APPLICANT BIOGRAPHICAL SKETCH

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NAME: Yuxuan Liu

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

POSITION TITLE: Research Scientist

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/YY	FIELD OF STUDY
Peking University, Beijing, CHINA	BS	06/2008	Experimental Medicine
Peking University, Beijing, CHINA	MS	06/2011	Pathology
University of Groningen, Groningen, Netherlands	PhD	12/2013	Pathology and Medical Biology
Memorial Sloan Kettering Cancer Center, New York, NY		11/2016	Hematology-Oncology Postdoctoral fellowship
Columbia University Medical Center, New York, NY		06/2018	Hematology-Oncology Postdoctoral scholarship

A. Personal Statement

I am a research scientist in the field of hematology. Cancers relapse due to the survival of therapy-resistant cells. My research is focused on identifying why the therapy-resistant cells escape from treatment and how to better target them in B-cell malignancies. I have a broad background in hematology with specific training and expertise in hemopathology, epigenetics and drug developments in different subtypes of B-cell malignancies. I have conducted research in 1) identifying the resistance mechanisms to the FDA-approved drug, BCL2 inhibitor (venetoclax) in DLBCL and developing the combinational therapeutic approaches to overcome the resistance during my postdoctoral fellowship. 2) developing novel chemical entities to precisely target epigenetic derangements in germinal center derived DLBCL with mutations in epigenetic modifiers (CREBBP and EP300), which is underway for pre-IND enabling study for first-in-human clinical trial. All these works have been published as first-authored papers in high profile journals.

Given that the therapy-resistant cells are small cell subsets in billions of cancer cells of each patient, to study the intratumor heterogeneity needs better resolution at single cell level. I joined Dr. Kara Davis lab to use single cell technology, i.e. mass cytometry and lead the project to study the therapy-resistant cells in leukemia patient samples at the time of diagnosis. The goal is to identify the novel therapeutic target, design better approach to target these therapy-resistant cells and eventually prevent relapse.

B. Positions, Honors and other Scientific Experience

Positions

2023- Senior Research Scientist, Department of Pediatrics, Stanford University
2019-2022 Research Scientist, Department of Pediatrics, Stanford University
2016-2019 Associate Research Scientist/Postdoctoral Research Scientist, Department of Medicine and Experimental Therapeutics, Columbia University Medical Center, New York, NY
2014-2016 Post-doctoral Research Fellow, Memorial Sloan Kettering Cancer Center, New York
2008-2011 Teaching Assistant, Molecular Pathology Department, Peking University

Honors

2018-2020 Lymphoma Research Foundation Fellowship Award
2018 ASH Abstract Achievement Award
2011-2013 Abel Tasman Talent Program (ATTP) Scholarship, University of Groningen
2008-2011 First-Class Post-Graduate Scholarship, Peking University

Other Experience and Professional Memberships

2023-	Member	American Society of Hematology
2020	Abstract Review Committee	American Society of Hematology Annual Meeting
2017-	Reviewer	Oncotarget
2017-	Reviewer	Hematology
2016-	Academic Editor	Medicine
2015-	Reviewer	European Journal of Hematology

C. Contribution to Science

1. Study the treatment-resistant cells at single cell level and design the mechanism-based therapeutic approach in B-cell leukemias

Cellular metabolism is a hallmark of leukemia stem cells in acute myeloid leukemia and therapies to target metabolic derangements are currently in clinical trials. By contrast, far less is known about the role of cellular metabolism in B cell acute lymphoblastic leukemia (ALL), which remains a leading cause of cancer mortality in children/young adults with over 50% of patients dying of relapsed disease. Previous work in B-ALL has implicated that pre-B cells with active SYK/PI3K/Akt signaling are highly predictive of relapse. It is very critical to characterize these relapse-associated cells with active oncogenic signaling and better design therapies to target them. Working with Dr. Davis at Stanford University, I led the project to study how these relapse-associated cells use nutrients and metabolites that are essential to cell survival. I determined the cells with active oncogenic signaling (we called signaling+ cells) preferentially rely on glucose for their survival. Moreover, they use glucose primarily to make pyrimidines which are precursors that cells use to make the building blocks of DNA and RNA. This does not happen in leukemia cells without active oncogenic signaling. Inhibiting the process of pyrimidine synthesis leads to cell death in signaling+ cells, whereas uridine, the product of de novo pyrimidine synthesis can rescue the cell death from glucose deprivation. These results indicate that uridine synthesis is a metabolic vulnerability in B-ALL.

