Topics in High Throughput discovery: A multidisciplinary approach to cancer (CHEM 495/PHRM 495)

Spring 2022

Time: Tuesdays, 5:00 – 6:00 p.m. Plus ~10 hrs week independent lab time
Location: John Morgan, Room M100 (Mezzanine Level)
Texts: Editors G. Sitta Sittampalam, *Assay Guidance Manual*
             Online ebook: http://www.ncbi.nlm.nih.gov/books/NBK53196/
Web: Canvas for lectures and readings
Blue jeans: https://bluejeans.com/9268754685

Course Directors:
Jeffrey Field, PhD: Professor of Systems Pharmacology and Translational Therapeutics
jfield@upenn.edu
Dr. David Schultz, PhD: UPenn High Throughput Screening Core
dschultz@mail.med.upenn.edu

Requirements:
Prerequisites include a strong foundation in biology and chemistry. Students will prepare an abstract proposal by week four on their phase 2 projects, and a report, in scientific paper style, due on the last day of the semester. In addition to attending the class lecture, an estimated 10 hours a week Independent Laboratory Research is expected.

Expectations:
1 primary paper presentation and discussion
1 primary paper lead discussion
1 HTS profiling experiment (Phase 1)
1 independent screen (phase 2)
1 final presentation of phase 2 project
(students taking the course for graduate credit are required to submit a final paper on phase 2)

Course description:
The newly developed massively parallel technologies have enabled the simultaneous analysis of many pathways. There are several large scale international efforts to probe the genetics and drug sensitivity of cancer cell lines. However, there are some rare cancers that have not been analyzed in depth. One of these rare cancers is malignant peripheral nerve sheet tumors (MPNST). MPNST, although a rare cancer, are common in patients with neurofibromatosis type 1. We obtained funding from the Children's Tumor Foundation and the DOD to fill this gap, in a novel way by enlisting students in a hybrid research/education model through what is the first course in high throughput screening.   In the course, students take part in a high throughput discovery effort in two phases. Phase 1 is a training phase, which will consist of quantitative profiling the sensitivity of MPNST cell lines to a library of experimental cancer drugs. These will be conducted in the UPenn High Throughput Screening Core with Dr. David Schultz. (http://www.med.upenn.edu/cores/High-ThroughputScreeningCore.shtml). While we call this a training phase, the data from this will be subject to rigorous quality control for eventual publication and development of a public database for rare tumors. Phase 1 data will be organized and integrated into our database that already has 300 drugs profiled against ~10 cell lines in it. Phase 2 is an independent research project. Examples of Phase 2 projects include, but are not limited to: Combinatorial screens (synthetic lethal screening: White et. al. below); siRNA screens; novel compound screens; determining mechanisms of cell death; developing tools for data analysis and database development. We will sponsor phase 2 projects relevant to neurofibromatosis. However, in phase 2 students can also perform experiments in other areas if they develop sponsorships from professors. This course has been a hypothesis engine that generates ideas for further research. Several have built their thesis around ideas generated in our screens.

The thematic area in phase 2 projects in 2022 is Hippo pathways in NF1, NF2 and Mek inhibitor resistant NF1.

Chem 495 students and students who did the curricula as independent study projects participated in international conferences and earned authorship on the following publications (students underlined):

1 Lu Hezhe, Liu Shujing, Zhang Gao, Bin Wu, Zhu Yueyao, Frederick Dennie T, Hu Yi, Zhong Wenqun, Randell Sergio, Sadek Norah, Zhang Wei, Chen Gang, Cheng Chaoran, Zeng Jingwen, Wu Lawrence W, Zhang Jie, Liu Xiaoming, Xu Wei, Krepler Clemens, Sproesser Katrin, Xiao Min, Miao Benchun, Liu Jianglan, Song Claire D, Liu Jephrey Y, Karakousis Giorgos C, Schuchter Lynn M, Lu Yiling, Mills Gordon, Cong Yusheng, Chernoff Jonathan, Guo Jun, Boland Genevieve M, Sullivan Ryan J, Wei Zhi, Field Jeffrey, Amaravadi Ravi K, Flaherty Keith T, Herlyn Meenhard, Xu Xiaowei, Guo Wei: PAK signalling drives acquired drug resistance to MAPK inhibitors in BRAF-mutant melanomas. **Nature 550** (7674): 133-136, Oct 2017.

