BIOGRAPHICAL SKETCH

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NAME: HOU, PINGPING

eRA COMMONS USER NAME (credential, e.g., agency login): PHOU01

POSITION TITLE: Assistant Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
China Agricultural University, Beijing, China	BS	07/2007	Molecular Biology
Peking University, Beijing, China	PhD	01/2014	Cell Biology
The University of Texas MD Anderson Cancer Center, Houston, Texas, United States	Postdoctoral	08/2021	Cancer Biology

A. Personal Statement

I am a tenure-track assistant professor specialized in pancreatic ductal adenocarcinoma (PDAC). I have a broad background in biology, with specific training and expertise in cellular reprogramming, cancer genetics, signaling transduction, cancer metabolism, biochemistry, tumor microenvironment analysis and mouse model studies. I have been working on dissecting tumor cell autonomous and non-autonomous molecular mechanisms of KRAS targeted therapy resistance in PDAC genetically engineered mouse models since 2014 and have identified several novel factors such as HDAC5, USP21, TGFβ and macrophages involved in the regulation. My Ph.D work focused on chemical reprogramming of somatic cells into pluripotency, which provides me with an excellent background in the cellular plasticity and molecular remodeling. My lab has worked on macrophage cell therapy and the design of chimeric antigen receptors since 2021 and has established cell engineering platforms. As PI or key personnel on a number of nonprofit organization- and NIH-funded grants, I laid the groundwork for the proposed research by developing several *in vitro* and *in vivo* research models of PDAC, platforms for immune cell expansion, engineering and analysis, methods of synthetic biology, biochemical, transcriptomic, epigenetic and proteomic profiling and data analysis pipeline and by establishing strong ties with experts in biochemistry, immunology and bioinformatics at various institutions such as Rutgers University, MD Anderson Cancer Center and Harvard University that I can collaborate with to accelerate research progress. In addition, I successfully achieved research goals in a collaborative manner and published original research articles in peer-reviewed journals from each project. These accumulated experiences make me aware of the importance of pursuing fundamental scientific questions, of frequent communication with other experts, and of designing experiments with realistic aims, timeline and budget. My previous work strongly supports the rationale of current application. Collectively, I have the experience, expertise, leadership, training, passion, and a supportive research team to successfully address fundamental scientific questions and conduct innovative research projects when new opportunities arise.

Ongoing and recently completed projects that I would like to highlight include:

K22 K22CA251491-01
Hou (PI)
12/01/21-11/30/24
Tumor-TAMs crosstalk enables bypass of oncogenic KRAS dependency in pancreatic cancer

Lustgarten Foundation-AACR Career Development Award for Pancreatic Cancer Research, in Honor of Ruth Bader Ginsburg 22-20-67-HOU
Hou (PI)
07/01/22-06/30/25
Anti-KRAS therapy resistance and pancreatic tumor immune microenvironment

The Hirshberg Foundation Seed Grant Program
Hou (PI)
11/15/16-11/14/17
Identification of USP21 as a novel oncogene to drive Kras*-extinction resistance in pancreatic cancer

Citations:

1. **Hou P**, Ma X, Yang Z, Zhang Q, Wu CJ, Li J, Tan L, Yao W, Yan L, Zhou X, Kimmelman AC, Lorenzi PL, Zhang J, Jiang S, Spring D, Wang YA, DePinho RA. USP21 deubiquitinase elevates macropinocytosis to enable oncogenic KRAS bypass in pancreatic cancer. Genes Dev. 2021 Oct 1;35(19-20):1327-1332.
2. **Hou P**, Kapoor A, Zhang Q, Li J, Wu CJ, Li J, Lan Z, Tang M, Ma X, Ackroyd JJ, Kalluri R, Zhang J, Jiang S, Spring DJ, Wang YA, DePinho RA. Tumor Microenvironment Remodeling Enables Bypass of Oncogenic KRAS Dependency in Pancreatic Cancer. Cancer Discov. 2020 Jul;10(7):1058-1077.
3. **Hou P**, Ma X, Zhang Q, Wu CJ, Liao W, Li J, Wang H, Zhao J, Zhou X, Guan C, Ackroyd J, Jiang S, Zhang J, Spring DJ, Wang YA, DePinho RA. USP21 deubiquitinase promotes pancreas cancer cell stemness via Wnt pathway activation. Genes Dev. 2019 Oct 1;33(19-20):1361-1366.
4. **Hou P**, Li Y, Zhang X, Liu C, Guan J, Li H, Zhao T, Ye J, Yang W, Liu K, Ge J, Xu J, Zhang Q, Zhao Y, Deng H. Pluripotent stem cells induced from mouse somatic cells by small-molecule compounds. Science. 2013 Aug 9;341(6146):651-4.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2021-present Assistant Professor, Department of Microbiology, Biochemistry and Molecular Genetics, Rutgers University RBHS-NJMS, Newark, NJ
2021-present Member, Center for Cell Signaling, Rutgers University RBHS-NJMS, Newark, NJ
2021-present Member, RBHS Institute for Infectious and Inflammatory Diseases, Newark, NJ
2021-present Member, Rutgers Cancer Institute of New Jersey
2014-present Member, American Association for Cancer Research (AACR)

