## BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Catlett, Jerrel

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

POSITION TITLE: MD PhD Candidate

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)* | Start Date MM/YYYY | Completion Date MM/YYYY | FIELD OF STUDY |
|---|---|---|---|---|
| Dartmouth College, Hanover, NH | BA | 08/2014 | 06/2018 | Biology, Concentration in Genetics |
| Icahn School of Medicine at Mount Sinai (ISMMS), New York, NY | MD PhD | 08/2020 | Expected 05/2028 | Disease Mechanisms and Therapeutics |

### A. Personal Statement

My long-term goal as a physician-scientist is to ideate, develop, and apply novel precision therapies toward pediatric disorders and diseases. Of particular interest to me is exploring novel uses of functional genomic tools and protein degradation platforms to target currently undruggable oncoproteins in pediatric tumors. My training plan outlined in the proposed research under the mentorship of **Dr. Jian Jin** (ISMMS) will offer essential and rigorous research training in medicinal chemistry and structural biology in addition to strong career development preparing me for my pursuit of a research-track residency program in Pediatrics, subsequent fellowship in Hematology/Oncology, and tenure as an independent principal investigator. I am passionate about leveraging these training experiences in my pursuit of a translational research career dedicated to therapeutic discovery that prioritizes molecules with tissue-specific and tumor-specific mechanisms of action.

My passion for pediatric precision medicine began after the tragic death of a close friend in high school following the sudden rupture of a congenital arteriovenous malformation (AVM), a condition her doctors were aware of but had gone untreated due to limited knowledge and actionable therapies for AVM at the time of her diagnosis. I was determined to become a physician-scientist that could advance medical knowledge and generate innovate solutions to the challenging diagnoses young patients face, affording them the opportunity to experience deeply fulfilling childhoods that are not cut short by disease and illness. To begin that journey, I sought out a research internship with physician-scientist **Dr. Charles Venditti** at the National Human Genome Research Institute (NIH) in Bethesda, Maryland during my junior year of high school. There, I generated and validated TALEN-edited zebrafish models of congenital disorders impairing vitamin B12 metabolism and trafficking (i.e. cobalamin C disease and methylmalonic acidemia). I remained in the Venditti laboratory at the NIH after beginning my undergraduate studies at Dartmouth College to continue my work validating these *in vivo* models, attempting therapeutic rescue with clinically approved cobalamin derivatives, and pioneering a fluorescent *in vivo* confocal microscopy approach to qualitatively measure impaired neuronal development in larval zebrafish specimen. These projects resulted in one published manuscript in *Human Molecular Genomics* for which I am a coauthor. My clinical shadowing experiences with Dr. Venditti at the National Institutes of Health solidified my research interest in pediatric disease and kindled my desire to become a physician.

After taking advanced coursework in genetics, epigenetics, biomedical engineering, and cancer biology at Dartmouth, I became passionate about pursuing a long-term research career in oncology. Upon graduating, I joined the laboratory of physician-scientist **Dr. Kimberly Stegmaier** as a senior research technician at the Dana-Farber Cancer Institute (DFCI) and Broad Institute of MIT and Harvard in Boston, Massachusetts. There, I worked for two years in the Department of Pediatric Oncology applying CRISPR-Cas9 genomic screening and targeted protein degradation platforms toward studying the epigenetic mechanisms underlying Ewing sarcoma tumor maintenance. My tenure at the DFCI resulted in co-authorship on a published manuscript in

*Clinical Cancer Research* and laid the groundwork for my current research interest in developing functional genomic tools and novel small molecule compounds to study and treat pediatric cancers. Fascinated by the prospect of leveraging proteolysis-targeting chimeras (PROTACs) and other chemical inducers of proximity to elucidate unknown mechanisms of tumor progression, I joined the laboratory of **Dr. Jian Jin** last year to begin my dissertation research. As a nationally recognized leader in medicinal chemistry and cancer biology with an extensive record for training predoctoral and postdoctoral fellows, I am confident Dr. Jin's tutelage will provide me exceptional predoctoral laboratory training in applying heterobifunctional molecules toward mechanistic and therapeutic discovery in a variety of cancer contexts. My proposed training plan as a student within Mount Sinai's Medical Scientist Training Program, Department of Pharmacological Sciences T32 awardee, and recent recipient of an R01 Diversity Supplement grant will outline a comprehensive set of career development activities and workshops to support my academic and scientific growth. I will also have ample opportunities to engage in public speaking, conduct literature analysis and clinical research, consider biomedical ethics, and learn about a wide variety of career options available to physician-scientists. As an African-American student who is the first in their family to graduate from college and the first to pursue graduate-level education, I am eager to continue braving new frontiers in my MD/PhD program that will provide a strong foundation for me to become a successful academic researcher.
I have never published or created research under a name other than Jerrel Lewis Catlett, II.

