Title	Finding a Reliable Hit: Optimized tools for reproducible drug screening
Course Director	Jennifer Smith, Ph.D., Director of ICCB-Longwood Screening Facility and Discovery Service Center Laboratory
Instructors	Jennifer Smith, Ph.D., Director of ICCB-Longwood Screening Facility and Discovery Service Center Laboratory Caitlin Mills, Ph.D., Director of Preclinical Pharmacology, Laboratory of Systems Pharmacology Nicholas Clark, Ph.D., Postdoctoral Fellow, Laboratory of Systems Pharmacology
Education Fellow	Han Xu, Ph.D., Education Fellow at Harvard Program in Therapeutic Science
Overall Course Objectives:	1. Describe the design principles of microplate assays for compound screening 2. Identify challenges in designing and executing *reproducible* small molecule screening experiments 3. Understand the concepts behind growth rate inhibition (GR) metric and apply GR metrics to quantify antiproliferative drug activity in a reproducible manner 4. Analyze and interpret data from high-throughput screening and dose response studies 5. Recognize online tools and resources available to the HMS Community
Overall Description	Assaying cellular responses to compounds is a fundamental aspect of the development and characterization of therapeutic molecules and the investigation of drug mechanism of action. These assays are routinely conducted on the benchtop in basic research and used extensively in the pharmaceutical industry for drug discovery. However, accurate drug response measurements and their analysis are not as straightforward as they might seem. This nanocourse will introduce the design of cell response assays and high-throughput small molecule screens as well as relevant data analysis methods. We will present experimental and computational methods for generating reproducible dose-response measurements across cell lines, as well as computational approaches to quantifying the sensitivity of cells to single drugs and drug combinations. There are three 2-hour sessions in total. Students will engage in small group discussions and case studies in class, and solve one problem set with real data with support from the instructor team.
Enrollment	This course is limited to 40 participants. *Priority will be given to graduate students taking the course for credit. In order to receive credit, students must attend all sessions and complete the assignments. Postdocs may register and will be granted access to the course as space allows.*
Session Dates and Times	Oct 31, Nov 8 and Nov 14, 1-3pm
Location	TMEC 106 Learning Studio (No remote option)

Session 1 | Assay Automation and Quantification – From Benchtop to High Throughput Screening

Instructor: Jennifer Smith

Session Objectives:

1. Describe benefits and uses of automated high throughput (HTS) screening assays
2. Become aware of the resources available within the HMS Community
3. Define small molecule screens and understand the major steps in the design and execution of small molecule screens
4. Design a robust and physiologically relevant screening assay
5. Visualize and interpret HTS (microplate) data

Session 1 will introduce automated high throughput screening (HTS) and highlight pros and cons of this experimental approach for small molecule screens. We will discuss the major steps in designing and conducting small molecule screens as well as present a few options for visualization and analysis of HTS data. Students will have an opportunity to reflect on their own research and, in small groups, discuss whether HTS could help answer their scientific questions. We will explore the challenges and considerations of designing a rigorous and reproducible screening assay, and end the class with brainstorming on the experimental design for a case study topic in small groups.

Session 1 Homework: Continuing the experimental design that was started in the last classroom activity, expand on the experimental set up and submit a 1-page write-up that highlights a few considerations that specifically address reproducibility.

Session 2 | Optimized Experimental and Analytical Tools for Reproducible Drug-Response Studies

Instructors: Caitlin Mills and Nicholas Clark

Session Objectives:

1. Understand the challenges of cell-based dose response assays and the design steps that can improve reproducibility
2. Explain how the Deep Dye Drop assay differs from traditional protocols and how differences in design may improve reproducibility of the results
3. Describe the concepts and theory behind growth rate inhibition metrics (GR metrics)
4. Apply GR metrics to drug response data and explain when GR metrics should be used in drug response studies

Session 2 will be a practical guide to the wet lab, microscopy-based Deep Dye Drop protocol and the computational application of growth rate (GR) inhibition metrics to dose response data. We will discuss how these complementary methods improve the reproducibility of cell-based drug response studies. We will first review traditional cell viability screening assays and discuss their limitations. Then, we will introduce the GR approach to the analysis and interpretation of dose response data and present case studies with real data to compare the two types of metrics. In the second half of Session 2, we will revisit some of the considerations for reproducible experimental design introduced in Session 1 with a focus on designing a Deep Dye Drop dose response experiment. The session will conclude with an interactive discussion on tips for adopting Deep Dye Drop into one's own research.

Session 2 Homework: Students will receive two problem sets to apply the computational methods introduced in Session 1 and Session 2 to experimental data. Students will choose one to complete

before Session 3. Students will not be graded on their attempts before Session 3, *but they must submit an attempt for credit*. A part of Session 3 will be a flipped classroom session where students can bring their questions on the problem sets and trouble-shoot with instructor team.

Session 3 | Robust Methods for Drug Combination Studies

Instructors for first half: Nicholas Clark, Caitlin Mills, Jennifer Smith

Instructors for flipped session on problem sets: Nicholas Clark and Han Xu

Session Objectives:

1. Define drug combination studies and understand key concepts around their design and interpretation, including synergy and synergy scoring models
2. Understand how GR metrics, Deep Dye Drop and automated HTS can be applied to drug combination experiments

Session 3 will start with a high-level introduction to drug combination studies. The potential for increased therapeutic effects and decreased adverse effects motivates ongoing efforts to identify synergistic drug combinations. However, screening for drug combinations brings unique challenges and new considerations in experimental design and data analysis. In this session, we will discuss the application of methods introduced in Sessions 1 & 2 to drug combination studies. This will conclude the instructor-led portion of the course. The second half of Session 3 will be a flipped format classroom where students will work with the instruction team on their individualized questions from the problem sets. For students who are not taking the class for credit, they may choose to discuss other questions on high throughput screening or other experimental design with the instruction team.