BIOGRAPHICAL SKETCH

NAME: Olive, Kenneth P.

eRA COMMONS USER NAME (credential, e.g., agency login): olivek

POSITION TITLE: Associate Professor, of Medicine

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Bucknell University, Lewisburg, PA	BS	06/1998	Biology
Massachusetts Institute of Technology, Cambridge, MA	PhD	12/2005	Biology
University of Pennsylvania, Philadelphia, PA & University of Cambridge, Cambridge, England	Postdoctoral	12/2009	Preclinical Therapeutics, Pancreatic Cancer

A. Personal Statement

My group was established in 2010 at the Columbia University Herbert Irving Comprehensive Cancer Center. I lead a multidisciplinary team of scientists and physicians at all levels of training who are devoted to the study of pancreatic cancer. We utilize human samples, advanced mouse models, tumor explant cultures, and computational techniques to identify and target critical tumor-specific vulnerabilities of pancreatic cancer. A core group within my lab runs our “Mouse Hospital”, preclinical implementation of a clinical multidisciplinary team that includes small animal imaging, surgery, treatment, pathology, molecular biology, tissue banking, and information management. These tools facilitate experiments ranging from basic studies of gene function, to translational studies of the molecular effects of drugs on pancreatic tumors, to clinical studies of human patient samples.

Over 24 years of training in biomedical research have prepared me to lead this work, beginning with 3 years of independent research as an undergraduate at Bucknell University. I received my Ph.D. in Cancer Biology from MIT in 2005. Working in the laboratory of Tyler Jacks at the MIT Center for Cancer Research, my doctoral studies addressed a long-standing question regarding the function of tumor-associated mutations in the p53 tumor suppressor gene. During that time, I also helped establish a genetically engineered mouse model of advanced lung adenocarcinoma that is now widely used by the research community. As part of my training, I also became adept at reading tumor pathology, generating and phenotyping mouse models of cancer, and adapting molecular biology assays for use on mammalian tissue samples.

I performed my postdoctoral fellowship in the laboratory of David Tuveson at the University of Pennsylvania and University of Cambridge (England). There I acquired a basic and clinical education in pancreatic cancer and I built the first incarnation of the Mouse Hospital. In the process I became adept at small animal imaging, pharmacology, mouse tissue sampling, small animal surgery, and translational therapeutics. I applied these skills to understanding the underlying cause of primary drug resistance in pancreatic cancer, leading to a landmark paper published in Science that illustrated the role of poor drug delivery in pancreatic cancer chemoresistance- a concept that has led to numerous clinical trials.

Upon joining the faculty of Columbia University, I built a laboratory dedicated to translational pancreatic cancer research. In addition to my prior interests in translational therapeutics and the tumor microenvironment, my research has also expanded into several new biological disciplines including tumor metabolism, systems biology, DNA damage response, imaging, and tumor immunology. The common goal of these diverse approaches is to identify and exploiting critical pancreatic cancer-selective dependencies.

In addition to my laboratory research, I have also built a large-scale translational core facility called the Oncology Precision Therapeutics and Imaging Core (OPTIC). This cancer center shared resource enables any investigator

to generate novel personalized models from patient materials, carry out preclinical therapeutics studies, and access state-of-the-art small animal imaging including optical, ultrasound, micro CT, and high field MRI. Most recently, I was appointed Director of GI Translational Research within the Department of Medicine, with a mandate to further built translational collaborations between GI basic scientists and physicians.

B. Positions and Honors

Positions and Employment

2010-	Member, Herbert Irving Comprehensive Cancer Center, Columbia University Medical Center, New York, NY
2010-2019	Assistant Professor, Department of Pathology, Columbia University, New York, NY
2010-2019	Assistant Professor, Department of Medicine, Columbia University, New York, NY
2011-2017	Director, HICCC Small Animal Imaging Shared Resource
2017-	Director, HICCC Oncology Precision Therapeutics and Imaging Core
2019-	Director of GI Translational Research, Department of Medicine, New York, NY
2019-	Associate Professor, Department of Medicine, Columbia University, New York, NY

Other Experience and Professional Memberships

2005-2009	Associate Member, American Association for Cancer Research
2009-	Member, American Association for the Advancement of Science
2010-2015	Member, New York Academy of Science Cancer & Signaling Discussion Group
2010-	Member, Executive Committee, The Pancreas Center, Columbia University Medical Center
2010-	Member, American Association for Cancer Research
2012-2013	Member, Institutional Animal Care and Use Committee
2012-	Scientific Review Board, Lustgarten Foundation for Pancreatic Cancer Research
2012-	Early Career Reviewer, NIH Study Section, ZRG1 BMCT-C(09)
2013-	Ad Hoc Reviewer, NIH Study Section, F09 Fellowship: Oncological Sciences
2015-	Ad Hoc Reviewer, NIH Study Section, Cancer Genetics
2017-	Ad Hoc Reviewer, NIH Study Section, ZRG1 BMCT-C(01)
2019-	Ad Hoc Reviewer, NIH Study Section, ZRG1 DKUS M(05)

