Biology 1107 - Topics in the Study of Life
PERSIST/FYRIS Section - Drug Development and Bioassay I
CRN 11835
Fall, 2018

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Day/Time: M/W 9:00 AM – 11:50 AM
Location: Physical Sciences 303

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Course Objectives: This course is designed to provide a broad understanding of the basic drug development process including understanding the molecular mechanisms of disease, drug target identification, high throughput drug screening, and hit-to-lead optimization with a focus on prostate cancer therapeutics. The practical aspects of this course will be focused on the hit-to-lead optimization of a novel prostate cancer drug that was initially identified and characterized for the treatment of hormone-refractory prostate cancer. Students will be expected to develop a yeast-based assay for use in screening compound libraries and use this assay to screen drug modifications for improved drug activity. A more detailed description of the course including learning outcomes and practical skills learned is provided in the weekly schedule.

Textbook: There is no required textbook. All reading material will be provided.

Quizzes: An in-class quiz will be administered at the end of each learning module for a total of 7 quizzes.

Laboratory Notebooks: Laboratory notebooks will be checked (i.e. graded) at the end of each learning module. The grades will be based on legibility and detailed documentation of experimental procedures and results.

Experimental Summaries (Lab Reports): At the end of each learning module students will submit a brief summary report including the study objective, experimental design, and data analysis with an interpretation of results.

Data Presentation: Each group will present their findings for discussion at the end of the semester.

Final Report: Each individual student will compile their brief summary reports that they have written throughout the semester into a larger final report that includes a final analysis and discussion of the data, and provides conclusions and potential future directions.

Grading: All quizzes combined are worth 20% of your final grade. Attendance is worth 10% of your final grade. The laboratory notebooks are worth 10% of your final grade. The experimental summaries and data presentation are each worth 15% of your final grade. The final report is worth 30% of your final grade. **Grading scale:** A=90-100%; B=80-89%; C=70-79%; D=60-69%; F is <60%.

Make-up Policy: There are no make-up quizzes except in extraordinary circumstances. If you have a serious illness, call me before the quiz is given and bring documentation of your excuse to me. If you have a legitimate excuse for being out-of-town, make arrangements with me to take the quiz before you leave.

Attendance It is your responsibility to attend class regularly. Your attendance will be monitored and graded. If you have a serious illness or a legitimate excuse (includes military personnel called to active duty or training) for being out-of-town, make arrangements with me before you leave. Please do not wear hats in class during quizzes.

Drop Policy: November 2nd is the last day students may drop with an automatic "W". Census day is September 12th.

Academic Integrity Policy: UTEP's policies regarding academic integrity apply in this course. Cheating will be reported to the appropriate administrative officer. Failure to take the final exam may result in receiving an F in this course. Incompletes are only given in exceptional circumstances.

Civility Statement: Please be respectful of all students' right to learn without disruptions. In line with this statement please make an active effort to keep the talking to a minimum during lectures and presentations. Also make an active effort to either turn cell phones off or turn them to vibrate mode prior to the start of class.

Disability Statement: If you have a disability and need classroom accommodations, please contact The Center for Accommodations and Support Services (CASS) at 747-5148, or by email to cass@utep.edu, or visit their office located in UTEP Union East, Room 106. For additional information, please visit the CASS website at www.sa.utep.edu/cass.

Learning Modules

Semester I (Fall 2017) - Weekly Schedule and Learning Outcomes

Module 1
Week 1: Introduction to Drug Discovery - A general introduction to the drug discovery process will be provided with an emphasis on current research in prostate cancer therapeutics. This general information will lead into the current efforts within the Cox laboratory to develop novel strategies for the treatment of prostate cancer. The students' work throughout the semester will directly contribute to these efforts through the development and utilization of a yeast-based screening assay to screen drug analogs for increased potency.

Learning Outcomes:

Key Concepts: At the end of this module students will:
1. understand the essential role of academic science in the development of new therapeutic strategies.
2. understand the process of drug target identification and validation.
3. have a broad understanding of innovative approaches to drug discovery.
4. understand the current challenges in the treatment of prostate cancer and the molecular pathways that contribute to disease progression.

