BIOGRAPHICAL SKETCH

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NAME: Shin-Heng Chiou

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

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
National Taiwan University, Taipei, Taiwan	B.S.	07/2000	Zoology
National Taiwan University, Taipei, Taiwan	M.S	07/2003	Immunology
Baylor College of Medicine, Houston, TX	Ph.D.	09/2011	Immunology
Stanford University, Stanford, CA	Postdoc	12/2015	Cancer Biology (Laboratory of Monte Winslow)
Stanford University, Stanford, CA	Postdoc	11/2019	Immune Oncology (Laboratory of Mark Davis)

A. Personal Statement

My laboratory focuses on both cancer biology and immunology. After receiving my PhD degree in Immunology, I trained as a postdoctoral researcher in Dr. Monte Winslow's laboratory at Stanford University focusing on the role of intratumoral hypoxia in metastasis as well as T cell biology in cancer. Within the tumor microenvironment of PDAC, I discovered that hypoxia induces a transient metastatic program in cancer cells (Chiou *et al*., 2017). I also pioneered CRISPR/Cas9-based methods for PDAC mouse modeling (Chiou *et al.*, 2015; Winters *et al*., 2017). These tools allowed me to address fundamental questions in PDAC biology. Following my training in PDAC studies, I pursued a second postdoctoral training in Dr. Mark M. Davis' group and focused on T cell biology in cancer. While in the Davis laboratory, I gained an extensive expertise in applying computational tools to study T cell biology in cancer, with a focus on the T cell antigen specificity. In 2020, I moved to Rutgers Cancer Institute of New Jersey (CINJ) as a tenure-track Assistant Professor of Medicine, Rutgers Robert Wood Johnson Medical School.

Antigen specificity is the key determinant of T cell function, but challenges posed by the extremely high diversity of the T cell receptor (TCR) repertoire and the polymorphic nature of human leukocyte antigens (HLA) have been two major obstacles to the understanding of the full spectrum of antigens recognized by tumor-infiltrating T cells. An overarching goal of my lab is to study the antigen specificity of T cells in cancer patients and ultimately translate this knowledge into clinical practice. In my lab, we implement state-of-the-art computational algorithms and develop innovative antigen screen platforms to uncover novel T cell specificities in solid tumors, including PDAC, non-small cell lung cancer (NSCLC), and other solid cancer types. Using this approach, our recent study uncovered novel cross-reactive epitopes from both tumor antigen and pathogens in NSCLC patients.

High level of intratumoral hypoxia has been implicated in the recalcitrance to therapy, proclivity to metastasis, and high incidence of postoperative relapse in pancreatic ductal adenocarcinoma (PDAC). However, our current understanding of how intratumoral hypoxia modulates the disease progression remains incomplete. Recent findings showed that the hypoxia-induced factor (HIF) appeared to play a negligible role in the changes of chromatin modification induced by hypoxia. Consistently, our preliminary results show that hypoxia is a strong

inducer for chromatin reprogramming through members of the oxygen-sensing, histone lysine demethylases in PDAC. Thus, **the second overarching goal of my laboratory is to uncover the molecular mechanisms of hypoxia-induced chromatin changes that drive disease progression and metastasis of pancreas cancer**. To achieve this, we are developing novel genetically engineered mouse models of PDAC that allow us to use CRISPR/Cas9-based somatic genome engineering in combination with quantitative genomic approaches in order to understand how different genetic regulators of PDAC progression interact with and respond to the tumor hypoxic microenvironment. Most recently, we found that inactivation of the histone demethylase *Kdm8* reprograms PDAC cells into a highly metastatic state. Genetic depletion of *Kdm8* reduces the expression of genes defining the classical PDAC subtype and drives a profound loss of differentiation in our unique genetically-engineered PDAC mouse model. Our study supports the model in which hypoxia within the tumor microenvironment can promote PDAC progression by suppressing the function of Kdm8. In addition to hypoxia, we are also interested in exploring other cancer cell extrinsic factors that play important roles in PDAC subtype determination and disease progression.

Ongoing projects that I would like to highlight include:

R01 1R01CA243547-01A1, Multi-PI 12/01/19-11/30/24
Chiou (PI), Role: Co-Investigator
Project Goals: To decipher the mechanisms by which high mutation burden alters the immune landscape and response to therapy using mouse models and begin to correlate these findings using specimens from our ongoing clinical trials to address mechanistic relevance in patients.