Honors

2003- 2004	Koch Graduate Fellowship in Cancer Research
2006-	AACR Scholar-in-Training Award, Gerald B. Grindey Memorial Fund
2006-2009	Ruth L. Kirschstein National Research Service Awards Postdoctoral Fellowship, NIH
2009-	AACR Scholar-in-Training Award, MMHCC Meeting, San Francisco.
2010-	Bernard L. Schwartz Designated Research Scholar Award in Pancreatic Cancer
2011-	PanCAN-AACR Career Development Award
2011-	Lustgarten Foundation Translational Innovator Award
2015-	Ruth Leff Siegel Award for Pancreatic Cancer Research (Internal), Columbia University

C. Contributions to Science

1. ***Pancreatic Tumor Stroma Limits Drug Delivery and is Sculpted by Modulated Paracrine Hedgehog Signaling:*** Beginning during my postdoctoral fellowship, and continuing as an independent scientist, my lab has examined the contributions of stromal desmoplasia in pancreatic cancer. We learned that the stroma of pancreatic tumors limits the delivery of drugs to the tumor parenchyma, resulting in ineffective intratumoral drug concentrations. Malignant PDA cells control stromal desmoplasia through numerous paracrine signals, including the Hedgehog pathway, which promotes activation of stromal fibroblasts. We targeted this axis with a Smoothened inhibitor and found that the combined treatment with chemotherapy led to greater drug delivery and improved overall survival. The understanding that drug delivery is compromised in pancreatic cancer has led to a large field of research aimed at improving drug delivery in this disease and numerous clinical trials After targeted Smoothened inhibition failed in clinical trials for pancreatic cancer, my lab carried out a post-clinical trial and learned that while short-term inhibition of Smoothened (as used in the preclinical trial) leads to stromal depletion and transient increases in drug delivery, long-term Smoothened inhibition (as used in clinical trials) leads to chronic loss of Hedgehog-

responsive stromal cells. This work provided direct evidence that stromal fibroblasts can in some cases serve to restrain tumor growth.

a. **Olive KP**, Davidson CJ, Jacobetz MA, Honess D, McIntyre D, Madhu B, Goldgraben MA, Frese K, Caldwell ME, DeNicola G, Feig C, Gopinathan A, Combs C, Winter SP, Ireland H, Wang L, Rückert F, Grützmann R, Pilarsky C, Izeradjene K, Hingorani SR, Huang P, Davies SE, Iacobuzio-Donahue C, Plunkett W, Egorin M, Hruban RH, McGovern K, Griffiths J, Tuveson DA (2009). inhibition of hedgehog signaling enhances delivery of chemotherapy in a mouse model of pancreatic cancer. *Science*. 324(5933), 1457-1461. PMCID: PMC2998180
b. Rhim AD, Oberstein PE, Thomas DH, Mirek ET, Palermo CF, Sastra SA, Dekleva EN, Saunders T, Becerra CP, Tattersall IW, Westphalen CB, Kitajewski J, Fernandez-Barrena MG, Fernandez-Zapico ME, Iacobuzio-Donahue C, **Olive KP,** Stanger BZ (2014). Stromal elements act to restrain, rather than support, pancreatic ductal adenocarcinoma*. Cancer Cell*. 25(6), 735-747. PMCID: PMC4096698

2. **Systems Biology Approaches to the Dissection of Compartment-Specific Gene Expression in PDA:** My team optimized an approach for RNA-sequencing of laser capture microdissected human PDA samples as well as associated preinvasive lesions. In the first of several planned manuscripts, we profiled the complement of long non-coding RNAs associated with pancreatic cancer, revealing thousands of previously uncharacterized transcripts. Functional assessment of two such genes identified roles in tumor differentiation and metastasis.
    a. Maurer C, Holmstrom SR, He J, Laise P, Su T, Ahmed A, Hibshoosh H, Chabot JA, Oberstein PE, Sepulveda AR, Genkinger JM, Zhang J, Iuga AC, Bansal M, Califano A, **Olive KP,** (2019) Experimental microdissection enables functional harmonisation of pancreatic cancer subtypes. *Gut.* 68(6), 1034-1043. PMID: 30658994
    b. Arnes L, Liu Z, Wang J, Carlo Maurer H, Sagalovskiy I, Sanchez-Martin M, Bommakanti N, Garofalo DC, Balderes DA, Sussel L, **Olive KP**, Rabadan R. (2018). Comprehensive characterisation of compartment-specific long non-coding RNAs associated with pancreatic ductal adenocarcinoma" *Gut.* advance online. PMID: 29440233