Practical Skills Gained:
1. General Laboratory Safety
2. Keeping and maintaining a proper laboratory notebook.

Daily Schedule:

Date		Topic	Assignment
8/27	M	Introduction to General Laboratory Safety	None
8/29	W	Prostate Cancer Drug Development	Quiz 1

Module 2
Week 2: Preparation of Hormone and Drug Molecule Stocks - In preparation for the drug screening project students will be required to prepare serially diluted stocks of the hormone and drug molecules that will be used in the drug screening assay that the students will develop over the course of the semester. In order to achieve competency in basic sterile technique and pipetting the students will generate a protein standard curve using the Bradford method. This standard curve will be used to assess technical accuracy and reproducibility before using these newly acquired skills to prepare the hormone and drug stocks.

Learning Outcomes:

Key Concepts: At the end of this module students will:
1. understand the utility of colorimetric assays in biomedical research.
2. have a broad understanding of drug solubility.
3. understand drug delivery strategies for poorly water-soluble drugs.

Practical Skills Gained:
1. Proper Sterile Technique
2. Proper Pipetting Technique
3. Serial Dilution
4. Bradford Assay for Measuring Protein Concentration

Daily Schedule:

Date		Topic	Assignment
9/3	M	Labor Day – No Class	None
9/5	W	Pipetting/Protein Standard Curve and Serial Dilution/Hormone Stocks	Quiz 2, present notebook for inspection

Module 3

Weeks 3-4: Preparation of Recombinant DNA for Expression of Androgen Receptor and the Androgen Receptor-Dependent Reporter - The yeast-based screening assay will be used to assess the effects of candidate drug molecules on human androgen receptor activity. Thus, DNA plasmids for the expression of the human androgen receptor gene and the reporter gene will first need to be amplified in bacteria, extracted and purified.

Key Concepts: At the end of this module students will:
1. have a broad understanding of recombinant DNA technology.

Practical Skills Gained:
1. General growth and maintenance of bacterial cultures
2. bacterial transformation
3. plasmid mini-prep
4. DNA separation, agarose gel electrophoresis

Daily Schedule:

Date		Topic	Assignment
9/10	M	Bacterial Transformation	Turn in Experimental Summary from Module 2
9/12	W	Bacterial Transformation	None
9/17	M	Plasmid Isolation & Analysis	None
9/19	W	Plasmid Isolation & Analysis	Quiz 3, present notebook for inspection

Module 4

Weeks 5-6: Develop the Strain for the Yeast-Based Screening Assay - Although *Saccharomyces cerevisiae* lacks steroid hormone receptors, most of the chaperone components known to function in steroid hormone receptor complexes are highly conserved in yeast. Thus, vertebrate receptors exogenously expressed in yeast can fold to a hormone binding conformation and, in the presence of hormone, activate a hormone-inducible reporter gene. This, combined with the fact that yeast is a genetically tractable organism, makes yeast genetics a highly attractive model system for the identification and characterization of steroid hormone receptor modulators. The yeast-based androgen receptor (AR)-mediated β-galactosidase reporter assay can be used as a quantitative measure of androgen receptor function. This assay is used for the identification and characterization of androgen receptor regulatory proteins, and to screen compound libraries for androgen receptor inhibitors (i.e. prostate cancer drugs). Thus, students will transform the androgen receptor plasmid and β-galactosidase reporter plasmid into yeast

and select for plasmid maintenance. Once complete these strains will be stored at -80°C and can be recovered at any time for growth and assays.

Key Concepts: At the end of this module students will:
1. understand the use of yeast as a model system for the study of human signaling pathways.
2. understand the use of plasmids for exogenous expression of genes in yeast.