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2020-	Assistant Professor (tenure-track), Department of Medicine, Rutgers Robert Wood Johnson Medical School, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ
2016-2019	Research Scientist, Laboratory of Dr. Mark M Davis, Institute for Immunity, Transplantation, and Infection, Stanford University, Stanford, CA
2011-2015	Postdoctoral Fellow, Laboratory of Dr. Monte Winslow, Department of Genetics, Stanford University, Stanford, CA
2005-2011	Graduate Student (Ph.D.), Program in Immunology, Laboratory of Dr. David Spencer, Baylor College of Medicine, Houston, TX
2003-2005	Research Associate, National Taiwan University Hospital, Taipei, Taiwan
2000-2003	Graduate Student (M.Sc.), National Taiwan University, Taipei, Taiwan

Honors

2020-2022	The V Foundation for Cancer Research Award
2018-2019	The Anderman Pancreatic Cancer Research Fellowship
2013-2014	Dean's Postdoctoral Fellowship, School of Medicine, Stanford University
2009-2011	Department of Immunology Training Grant (5T32AI007495), Baylor College of Medicine

C. Contributions to Science

1. Contributions to immuno-oncology:

   The field of immuno-oncology has gained significant public attention in recent years, a strong testament to the feasibility of using the immune system to fight cancer. Despite the advances, only a small subset of patients responds to treatment and many of these patients would eventually succumb to a relapse. Thus, it is imperative to understand the underlying mechanism of responses to ICB. During the training in earning my M.S. degree, I first reported the phenotypic feature of tumor-infiltrating $CD8^+$ T cells in human cervical cancer. During my PhD training, I was involved in the effort of engineering the therapeutic dendritic cell vaccines for cancer. As a postdoc in the Mark Davis group at Stanford, I focused on studies of the antigen specificity landscape of tumor-infiltrating T cells in human NSCLC. Together with my collaborators from the MD Anderson Cancer Center, we recently discovered that patients with higher TCR repertoire homology between the tumor and the adjacent lung tended to have worse outcome. Furthermore, we recently pioneered an innovative platform to study T cell specificities in NSCLC and showed that at least some pathogen-specific T cells found in tumors (a.k.a. "bystander T cells") could cross-recognize both tumor antigens and microbial

antigens. Our findings further suggested an involvement of these cross-reactive T cells in the clinical response to anti-PD1 treatment in lung cancer.

a. **Chiou SH***, Tseng D*, Reuben A, Mallajosyula A, Molina IS, Conley S, Wilhelmy J, McSween AM, Yang X, Nishimiya D, Sinha R, Nabet BY, Wang C, Shrager JB, Berry MF, Backhus L, Lui N, Wakelee HA, Neal JW, Sukhmani PK, Berry GJ, Delaidelli A, Sorensen PH, Sotillo E, Tran P, Benson JA, Richards R, Labanieh L, Klysz DD, Louis DM, Feldman S, Diehn M, Weissman IL, Zhang J, Wistuba II, Futreal PA, Heymach JV, Garcia KC, Mackall CL[#], Davis MM[#]. (2021) Global analysis of shared T cell specificities in human non-small cell lung cancer enables HLA inference and antigen discovery. ***Immunity***. Volume 54(3), 586. PMID: 33691136. *co-first authorship; [#]co-senior authorship

b. Reuben A*, Zhang J*, **Chiou SH***, Gittelman RM*, Li J, Lee WC, Fujimoto J, Behrens C, Liu X, Wang F, Quek K, Wang C, Kheradmand F, Chen R, Chow CW, Lin H, Bernatchez C, Jalali A, Hu X, Wu CJ, Eterovic AK, Parra ER, Yusko E, Emerson R, Benzeno S, Vignali M, Wu X, Ye Y, Little LD, Gumbs C, Mao X, Song X, Tippen S, Thornton RL, Cascone T, Snyder A, Wargo JA, Herbst R, Swisher S, Kadara H, Moran C, Kalhor N, Zhang J, Scheet P, Vaporciyan AA, Sepesi B, Gibbons DL, Robins H, Hwu P, Heymach JV, Sharma P, Allison JP, Baladandayuthapani V, Lee JJ, Davis MM, Wistuba II, Futreal PA, Zhang J. (2020) Comprehensive T cell repertoire characterization of non-small cell lung cancer. ***Nature Communication*** Volume 11(1), 603. *co-f**irst** authorship. PMID: 32001676.

c. **Chiou SH**, Shahi P, Wagner RT, Hu H, Lapteva N, Seethammagari M, Sun SC, Levitt JM, and Spencer DM. (2011) The E3 ligase c-Cbl regulates dendritic cell activation. ***EMBO Reports*** Volume 12(9), 971-979. PMID: 21799517.

d. Sheu BC, **Chiou SH**, Lin HH, Chow SN, Huang SC, Ho HN, Hsu SM. (2005) Up-regulation of inhibitory natural killer receptors CD94/NKG2A with suppressed intracellular perforin expression of tumor-infiltrating CD8+ T lymphocytes in human cervical carcinoma. ***Cancer Research*** Volume 65(7), 2921-2929. PMID: 15805295.

