BICD 194 Cancer: Origins and Therapeutic Strategies

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[please include BICD 194 in subject line of emails related to the class]

Class meetings: Mondays 1:00 – 2:20 PM, York 3010

Course Description: In this course, we will read primary scientific literature highlighting key discoveries in cancer biology and how they are leading to new therapeutic approaches. Students will read and lead the discussion of scientific papers and turn in a final written assignment analyzing an assigned paper.

Course Expectations and Discussion Guidelines

Attendance link

Pre-discussion questions and submission link
(questions will be posted by midnight on Wednesday of the week before class and answers will be due by noon on Monday of the day the paper will be discussed)

4/1 – Introductory lecture and discussion of how to present a paper.

Link to introductory slides

4/8 – Student-led discussion of paper 1

THEME 1: Synthetic Lethality in Cancer: (PARP inhibition in breast cancer, mechanism of sensitivity to PARP inhibition)

Paper 1- Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy.
Nature. 2005 Apr 14;434(7035):917-21.
Farmer H, McCabe N, Lord CJ, Tutt AN, Johnson DA, Richardson TB, Santarosa M, Dillon KJ, Hickson I, Knights C, Martin NM, Jackson SP, Smith GC, Ashworth A. PMID: 15829967
Link to paper 1

4/15 – Student-led discussions of papers 2 and 3

Paper 2- Maintenance olaparib for patients with newly diagnosed advanced ovarian cancer and a BRCA mutation (SOLO1/GOG 3004): 5-year follow-up of a randomised, double-blind, placebo-controlled, phase 3 trial.

Clinical Trial Lancet Oncol. 2021 Dec;22(12):1721-1731. doi: 10.1016/S1470-2045(21)00531-3. Epub 2021 Oct 26.
Banerjee S, Moore KN, Colombo N, Scambia G, Kim B-G, Oaknin A, Friedlander M, Lisyanskaya A, Floquet A, Leary A, Sonke GS, Gourley C, Oza A, González-Martín A, Aghajanian C, Bradley WH, Holmes E, Lowe ES, DiSilvestro P. PMID: 34715071
Link to paper 2

THEME 2: Small molecule targeting of a cancer-driving mutation: (BRAF in melanoma)

Paper 3- Mutations of the BRAF gene in human cancer.
Nature. 2002 Jun 27;417(6892):949-54.
Davies H, Bignell GR, Cox C, Stephens P, Edkins S, Clegg S, Teague J, Woffendin H, Garnett MJ, Bottomley W, Davis N, Dicks E, Ewing R, Floyd Y, Gray K, Hall S, Hawes R, Hughes J, Kosmidou V, Menzies A, Mould C, Parker A, Stevens C, Watt S, Hooper S, Wilson R, Jayatilake H, Gusterson BA, Cooper C, Shipley J, Hargrave D, Pritchard-Jones K, Maitland N, Chenevix-Trench G, Riggins GJ, Bigner DD, Palmieri G, Cossu A, Flanagan A, Nicholson A, Ho JW, Leung SY, Yuen ST, Weber BL, Seigler HF, Darrow TL, Paterson H, Marais R, Marshall CJ, Wooster R, Stratton MR, Futreal PA. PMID: 12068308
Link to paper 3

4/22 – Student-led discussion paper 4

Paper 4- Discovery of a selective inhibitor of oncogenic B-Raf kinase with potent antimelanoma activity.
Proc Natl Acad Sci USA. 2008 Feb 26;105(8):3041-6. doi: 10.1073/pnas.0711741105.
Tsai J1, Lee JT, Wang W, Zhang J, Cho H, Mamo S, Bremer R, Gillette S, Kong J, Haass NK, Sproesser K, Li L, Smalley KS, Fong D, Zhu YL, Marimuthu A, Nguyen H, Lam B, Liu J, Cheung I, Rice J, Suzuki Y, Luu C, Settachatgul C, Shellooe R, Cantwell J, Kim SH, Schlessinger J, Zhang KY, West BL, Powell B, Habets G, Zhang C, Ibrahim PN, Hirth P, Artis DR, Herlyn M, Bollag G. PMID: 18287029.
Link to paper 4

4/29 – Student-led discussion paper 5

THEME 3: Biologic (antibody) targeting of a cancer-driving gene amplification: (HER2 in breast cancer)

Paper 5: Down-modulation of an oncogene protein product and reversion of the transformed phenotype by monoclonal antibodies.
Cell. 1985 Jul;41(3):697-706.
Drebin JA, Link VC, Stern DF, Weinberg RA, Greene MI. PMID: 2860972.