3. **Translational Therapeutics for Pancreatic Ductal Adenocarcinoma***:* Designed, built, and utilized the Mouse Hospital translational therapeutics infrastructure in order to carry out translational studies in mouse models of pancreatic cancer. We developed a number of technical advances, including novel imaging techniques and a novel surgery to acquire biopsies from abdominal tumors. We applied these techniques in order to evaluate promising preclinical agents and aid their translation into the clinic. One example is PTC596, novel anticancer agent with advantageous pharmacological properties. We determined that PTC596 synergizes potently with standard of care therapy for pancreatic cancer resulting in tumor regressions in a patient-derived xenograft model and a significant extension of overall survival in the KPC mouse model of PDA. Based on our work, a Phase 1b/2 clinical trial is in development. I also led a clinical protocol to evaluate a novel form of function ultrasound in freshly resected pancreatic specimens.
    a. Eberle-Singh JA, Sagalovskiy I, Maurer HC, Sastra SA, Palermo CF, Decker AR, Kim MJ, Sheedy J, Mollin A, Cao L, Hu J, Branstrom A, Weetall M, Olive KP, (2019). Effective delivery of a microtubule polymerization inhibitor synergizes with standard regimens in models of pancreatic ductal adenocarcinoma. *Clinical Cancer Research,.* PMID: 31175095
    b. Payen T, Palermo CF, Sastra SA, Chen H, Han Y, **Olive KP,** Konofagou EE (2016). Elasticity mapping of murine abdominal organs in vivo using harmonic motion imaging (HMI). *Phys Med Biol,* 61(15), 5741-5754. PMCID: PMC5048218
    c. Sastra, SA & **Olive, KP** (2014). Acquisition of tumor biopsies through abdominal laparotomy. *Cold Spring Harb Protoc.* (1), 47-56. PMCID: PMC4084730
    d. Sastra SA, **Olive KP** (2013). Quantification of murine pancreatic tumors by high-resolution ultrasound. *Methods Mol Biol,* 980, 249-66. PMCID: PMC3879959

4. **Established the Neomorphic Effects of Mutant p53 in Cancer in Vivo:** In work that answered a long-standing question in the p53 field, we asked whether tumor-associated point mutations conferred novel, pro-oncogenic functions to the p53 protein. We engineered strains of mice with conditional or germline point-mutant p53 alleles targeted to the endogenous p53 locus. Analysis of germline knock-in mice provided strong evidence that tumor associated mutations confer both novel gain-of-function effects as well as partial dominant negative effects. Addition of conditional mutant p53 alleles to a K-ras driven model

of lung adenocarcinoma resulted in a model of high-grade disease that is still widely used in the lung cancer field.

a. **Olive KP**, Tuveson DA, Ruhe ZC, Yin B, Willis NA, Bronson RT, Crowley D, Jacks T (2004). Mutant p53 gain of function in two mouse models of Li-Fraumeni syndrome. *Cell,* 119(6), 847-60. PMCID: PMC15607980
b. Wijnhoven SW, Zwart E, Speksnijder EN, Beems RB, **Olive KP**, Tuveson DA, Jonkers J, Schaap MM, van den Berg J, Jacks T, van Steeg H, de Vries A (2005). Mice expressing a mammary gland-specific r270h mutation in the p53 tumor suppressor gene mimic human breast cancer development. *Cancer Res*, 65 (18), 8166-8173. PMCD: 16166291
c. Jackson EL[†] & **Olive KP[†],** Tuveson DA, Bronson R, Crowley D, Brown M, Jacks T (2005). The Differential Effects of Mutant p53 Alleles on Advanced Murine Lung Cancer. *Cancer Res*, 65(22), 10280-10288. PMID: 16288016