Honors

2022 Lustgarten Foundation-AACR Career Development Award
2021 Wall of Science awardee, UT MD Anderson Cancer Center, Houston, TX
2021 Thomas H. and Mayme P. Scott Fellowship in Cancer Research, UT MD Anderson Cancer Center, Houston, TX
2021 Outstanding Research Publication Awards, UT MD Anderson Cancer Center, Houston, TX
2020 Harold C. and Mary L. Dailey Endowment Fellowship, UT MD Anderson Cancer Center, Houston, TX
2020 NIH-NCI K22 Career Transition Award
2018 AACR Scholar-in-Training Award, Aflac, Inc.

C. Contributions to Science

1. My early publications addressed the fundamental question whether somatic cells can be reprogrammed by non-genetic methods. Somatic reprogramming is an extreme case demonstrating cell fate plasticity supervened with huge clinical potential in cell therapy, regenerative medicine, and drug development. Since

small molecules are ideal for clinical applications due to its nonimmunogenic and standardized features, my colleagues and I have developed the first chemical method to induce pluripotency. As the group leader, I identified that the adenylyl cyclase (AC) activator- Forskolin efficiently replaces *Oct4*, the most important transcription factor for pluripotency, in reprogramming. Based on the discovery, I invented a step-wised method to induce pluripotency from mouse embryonic and neonatal fibroblast cells by five small molecules. Chemically induced mouse pluripotent stem cells resemble embryonic stem cells, while the reprogramming route is distinct from Yamanaka's method that activation of Sall4 and Sox2 is essential and sufficient for the process. The study suggests that it is practicable to reprogram cell fates by small molecules in mammals and provides new platforms for clinical research and great implications for regenerative medicine. I served as the primary investigator or co-investigator in all these studies.

a. Deng H, Zhao Y, **Hou P**, Li Y, Zhang X, Liu C, Guan J, Li H. Compositions and methods for reprograming non- pluripotent cells into pluripotent stem cells. Jan 15, 2015. Patent Number: WO2015003643A1 and CN104278008A.
b. **Hou P**, Li Y, Zhang X, Liu C, Guan J, Li H, Zhao T, Ye J, Yang W, Liu K, Ge J, Xu J, Zhang Q, Zhao Y, Deng H. Pluripotent stem cells induced from mouse somatic cells by small-molecule compounds. Science. 2013 Aug 9;341(6146):651-4.
c. Li Y, Zhang Q, Yin X, Yang W, Du Y, **Hou P**, Ge J, Liu C, Zhang W, Zhang X, Wu Y, Li H, Liu K, Wu C, Song Z, Zhao Y, Shi Y, Deng H. Generation of iPSCs from mouse fibroblasts with a single gene, Oct4, and small molecules. Cell Res. 2011 Jan;21(1):196-204.
d. Liu H, Zhu F, Yong J, Zhang P, **Hou P**, Li H, Jiang W, Cai J, Liu M, Cui K, Qu X, Xiang T, Lu D, Chi X, Gao G, Ji W, Ding M, Deng H. Generation of induced pluripotent stem cells from adult rhesus monkey fibroblasts. Cell Stem Cell. 2008 Dec 4;3(6):587-90.

2. Studies of acquired resistance to oncogenic KRAS (KRAS*) inhibition in cancer cells majorly focus on tumor cell intrinsic mechanisms, while non-tumor cell autonomous resistance mechanisms are underexplored. By using a doxycycline-inducible KRAS(G12D) p53 mutant genetically engineered mouse (iKPC GEM) PDAC model, I demonstrated that tumor-associated macrophages (TAMs) promote PDAC cells to bypass KRAS* dependency by providing tumor cells with paracrine TGFβ. In detail, KRAS depletion upregulates HDAC5 in PDAC cells, which increases CCL2 secretion via epigenetic suppression of *Socs3* to remodel myeloid cells in tumor microenvironment (TME) from neutrophil- to macrophage-rich phenotype. Inhibition of HDAC5, CCL2-CCR2 axis, or macrophage infiltration impairs HDAC5-driven KRAS* bypass in vivo. Accordingly, enforced expression of Ccl2 in PDAC cells recruits macrophages to bypass KRAS* dependency. Mechanistically, the infiltrated M2-like CCR2+ TAMs are the major source of TGFβ in TME, which efficiently promotes KRAS*-independent PDAC cell growth via canonical SMADs pathway activation. My work, for the first time, establishes tumor-TME crosstalk as a mechanism for PDAC to escape from KRAS* dependency. The importance of activated TGFβ signaling in KRAS* bypass and the high frequency of SMAD4 loss in human PDAC support clinical testing of KRAS* inhibitors in SMAD4 null patients. I served as the primary investigator or co-investigator in these studies.