- **Y Liu** et al. Uridine synthesis Is the metabolic vulnerability in relapse-associated B-ALL cells with active pre-BCR signaling. *Blood* 2023; 142 (Supplement 1): 4340.
- Lo, YC*., **Liu, Y*** et al. Single-cell technologies uncover intra-tumor heterogeneity in childhood cancers. *Semin Immunopathol* 45, 61–69 (2023). **(*equally contributed)**
- C Simpson*, **Y Liu***, L Stuani, …K L. Davis et al. Enrichment in metabolic pathway activation corresponds to Immunoglobulin gene diversity across B cell developmental stages in B-lymphoblastic leukemia *Blood* 2023; 142 (Supplement 1): 2972. **(*equally contributed)**
- A Koladiya, A Jager, …**Y Liu**,…,K L. Davis. Prior knowledge integration improves relapse prediction and identifies relapse associated mechanisms in childhood B cell acute lymphoblastic leukemia*. Blood* 2023; 142 (Supplement 1): 1603.
- Sarno, J., Domizi, P., **Liu, Y** et al. Dasatinib overcomes glucocorticoid resistance in B-cell acute lymphoblastic leukemia. *Nat Commun* 14, 2935 (2023).

2. Identify the mechanism of resistance of selective BCL2 inhibitor in B cell malignancies

Anti-apoptotic protein B cell lymphoma 2 (BCL2) is an anti-apoptotic protein and a regulator of mitochondrial metabolism. BCL2 selective inhibitor (venetoclax) has been approved for adult patients with CLL and AML. However, the clinical activity of BCL2 inhibitors in patients with diffuse large B cell lymphoma (DLBCL) has been disappointing. To identify the resistance mechanism, I conducted the postdoctoral fellowship at MSKCC. I found that inhibiting BCL2 induces acquired resistance in different subtypes of B-cell malignancies. I identified NOXA genetic amplification as a biomarker to indicate the sensitivity to BCL2 inhibitor. Cells lacking NOXA amplification were less sensitive to BCL2 inhibition due to codependency of MCL1 and BCL2 proteins. Pharmacologic induction of NOXA, using the histone deacetylase (HDAC) inhibitor panobinostat, decreased MCL1 protein abundance and increased lymphoma cell vulnerability to BCL2 inhibitors in vitro and in vivo. My data provide a mechanistic rationale for combining HDAC inhibitors with BCL2 inhibitors in B-cell malignancies.

- **Y Liu** et al. NOXA genetic amplification or pharmacologic induction primes lymphoma cells to BCL2 inhibitors induced cell death. *PNAS* 2018 115 (47) 12034-12039

3. Develop novel chemical identities (NCEs) and the mechanism-based combinational therapeutic approaches in B cell malignancies

Of patients with Germinal Center (GC)-DLBCL treated with standard frontline therapy, 30% will relapse [ref] and less than half of these patients will be eligible for intensive salvage therapy. To date, the focus across cancer biology has been to target a single mutation or pathway dysregulation. However, diseases such as leukemias and lymphomas harbor a multiplicity of mutations and therefore the real challenge is to define the optimal combination of drugs that targets a specific suite of mutations. Inactivating mutations in epigenetic modifiers such as histone methyltransferase (EZH2) and acetyltransferases (HAT), CBP and p300, which potentially contribute to lymphomagenesis and portend a more aggressive phenotype of disease. I performed substantive research on EZH2 dysregulation in GC-derived lymphoma subtypes.