Link to paper 5

5/6 – Student-led discussion paper 6

Paper 6: A Biparatopic HER2-Targeting Antibody-Drug Conjugate Induces Tumor Regression in Primary Models Refractory to or Ineligible for HER2-Targeted Therapy.
Cancer Cell. 2016 Jan 11;29(1):117-29. doi: 10.1016/j.ccell.2015.12.008.
Li JY, Perry SR, Muniz-Medina V, Wang X, Wetzel LK, Rebelatto MC, Hinrichs MJ, Bezabeh BZ, Fleming RL, Dimasi N, Feng H, Toader D, Yuan AQ, Xu L, Lin J, Gao C5, Wu H, Dixit R, Osbourn JK, Coats SR. PMID: 26766593.
Link to paper 6

5/13 – Student-led discussions of papers 7 & 8

THEME 4: Engineering/Unleashing the immune system to fight cancer: (CAR-T & checkpoint inhibition)

Paper 7: Enhancement of antitumor immunity by CTLA-4 blockade.
Science. 1996 Mar 22;271(5256):1734-6.
Leach DR, Krummel MF, Allison JP. PMID: 8596936.
Link to paper 7

Paper 8: Cancer regression and autoimmunity induced by cytotoxic T lymphocyte-associated antigen 4 blockade in patients with metastatic melanoma.
Proc Natl Acad Sci U S A. 2003 Jul 8;100(14):8372-7.
Phan GQ, Yang JC, Sherry RM, Hwu P, Topalian SL, Schwartzentruber DJ, Restifo NP, Haworth LR, Seipp CA, Freezer LJ, Morton KE, Mavroukakis SA, Duray PH, Steinberg SM, Allison JP, Davis TA, Rosenberg SA. PMID: 12826605.
Link to paper 8

5/20 – Student-led discussion of paper 9

Paper 9: IL-10-expressing CAR T cells resist dysfunction and mediate durable clearance of solid tumors and metastases.
Nat Biotechnology 2024 Jan 2. doi: 10.1038/s41587-023-02060-8.
Zhao Y, Chen J, Andreatta M, Feng B, Xie Y-Q, Wenes M, Wang Y, Gao M, Hu X, Romero P, Carmona S, Sun J, Guo Y, Tang L. PMID: 38168996.
Link to paper 9

5/27 – NO CLASS – MEMORIAL DAY HOLIDAY

6/3 – Student-led discussion of paper 10

Paper 10: Hyperactive Rac stimulates cannibalism of living target cells and enhances CAR-M-mediated cancer cell killing.
Proc Natl Acad Sci U S A. 2023 Dec 26;120(52):e2310221120.
doi: 10.1073/pnas.2310221120. Epub 2023 Dec 18.
Mishra AK, Rodriguez M, Torres AY, Smith M, Rodriguez A, Bond A, Morrissey MA, Montell DJ. PMID: 38109551
Link to paper 10

Course Expectations and Discussion Guidelines:

Evaluation: There is NO final exam. Your grade will be based on four equal components:

(1) Your ***attendance*** AND ***participation*** in paper discussions

(2) Your performance in your group's leading of a paper discussion

(3) Your answers to the pre-discussion questions; submitted via the Google form link on the syllabus. Answers are due at noon on the Monday that the paper will be discussed.

(4) Your final paper in which you will evaluate an assigned paper.

There is no textbook for this course: Expect to spend at least 3 hours a week on the reading, more if you are leading the paper discussion.

ATTENDANCE:

You are expected to attend ALL class meetings. Acceptable reasons for missing a class are a documented medical emergency; family emergency; or university-sponsored event. Vacation, missing the bus, oversleeping, or deadlines or demands from other courses/exams are NOT acceptable reasons.

If you must miss class, communicate with the instructors in advance by email (koegema@ucsd.edu; abdesai@ucsd.edu), and we will give you a written assignment to make up for the missed class. If three classes are missed without an acceptable excuse, you will not receive a passing grade.

DISCUSSION LEADER AND PARTICIPANT INSTRUCTIONS:

DISCUSSION LEADERS:
Each group will be tasked with putting together a powerpoint and leading a discussion of one of the assigned research papers. The discussion is expected to take about an hour and 10 minutes.

DISCUSSION PARTICIPANTS:
All students are expected to read EVERY paper before coming to class and to be prepared to discuss it. The discussion leaders will think of questions to help take the group through the figures and stimulate discussion. In preparation for class, discussion participants are required to submit answers to the paper pre-discussion questions via the google form link on the syllabus. Answers must be received by noon on the day of the class – late submissions will receive no credit: NO EXCEPTIONS!

During the presentation and discussion, you are expected to participate actively.

DISCUSSION LEADER POWERPOINT FORMAT
Each discussion leader group should prepare a single unified powerpoint to help lead the class discussion.

TO INCLUDE IN POWERPOINT PRESENTATION:
1. *Background/Introduction*: Prepare to start by leading a discussion of the question(s) the authors are trying to address and how this work fits into the overall field.
2. *Results/data*: Break down the figures, putting the components on slides to help focus the discussion. Think of questions to ask to help guide the discussion. When needed, include background information that introduces the methods being used and include an outline of the experimental protocol. What do the results of the experiment suggest? Also, discuss any reservations or questions you have about the data or about its presentation in the paper.
3. *Conclusions:* What are the conclusions? What are the 'next steps' or remaining questions?

MEETINGS WITH PROFESSORS PRIOR TO PRESENTATION: Each group leading the paper discussion needs to coordinate and set up a time to meet with the assigned professor to discuss the paper. The groups should also set up a time to meet again to discuss how to set up the PowerPoint and effectively lead the discussion. The papers are complicated, and the level of background knowledge within class members varies. By working as a team you can give an effective presentation.