a. Deng D, Patel R, Chiang C, **Hou P**. Role of the tumor microenvironment in regulating pancreatic cancer therapy resistance. Cells. 2022, 11, 2952. (Corresponding author)
b. **Hou P**, Wang YA. Conquering oncogenic KRAS and its bypass mechanisms. Theranostics. 2022 Jul 18;12(13):5691-5709. (Co-corresponding author)
c. **Hou P**, Kapoor A, Zhang Q, Li J, Wu CJ, Li J, Lan Z, Tang M, Ma X, Ackroyd JJ, Kalluri R, Zhang J, Jiang S, Spring DJ, Wang YA, DePinho RA. Tumor microenvironment remodeling enables bypass of oncogenic KRAS dependency in pancreatic cancer. Cancer Discov. 2020 Apr 27:CD-19-0597.
d. Wang G, Lu X, Dey P, Deng P, Wu CC, Jiang S, Fang Z, Zhao K, Konaparthi R, Hua S, Zhang J, Li-Ning-Tapia EM, Kapoor A, Wu CJ, Patel NB, Guo Z, Ramamoorthy V, Tieu TN, Heffernan T, Zhao D, Shang X, Khadka S, **Hou P**, Hu B, Jin EJ, Yao W, Pan X, Ding Z, Shi Y, Li L, Chang Q, Troncoso P, Logothetis CJ, McArthur MJ, Chin L, Wang YA, DePinho RA. Targeting YAP-Dependent MDSC Infiltration Impairs Tumor Progression. Cancer Discov. 2016 Jan;6(1):80-95.

3. To address the role of genetic alternations in regulating KRAS* targeted therapy resistance in pancreatic cancer, I focused on protein ubiquitination regulators that are usually altered in human cancers. My efforts to identify actionable drivers in pancreatic ductal adenocarcinoma (PDAC) led to the discovery of a novel

PDAC oncogene, USP21 deubiquintinase, which is recurrently amplified in 22% of PDAC cases and shows increased expression with disease progression. I established that USP21 not only promotes PDAC growth, cancer stemness and human pancreatic ductal epithelial cell transformation, but also drives KRAS* bypass. USP21 deubiquintinates and stabilizes TCF7 protein, a downstream transcription factor of the Wnt pathway, to increase tumor-initiating capacity. Alternatively, USP21 elevated macropinocytosis activity via its substrate MARK3, a regulator of microtubule dynamics, in KRAS*-depleted cancer cells to maintain amino acid homeostasis, reactivate mTOR signaling pathway and support KRAS*-independent growth. Depletion of USP21 impairs PDAC tumor growth, suggesting USP21 as a novel therapeutic target for the deadly disease. The work reinforces the importance of metabolic salvage pathway activation in regulating KRAS* targeted therapy resistance. I served as the primary investigator or co-investigator in these studies.

a. **Hou P**, Ma X, Yang Z, Zhang Q, Wu CJ, Li J, Tan L, Yao W, Yan L, Zhou X, Kimmelman AC, Lorenzi PL, Zhang J, Jiang S, Spring D, Wang YA, DePinho RA. USP21 deubiquitinase elevates macropinocytosis to enable oncogenic KRAS bypass in pancreatic cancer. Genes Dev. 2021 Oct 1;35(19-20):1327-1332.
b. **Hou P**, Ma X, Zhang Q, Wu CJ, Liao W, Li J, Wang H, Zhao J, Zhou X, Guan C, Ackroyd J, Jiang S, Zhang J, Spring DJ, Wang YA, DePinho RA. USP21 deubiquitinase promotes pancreas cancer cell stemness via Wnt pathway activation. Genes Dev. 2019 Oct 1;33(19-20):1361-1366.
c. Yao W, Rose JL, Wang W, Seth S, Jiang H, Taguchi A, Liu J, Yan L, Kapoor A, **Hou P**, Chen Z, Wang Q, Nezi L, Xu Z, Yao J, Hu B, Pettazzoni PF, Ho IL, Feng N, Ramamoorthy V, Jiang S, Deng P, Ma GJ, Den P, Tan Z, Zhang SX, Wang H, Wang YA, Deem AK, Fleming JB, Carugo A, Heffernan TP, Maitra A, Viale A, Ying H, Hanash S, DePinho RA, Draetta GF. Syndecan 1 is a critical mediator of macropinocytosis in pancreatic cancer. Nature. 2019 Apr;568(7752):410-414.

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/1nGjaK52LKHluk/bibliography/public/