5. **Collaborative Efforts in Cancer Research:** We have used the expertise of the Olive laboratory to support high impact efforts in a range of cancer biology fields, in particular providing *in vivo* support for findings.
   a. Welsch ME, Kaplan A, Chambers JM, Stokes ME, Bos PH, Zask A, Zhang Y, Sanchez-Martin M, Badgley MA, Huang CS, Tran TH, Akkiraju H, Brown LM, Nandakumar R, Cremers S, Yang WS, Tong L, **Olive KP**, Ferrando A, Stockwell BR (2017). Multivalent small-molecule Pan-RAS inhibitors. *Cell*, 168(5), 878-889.e29, PMCID: PMC5362268
   b. Westphalen CB, Takemoto Y, Tanaka T, Macchini M, Jiang Z, Renz BW, Chen X, Ormanns S, Nagar K, Tailor Y, May R, Cho Y, Asfaha S, Worthley DL, Hayakawa Y, Urbanska AM, Quante M, Reichert M, Broyde J, Subramaniam PS, Remotti H, Su GH, Rustgi AK, Friedman RA, Honig B, Califano A, Houchen CW, **Olive KP**, Wang TC (2016). Dclk1 defines quiescent pancreatic progenitors that promote injury-induced regeneration and tumorigenesis. *Cell Stem Cell* 18(4), 441-455. PMCID: PMC4826481
   c. Harmsen S, Huang R, Wall MA, Karabeber H, Samii JM, Spaliviero M, White JR, Monette S, O'Connor R, Pitter KL, Sastra SA, Saborowski M, Holland EC, Singer S, **Olive KP**, Lowe SW, Blasberg RG, Kircher *MF* (2015). Surface-enhanced resonance Raman scattering nanostars for high-precision cancer imaging. *Sci Transl Med,* 7(271), 271ra7. PMCID: PMC4414254
   d. Shakya R, Gonda T, Quante M, Salas M, Kim S, Brooks J, Hirsch S, Davies J, Cullo A, **Olive KP,** Wang TC, Szabolcs M, Tycko B, Ludwig T (2014). Hypomethylating therapy in an aggressive stroma-rich model of pancreatic carcinoma. *Cancer Res,* 73(2), 885-896. PMCID: PMC3548986

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/1rYqyyWbRbZ/bibliography/41121165/public

D. Research Support

Ongoing Research Support

P30 CA013696 Rustgi (PI) 07/01/97-06/30/20
NIH/NCI
Cancer Center Support Grant
This grant supports the leadership of Columbia University's laboratory, clinical, and population-based cancer research programs and the shared resources serving Columbia University's Cancer Center members.
Role: Director, Oncology Precision Therapeutics and Imaging Core

Bristol Meyers Squibb Olive (PI) 09/01/17-08/31/20
IION Award
This grant supports a computational analysis of pancreatic tumors combined with immunophenotyping of cellular populations across a large cohort of human PDA cases.

Lustgarten Foundation Olive (PI) 02/01/18-01/31/21
Translational Clinical Program
This program-level grant will support a clinical trial of network-based precision medicine for pancreatic cancer as well as a complementary preclinical research effort to develop combination therapies.
Role: PI

U54 CA209997 Califano (PI) 08/08/16-07/31/21
NIH/NCI
Centers for Cancer Systems Therapeutics (CaST)
Supports a project within CaST to study genome-wide paracrine communication between the malignant epithelium and stroma of pancreatic cancer.
Role: Co-investigator

R01 CA215607 03/01/17-02/28/22
NIH/NCI
Targeting Cysteine Import to Induce Ferroptotic Cell Death in Pancreatic Cancer
Metabolism experiments designed to explore the function of cysteine in pancreatic cancer and its relationship to ferroptosis (an ROS-mediated cell death), using cell culture, metabolomics, and mouse models.
Role: PI

Completed Research Support

P30 CA13696 Emerson (PI) 07/01/14-06/30/19
NIH/NCI
Cancer Center Support Grant – Administrative Supplement
Targeting the granulocyte/fibroblast axis to overcome immunosuppression in pancreatic ductal adenocarcinoma. This project explores the role of the Hedgehog-pathway in fibroblasts signaling to myeloid derived suppressor cells in pancreatic cancer.
Role: Project Leader

R21CA188857 07/01/14-06/30/16
NIH/NCI
Preclinical Evaluation of a Targeted Bmi1 Inhibitor in Pancreatic Cancer
This pilot study will fund the preclinical evaluation of the indirect Bmi1 inhibitor, PTC-596, including preclinical efficacy experiments in genetically engineered mouse models of PDA.
Role: PI

ACS Grant #122801 07/1/12-06/30/16
American Cancer Society
Preclinical Evaluation of Parp Inhibition in Pancreatic Cancer
The goal of this proposal is to evaluate a Parp inhibitor in the context of BRCA2 wild type and deficient pancreatic tumors to determine sensitivity, and to identify biomarkers of resistance versus sensitivity.
Role: PI

Lustgarten Foundation Grant 08/1/13-07/31/16
Lustgarten Foundation
Focused Ultrasound Technologies for Diagnosis, Monitoring, and Treatment of Pancreatic Cancer
Preclinical development and clinical translation of a novel functional ultrasound technology for pancreatic cancer.
Role: PI