Practical Skills Gained:
1. General growth and maintenance of yeast
2. yeast transformation
3. cryopreservation

Daily Schedule:

Date		Topic	Assignment
9/24	M	Yeast Transformation	Turn in Experimental Summary from Module 3
9/26	W	Yeast Transformation	None
10/1	M	Yeast Transformation and Clone Selection	None
10/3	W	Yeast Transformation, Clone Selection and Cryopreservation	Quiz 4, present notebook for inspection

Module 5
Weeks 7-8: Determination of Optimal Hormone Dose for Drug Screening - Students will be using the androgen receptor-dependent reporter assay to screen drug molecules for inhibition of hormone-dependent receptor activity. Thus, the drug candidates will be assayed for the ability to inhibit the receptor in the presence of hormone. The hormone concentration used in these assays typically falls within the middle of the hormone dose response curve. Thus, students will perform a reporter assay in the presence of a range of hormone concentrations to generate a hormone dose response curve and use that curve to determine the effective concentration 50% (EC_{50}) for the hormone. This will be the hormone concentration used in the drug screens.

Key Concepts: At the end of this module students will:
1. have a broad understanding of the use of reporter assays for the assessment of transcription factor function.
2. understand dose response for the assessment of compound potency and efficacy.
3. understand the principles of chemiluminescent detection.

Practical Skills Gained:
1. hormone-dependent reporter assay

2. dose response analysis

Daily Schedule:

Date		Topic	Assignment
10/8	M	Reporter Assay	Turn in Experimental Summary from Module 4
10/10	W	Reporter Assay	None
10/15	M	Reporter Assay	None
10/17	W	Dose-Response Curve Assessment and Determination of EC50	Quiz 5, present notebook for inspection

Module 6

Weeks 9-12: Perform Drug Screen - Starting with a hit molecule that was identified in a high throughput drug screen combinatorial chemistry was used to make a library of analogs. Each molecule in the library is a slightly modified version of the hit molecule. The goal will be to screen the entire library of analogs for inhibitory activity. The primary goal will be to identify a more potent analog. The secondary goal will be to elucidate the chemical structure leading to effective drug inhibition. Students will use the hormone-dependent reporter assay that they have developed to screen as many molecules as they can for hormone receptor inhibition within the allotted time frame.

Key Concepts: At the end of this module students will:
1. have a broad understanding of the hit-to-lead optimization process.
2. know how to design proper positive and negative experimental controls.

Practical Skills Gained: Students will be expected to have achieved competency in all practical skills needed to complete this section during previous sections.

Daily Schedule:

Date		Topic	Assignment
10/22	M	Small Molecule Screening	Turn in Experimental Summary from Module 5
10/24	W	Small Molecule Screening	None

10/29	M	Small Molecule Screening	None
10/31	W	Small Molecule Screening	None
11/5	M	Small Molecule Screening	None
11/7	W	Small Molecule Screening	Quiz 6, present notebook for inspection

Module 7
Weeks 13-14: Structure Activity Relationship Analysis - The functional data gleaned from the screening assays will be combined and each group will work to compare molecular structure and function. The groups will be expected to use the entire dataset to draw conclusions about the chemical structure of the drugs and how that chemistry affects function. This information and resulting conclusions can be used to modify the chemical structure to optimize drug potency. By the end of this semester students should be able to hypothesize what molecular structure would be an ideal drug.

Concepts: At the end of this module students will:
1. have a broad understanding of the relationship between the chemical structure of a molecule and its biological activity.

Daily Schedule:

Date		Topic	Assignment
11/12	M	Small Molecule Screening and Data Analysis	Turn in Experimental Summary from Module 6
11/14	W	Small Molecule Screening and Data Analysis	None
11/19	M	Small Molecule Screening and Data Analysis	None
11/21	W	Small Molecule Screening and Data Analysis	Quiz 7, present notebook for inspection

Module 8
Week 15: Group Discussions and Analysis of Data

Daily Schedule:

Date		Topic	Assignment
11/26	M	Lab Group Presentations	Turn in Experimental Summary from Module 7
11/28	W	Lab Group Presentations	None
12/3	M	Lab Group Presentations	None
12/5	W	Final Class Discussions	Final Lab Reports Due

Semester II (Spring 2018) - Weekly Schedule and Learning Outcomes

To Be Determined

Synopsis - In Semester I the students will have learned the concepts of basic drug development and the application of a yeast-based bioassay for drug screening. In semester II the students will use their newly acquired knowledge and adapt their bioassay for use in screening environmental samples for the presence of hormone mimicking contaminants.