments in Inhibitor Design" *Chem. Rev.* **2002**, *102,* 4459-4488.
J.-B. Denault and G. S. Salvesen "Caspases: Keys in the Ignition of Cell Death" *Chem. Rev.* **2002**, *102,* 4489-4499.

Discussion Section (4/5)
L. Hong *et al.* "Structure of the Protease Domain of Memapsin 2 (β-Secretase) Complexed with Inhibitor" *Science* **2000**, *290,* 150-153.
R. T. Turner *et al.* "Structural Locations and Functional Roles of New Subsites S_5, S_6, and S_7 in Memapsin 2 (β-Secretase)" *Biochemistry* **2002**, *44,* 105.

Module 10 – PI_3 Kinase Pathway (Geahlen; Apr. 6 – Apr. 12)
Section Content: TBA
Reading Assignments:
4/10 – TBA
4/12A – TBA
4/12B - TBA

Module 11 – Topoisomerases (Cushman; Apr. 13 – Apr. 19)
Human topoisomerase I is essential for most cellular processes involving DNA, including transcription, replication, and recombination, and it is the target of the clinically useful camptothecin series of anticancer drugs. Human topoisomerase I breaks one strand of duplex DNA and relaxes superhelical tension by a hypothetical "controlled rotation" mechanism, which involves cleavage of one DNA strand, rotation of the broken strand around the unbroken strand, and religation. The religation step is inhibited by camptothecin, resulting in "cleavable complexes" that generate cytotoxic double-strand breaks after collision with replication forks. Several crystal structures of human topoisomerase I in both covalent and noncovalent complex with DNA have been reported, and these structures have defined the architecture of the active site, which includes one tyrosine residue (Tyr-723), two arginines (Arg-488 and Arg-590), one histidine (His-632), and one lysine (Lys-532). Furthermore, a crystal structure has recently been determined of a covalent ternary complex of topoisomerase I with DNA and the clinically approved anticancer drug Topotecan. This structure provides insight into the mechanism of the inhibition of the religation step by the camptothecins, and it provides a framework for understanding the known structure-activity relationships of the camptothecins. It can be expected that the recent advancements in our understanding of the structure and function of human topoisomerase I, as well as the mechanism of action of the camptothecins, will lead to the design and synthesis of new enzyme inhibitors that will address the clinical limitations of the camptothecins. These limitations result from instability due to lactone ring opening and rapid reversibility of the cleavable complexes after drug removal.

Literature for discussion:

Discussion Section 1 (4/17A): Stewart, L.; Redinbo, M. R.; Qiu, X.; Hol, W. G. J.; Champoux, J. J. A Model for the Mechanism of Human Topoisomerase I. Science 1998, 279, 1534-1541.

Discussion Section 2 (4/17B): Staker, B. L.; Hjerrild, K.; Feese, M. D.; Behnke, C. A.; Burgin Jr., A. B.; Stewart, L. The Mechanism of Topoisomerase I Poisoning by a Camptothecin Analog. Proc. Natl. Acad. Sci. U.S.A. 2002, 99, 15387-15392.

Discussion Section 3 (4/19): B. L. Staker, M. D. Feese, M. Cushman, Y. Pommier, D. Zembower, L. Stewart, and A. B. Burgin, "Structures of Three Classes of Anticancer Agents Bound to the Human Topoisomerase I-DNA Covalent Complex, " *J. Med. Chem.* **48**, 2336-2345 (2005).

Module 12 – Crosstalk/Integration (Gibbs/TBA; Apr. 20 – Apr. 27)
The topics to be discussed in these modules, and the instructors who will present them, will be given later on in the semester.

Literature for discussion: TBA