**B. Positions, Scientific Appointments, and Honors**

**Positions and Scientific Appointments**

| | |
|---|---|
| 2023 – Present | **Teaching Assistant**, Biomedical Sciences for MD PhD, ISMMS |
| 2021 – Present | **MD PhD Candidate**, Icahn School of Medicine at Mount Sinai (ISMMS) |
| 2020-2021 | **MD Candidate,** ISMMS |
| 2020-2021 | **Member**, Institutional Workgroup on Genomics, Race, and Ancestral Origin, ISMMS |
| 2020-2021 | **Scholar**, Human Rights and Social Justice Program, ISMMS |
| 2018-2020 | **Senior Research Technician**, Stegmaier Laboratory, Dana-Farber Cancer Institute |
| 2014-2017 | **Undergraduate Research Technician**, Venditti Lab, NHGRI-NIH |
| 2012-2014 | **Research Intern**, Venditti Lab, NHGRI-NIH, Organic Acid Research Section |

**Leadership Positions**

| | |
|---|---|
| 2023-2024 | **Volunteer Chef**, Refettorio Harlem, Food for Soul, INC. |
| 2023-2024 | **MD/PhD Admissions Committee Interviewer**, ISMMS |
| 2021-2024 | **Phlebotomist**, East Harlem Health Outreach Partnership, Mount Sinai Health System |
| 2020-2022 | **Founder and Discussion Facilitator**, Racial Justice and Antiracist Reading Group Initiative, ISMMS |
| 2020-2021 | **Discussion Facilitator**, Medical Discovery of Careers (MedDOCs) Program, ISMMS |
| 2020-2021 | **Course Representative**, Biomedical Sciences for MD PhD, ISMMS |

**Honors**

| | |
|---|---|
| 2024 | Irving L. Schwartz Poster Presentation Award |
| 2024 – Present | Scholar of Oncology, Johnson and Johnson Innovative Medicine |
| 2023 – Present | Mount Sinai Innovation Partners Fellowship, Mount Sinai Health System |
| 2023 | Panelist, Inaugural New York City Anti-Racism in Medical Education Symposium |
| 2021 – 2024 | Center for Antiracism in Practice Fellowship, Icahn School of Medicine at Mount Sinai |
| 2018 | Fannie Lou Hamer Community Service Award, Black Alumni of Dartmouth Association |
| 2014 – 2017 | Intramural Research Training Award, National Institutes of Health |

**C. Contributions to Science**

1. **Elucidating role of metabolic enzyme mmachc in zebrafish survival and development** (High School and Undergraduate Research)

In high school, I conducted a two-year research internship with Dr. Charles Venditti at the National Human Genome Research Institute (NHGRI) where I validated genome-edited *Danio rerio* models for two congenital disorders of cobalamin metabolism, cobalamin C (cblC) deficiency and methylmalonic acidemia (MMA). I performed all animal husbandry and produced *in vivo* data suggesting that loss-of-function mutation of the *cblC* and *mmachc* genes respectively induce metabolic dysfunction, early developmental delays, and failure to thrive recapitulating clinical manifestations of the disorder. I continued this work during my off-terms at

Dartmouth College for nine months of on-site and full-time internship at the NHGRI. I characterized the cellular phenotype of cblC deficiency with tissue histology, finding renal impairment, liver atrophy, and progressive degeneration of the retinal pigmented epithelium. I also designed experiments to achieve *in vivo* phenotypic rescue by treating our models with clinical derivatives of vitamin B12. Lastly, I generated a transgenic zebrafish model of high-severity MMA to investigate the pathophysiology of comorbid basal ganglia stroke observed in patients, which featured fluorescently labeled glutamatergic and GABAergic neurons. Using an *in vivo* confocal microscopy approach that I pioneered in the lab, I observed significant delay in GABAergic neuron development in the telencephalon preceding classical disease phenotypes.