Specifically, I demonstrated that the dual inhibition of EZH2 and HDAC is highly synergistic. As a result, the presence of EZH2 dysregulation and a common basal gene signature is useful to predict responses. In addition, working with Jennifer Amengual, MD at Columbia University, we developed a group of NCEs, HAT activators. I observed greater drug sensitivity of HAT activators in EP300 mutated lines compared to the wild-type lines. The leading compound induces HAT-mediated acetylation of histone and p53 and is well-tolerated and effective in xenograft mouse models of lymphoma. It suggests potential clinical application and precision medicine opportunities for patients harboring this mutation.

- J Cogan, **Y Liu**, Amengual E. Hypomethylating Agents in Lymphoma. *Curr. Treat. Options in Oncol*. **21,** 61 (2020)
- **Y Liu**., Y Gonzalez, J Amengual. Chromatin-Remodeled State in Lymphoma. *Curr Hematol Malig Rep* **14,** 439–450 (2019)
- **Y Liu**, J Fiorito, Y Gonzalez, B Estrella, E Calcagno, E Zuccarello, H Hwang, B Honig, S Deng, D Landry, O A. O'Connor, O Arancio, J Amengual; Strategy for Overcoming Crebbp and EP300 Mutations in Lymphoma: Development of First-in-Class HAT Activators. *Blood* 2019; 134 (Supplement_1): 4068.
- J Lue, S A Prabhu, **Y Liu** et al. Precision Targeting with EZH2 and HDAC Inhibitors in Epigenetically Dysregulated Lymphomas. *Clin Cancer Res* April 12 2019

4. Identify the immune escape mechanism in B-cell malignancies

Classical Hodgkin lymphoma (cHL) is characterized by a minority of tumor cells derived from germinal center B-cells and a vast majority of non-malignant reactive cells. It is very critical to understand how the tumor cells escape from immune surveillance from the microenvironment. By integrating genome-wide genomic and transcriptomic analyses, I have been identified the genetic lesions in Hodgkin lymphoma (HL). In particular, I identified *B2M* loss-of-function mutations which contribute to the loss of human leukocytes antigen (HLA) expression in tumor cells and elucidate why these tumor cells can escape from the immune microenvironment. This was the very first study to demonstrate that genetic lesions mediate the down-modulation of HLA-I expression in Hodgkin Reed-Sternberg cells. In addition, I provided essential whole exome sequencing data that includes an analysis of the TCF3 mutation and its role in cHL. My results have thus addressed some of the critical limitations of the current understanding of immune escape mechanism.

- **Liu Y**, Razak FR, Terpstra M, Chan FC, Saber A, Nijland M, van Imhoff G, Visser L, Gascoyne R, Steidl C, Kluiver J, Diepstra A, Kok K and van den Berg A. The mutational landscape of Hodgkin lymphoma cell lines determined by whole exome sequencing. *Leukemia.* 2014 Jul
- **Liu Y**, Sattarzadeh A, Diepstra A, Visser L, van den Berg A. Hodgkin lymphoma: driven by the microenvironment or shaping the microenvironment. *Seminars in Cancer Biology*. 2013 Jul
- **Liu Y**, van den Berg A, Veenstra R, Rutgers B, Nolte I, van Imhoff G, Visser L, Diepstra A. PML nuclear bodies and SATB1 are associated with HLA class I expression in EBV+ Hodgkin lymphoma. *PLoS One*. 2013 Aug
- W Cozen, MN Timofeeva, D Li, A Diepstra, …, RN Veenstra, L Visser, **Y Liu**, …, A Van Den Berg, JD McKay. A meta-analysis of Hodgkin lymphoma reveals 19p13.3 TCF3 as a novel susceptibility locus. *Nat Commun.* 2014 Jun 12

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