2 Guo Jianman, Grovola Michael R, Xie Hong, Coggins Grace E, Duggan Patrick, Hasan Rukhsana, Huang Jiale, Lin Danny W, Song Claire, Witek Gabriela M, Berritt Simon, Schultz David C, Field Jeffrey: Comprehensive pharmacological profiling of neurofibromatosis cell lines. **American journal of cancer research 7**(4): 923-934, 2017. PMCID: PMC5411799.

3 White, S. M., M. L. Avantaggiati, I. Nemazanyy, C. Di Poto, Y. Yang, M. Pende, G. T. Gibney, H. W. Ressom, J. Field, M. B. Atkins and C. Yi (2019). "YAP/TAZ Inhibition Induces Metabolic and Signaling Rewiring Resulting in Targetable Vulnerabilities in NF2-Deficient Tumor Cells." **Dev Cell 49**(3): 425-443 e429.

4 Guo J, Chaney KE, Choi K, Witek G, Patel AV, Xie H, Lin D, Whig K, Xiong Y, Schultz DC, Ratner N, Field J. Polo-like kinase 1 as a therapeutic target for malignant peripheral nerve sheath tumors (MPNST) and schwannomas. **Am J Cancer Res**. 2020;10(3):856-869. PubMed Central PMCID: PMC7136923.

5 Yool Lee, Shi Yi Fong, Joy Shon, Shirley L Zhang, Rebekah Brooks, Nicholas F Lahens, Dechun Chen, Chi Van Dang, Jeffrey M Field, Amita Sehgal Time-of-day specificity of anticancer drugs may be mediated by circadian regulation of the cell cycle 2021 **Science Advances** Vol 7, PMID: 33579708 PMCID: PMC7880601 DOI: 10.1126/sciadv.abd2645.

Notes:
1	Data analysis requires Excel and GraphPad Prism
Copies of Prism are in the biomedical library and in the Field lab. An individual copy is $150

2	Homework assignments are to be prepared as paragraphs for a publication, eg Introduction, Materials and Methods and Discussion. Cite the literature, especially in the introduction. We will use them!

3	We will perform screens throughout the semester as cells arrive from other labs, an extended form of phase 1…think of it as phase 1a; all students will pitch in to grow the cells for screening and archive the cells in liquid nitrogen.

SCHEDULE:
   this is a draft version and will be finalized after class meets to adjust it based on the number of students. There will be modifications when data comes in so you can learn to analyze data

Date	Title	Lecturer
Jan 18	**1** Introduction: Neurofibromatosis and course Goals (Tours of labs; Thurs screening demonstration/Friday assay read)	Field/ Schultz
Jan 25	**2** High Throughput cell based screening Lab assignment: phase 1 data analysis lecture: Clinical Intro to NF1 and NF2 Presentation: 1 student 53-16d Ras c12 amgen drug	Schultz
Feb 1	**3** Presentation: 1 student Schultz paper	Field/Schultz
Feb 8	**4** Presentation: 1 student 54-69- Tead...	Field
Feb 15	**5** Student presentations (5 min) of Phase 2 ideas/discussion Written: Ph 1 Methods description for Phase 2	Field/Schultz
Feb 22	**6** Data analysis 1 IC_{50} and heat maps/spearman (Phase 1 HTS cell and chemistry notebook check) Presentation: 1 student 53-14 HTS reproducibility	Field/Schultz/
March 1	**7** Data analysis 2 public databases and heat maps De Raedt Ras paper discussion. 38-92	De Raedt
March 8	No class spring break (Initiation of phase 2)	
March 15	**8** Phase 2 discussion and finalizing plans paper discussion	Schultz
March 22	**9** NF1 and NF2 clinical trials: 38-77c; 53-10	Fisher
March 29	**10** paper discussion	Schultz(if travel)
April 5	**11 writing workshop**	Field
April 12	**12** Presentation: 56-1 YAP BRAF resist	Field
April 19	**13** Data wrap up and organization	
April 26	**14** Student presentations Phase 2 results	
April 29	**15** Final papers due	