Sloan, J. L., Achilly, N. P., Arnold, M. L., **Catlett, J. L.,** Blake, T., Bishop, K., Jones, M., Harper, U., English, M. A., Anderson, S., Trivedi, N. S., Elkahloun, A., Hoffmann, V., Brooks, B. P., Sood, R., & Venditti, C. P. (2020). **The vitamin B12 processing enzyme, mmachc, is essential for zebrafish survival, growth and retinal morphology.** *Human Molecular Genetics*, *29*(13), 2109–2123.

2. **Discovering synergistic CDK4/6 and IGF1R inhibitor strategy for treating Ewing sarcoma**

During my post-baccalaureate research at the Dana-Farber Cancer Institute (DFCI), I combined CRISPR-Cas9 gene editing and preclinical drug synergy experiments to discover a mechanism underlying Ewing sarcoma's (EWS) therapeutic escape in response to CDK4/6 inhibitor monotherapy. After analyzing functional genomic screens from the Broad Institute of MIT and Harvard to identify that IGF1R upregulation conferred a growth advantage to CDK4/6 inhibited EWS cell lines, I performed a series of functional experiments to verify that this signaling pathway induced drug resistance. I generated ribociclib-resistant cell lines and observed progressive increase in IGF1R signaling; performed CRISPR-Cas9 knockout of IGF1R to re-sensitize those cells to CDK4/6 therapy; and observed synergistic anti-viability effect with potent suppression of the cell cycle following dual inhibition of CDK4/6 and IGF1R. This work inspired the development of a novel therapeutic regimen at the DFCI combining palbociclib (CDK4/6 inhibitor) with ganitumab (IGF-1R monoclonal antibody), and is currently undergoing phase 2 clinical trial for pediatric patients with relapsed or refractory EWS (Clinical Trial Number: NCT04129151).

Guenther, L. M., Dharia, N. V., Ross, L., Saur Conway, A., Robichaud, A. L., **Catlett, J. L.,** Wechsler, C., Frank, E. S., Goodale, A. B., Church, A. J., Tseng, Y.-Y., Guha, R., McKnight, C., Janeway, K. A., Boehm, J. S., Mora, J., Davis, M. I., Alexe, G., Piccioni, F., & Stegmaier, K. (2019). **A combination CDK4/6 and IGF1R inhibitor strategy for Ewing sarcoma**. *Clinical Cancer Research, 25(4),* 1343-1357.

3. **Establishing SMARCAL1 helicase as selective therapeutic dependency in osteosarcoma**

I additionally worked on a project at the DFCI leveraging the Broad Institute's loss-of-function CRISPR-Cas9 screening to identify the helicase SMARCAL1 as an osteosarcoma-specific cancer dependency. I generated SMARCAL1 knockout osteosarcoma cell lines (including a patient-derived cell line model) and used flow cytometry to measure significantly increased γ-H2AX expression suggesting increased levels of cellular DNA damage. To orthogonally validate SMARCAL1 as a genetic dependency in this cancer context, I used bacterial cloning and site-directed mutagenesis techniques to generate a lentiviral degradation tag (dTAG) system that exogenously expresses SMARCAL1 protein fused to an FKBP-based degron – modeled after the targeted protein degradation approach pioneered by former DFCI colleague Nathanael Gray, PhD. The transduced cell lines could then be treated with a hetero-bifunctional small molecule that induces selective ubiquitination of SMARCAL1 by the VHL E3 ubiquitin ligase, triggering its subsequent degradation by the 26S proteasome. This degradation approach produced an anti-viability effect phenocopying genetic knockout. After leaving DFCI, my former postdoctoral mentor Lillian Guenther used these models I generated to discover and confirm synthetic lethality between SMARCAL1 and the chromatin remodeler ATRX/DAXX in osteosarcoma lines expressing the alternative lengthening of telomeres protein (ALT).

Wierdl, M., **Catlett, J.L.,** O'Casio-Martinez, N., Johnson Jr, J.D., Herman, A., Dharia, N.V., Alexe, G., Bernstein, E., Stegmaier, K., Guenther, L.M. **SMARCAL1 is a selective dependency and a novel synthetic lethality with ATRX/DAXX in ALT+ osteosarcoma and neuroblastoma.** American Association for Cancer Research Annual Meeting. April 5, 2024. San Diego, CA.