2. Development of novel methods to study cancer *in vivo*:

Due to the lack of efficacious treatment strategies, PDAC is projected to be the second most lethal solid cancer type in the United States before 2025. As most patients have already developed locally advanced and/or metastatic diseases upon diagnosis, it is critical to understand the mechanism of PDAC progression. To do so, genetically engineered mouse (GEM) models that recapitulate the key genetic events found in human disease proved to be a power tool in helping us gain a better understanding of PDAC dissemination and metastasis. Despite the advantages, current PDAC GEM models are notoriously labor-intensive and costly to work with. This technical limitation further motivated us to pioneer a novel PDAC GEM model that allowed the use of CRISPR technology to modify any conceivable genetic component in the pancreas of adult mice. By using the retrograde pancreatic ductal injection procedure, I initially demonstrated, as proof of principle, that it was possible to deplete tumor suppressors with CRISPR and induce PDAC in mice. Furthermore, I developed a platform using barcoded adeno-associated virus that allowed a comprehensive quantification of the impact from distinct *Kras* point mutations on PDAC progression. In summary, these inventions help us robustly model PDAC in mice and study the progression of the disease at a deeper and physiologic level.

a. Winters IP, **Chiou SH**, Paulk NK, McFarland CD, Lalgudi PV, Ma RK, Lisowski L, Connolly AJ, Petrov DA, Kay MA, and Winslow MM. (2017) Multiplexed in vivo homology-directed repair and tumor barcoding enables parallel quantification of Kras variant oncogenicity. ***Nature Communication*** Volume 8(1), 2053. PMID: 29233960.

b. **Chiou SH***, Winters IP*, Wang J, Naranjo S, Yang D, Tamburini FB, Grüner BM, Chuang CH, Brady JJ, Caswell DR, Lisowski L, Zeng H, Chu P, Kay MA, Kim GE, Kim SK, and Winslow MM. (2015) Pancreatic cancer modeling with viral vectors and in vivo CRISPR/Cas9-mediated somatic genome editing. ***Genes and Development*** Volume 29(14), 1576-1585. *co-first authorship. PMID: 26178787.

c. **Chiou SH**, Kim-Kiselak C, Risca VI, Heimann M, Chuang CH, Burds AA, Greenleaf WJ, Jacks TE, Feldser DM, and Winslow MM. (2014) A conditional system to specifically link disruption of protein coding function with reporter expression in mice. ***Cell Reports*** Volume 7(6), 2078-2086. PMID: 24931605.

d. Grüner BM, Schulze CJ, Yang D, Ogasawara D, Dix MM, Rogers ZN, Chuang CH, McFarland CD, **Chiou SH**, Brown JM, Cravatt BF, Bogyo M, Winslow MM. (2016) An in vivo multiplexed small-molecule screening platform. ***Nat Methods*** Volume 13(10), 883-889. PMID: 27617390.

3. *Contributions to cancer studies (biology):*

Most PDAC patients eventually develop metastases, therefore, it is important to uncover the mechanisms for metastasis. As a postdoc in Monte Winslow's group at Stanford, I first pioneered a unique PDAC GEM model that allowed me to fluorescently label highly metastatic PDAC cancer cells from the less metastatic counterparts with our unique genetic reporter. This enabled sorting of pure cancer cell populations with differential capacities to disseminate and metastasize to distal organs, as often data derived from bulk RNA sequencing were confounded by the inclusion of non-cancer cell types within tumors. The unique design led to the identification of a hypoxia-induced master regulator Blimp1 in driving the metastatic programs in PDAC. In addition to PDAC studies, I was involved in various collaborative works within the Winslow group that focused on both small cell lung cancer as well as lung adenocarcinoma.

a. **Chiou SH**, Dorsch M, Kusch E, Naranjo S, Kozak MM, Koong AC, Winslow MM, Grüner BM. (2018) Hmga2 is dispensable for pancreatic cancer development, metastasis, and therapy resistance. ***Scientific Reports*** Volume 8(1), 14008. PMID: 30228296.

b. **Chiou SH**, Risca VI, Wang GX, Yang D, Grüner BM, Kathiria AS, Ma RK, Vaka D, Chu P, Kozak M, Castellini L, Graves EE, Kim GE, Mourrain P, Koong AC, Giaccia AJ, Winslow MM. (2017) Blimp1 induces transient metastatic heterogeneity in pancreatic cancer. ***Cancer Discovery*** Volume 7(10), 1184-1199. PMID: 28790031.

c. Denny SK, Yang D, Chuang CH, Brady JJ, Lim JS, Grüner BM, **Chiou SH**, Schep AN, Baral J, Hamard C, Antoine M, Wislez M, Kong CS, Connolly AJ, Park KS, Sage J, Greenleaf WJ, Winslow MM. (2016) Nfib Promotes Metastasis through a Widespread Increase in Chromatin Accessibility. ***Cell*** 166(2), 328-342. PMID: 27374332.

d. Chuang CH, Greenside PG, Rogers ZN, Brady JJ, Yang D, Ma RK, Caswell DR, **Chiou SH**, Winters AF, Grüner BM, Ramaswami G, Spencley AL, Kopecky KE, Sayles LC, Sweet-Cordero EA, Li JB, Kundaje A, Winslow MM. (2017) Molecular definition of a metastatic lung cancer state reveals a targetable CD109-Janus kinase-Stat axis. ***Nat Med*** 2017 23(3), 291-300. PMID: 28191885.

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/pubmed/?term=Shin-Heng+Chiou+%5BAUTHOR%5D