4. **Developing educational programming and frameworks for addressing bias in science and medicine** (Medical School Research)

I work on several teams spearheading antiracist reforms within the Mount Sinai Health System and the ISMMS preclinical curriculum. A recent product of this work was a conference presentation and first-author publication where I performed a literature review of nephrology textbook resources and curricular materials for medical trainees that inappropriately uses Black race as a biological explanation for kidney disease pathology. We highlight the importance of eliminating the race-correction factor within the MDRD equation used clinically for measuring estimated glomerular filtration rate. I also propose a framework for ensuring that language used in educational materials referring to race or ancestry with regards to kidney disease is rooted in evidence-based rationale and does not use race as a proxy for polygenic contributions, social determinants of health, or systemic health care barriers. Additionally, I have developed standardized patient cases that train first- and second-year medical students on how to respond to racism inflicted on the healthcare team by the patient requiring care, teaching the students bystander skills that allow them to deescalate the situation while maintaining a therapeutic alliance with the patient. Lastly, I developed an anti-racism discussion series open to all members of the Mount Sinai community to engage in conversations focusing on how anti-Black biases and prejudices manifest in medical practice and research.

**Catlett, J. L.,** Scott, P. O., Seah, C., & Leisman, S. (2022). **A framework for antiracist curriculum changes in nephrology education.** *Advances in Chronic Kidney Disease*, *29*(6), 493-500.

5. **Developing proteolysis targeting chimeras (PROTACs) that recruit the SPOP E3 ubiquitin ligase for targeted protein degradation** (Dissertation Research)

As a third-year graduate student in the Jian Jin laboratory, I investigate the use of proteolysis targeting chimeras (PROTACs) to recruit currently unharnessed E3 ubiquitin ligases to degrade epigenetic oncoproteins in adult and pediatric tumor models. I have discovered and characterized a novel bridged-PROTAC synthesized by postdoctoral chemist Zhijie Deng that recruits the previously unharnessed SPOP E3 ubiquitin ligase to degrade epigenetic regulator BRD4, displaying therapeutic potential in colorectal cancer and triple-negative breast cancer. This molecule indirectly recruits SPOP through an endogenous protein substrate, serving as a novel platform for recruiting E3 ligases that do not have available small molecule ligands for therapeutic development.

**Catlett, J. L.,** Deng, Z., Lee, Y., Jin, J. **Discovery of a Bridged Proteolysis Targeting Chimera (PROTAC) Recruiting the SPOP E3 Ubiquitin Ligase for Targeted Protein Degradation.** Annual ISMMS Medical Scientist Training Program Retreat. September 21, 2024; Edith Macy Center, Briarcliff Manor, NY.

**D. Scholastic Performance**

| YEAR | COURSE TITLE | GRADE | YEAR | COURSE TITLE | GRADE |
|---|---|---|---|---|---|
| DARTMOUTH COLLEGE – UNDERGRADUATE | | | | | |
| 2014 | Ecology | B- | 2016 | Gene Expression and Inheritance | B |
| 2014 | Dialogues w/ the Classics (Honors Humanities) | B | 2016 | Reproductive Ethics | B+ |
| 2014 | Introductory Italian II | A- | 2016 | General Physics I | A- |
| 2015 | The Classical Tradition (Honors Humanities) | A- | 2016 | Organic Chemistry I | P |
| 2015 | Genetic Variation and Evolution | C | 2016 | Biotechnology and Biochemical Engineering | B |
| 2015 | Introduction to Calculus | B+ | 2017 | Italian Cinema | B+ |
| 2015 | The Graphic Novel | A | 2017 | 17$^{th}$ and 18$^{th}$ Century Italian Literature | A- |
| 2015 | Introductory Italian III | A- | 2017 | Organic Chemistry II | C |
| 2015 | General Chemistry I | B- | 2017 | Advanced Genetics | B |
| 2015 | Introductory Psychology | B- | 2017 | Quantitative Analysis of Social Data | A- |

| YEAR | COURSE TITLE | GRADE | YEAR | COURSE TITLE | GRADE |
|---|---|---|---|---|---|
| 2015 | Introductory Sociology | B | 2017 | Language Teaching and Methods | A |
| 2015 | Virtual Medicine and Cybercare | A- | 2017 | Cell Structure and Function | B |
| 2016 | Exploring Italian Culture and Language | A- | 2018 | Biochemistry | B |
| 2016 | Advanced Writing and Speaking in Italian | A- | 2018 | Inoculation Rhetoric | A |
| 2016 | Intro to Italian Literature | A- | 2018 | General Physics II | B+ |
| 2016 | Black Theater, U.S.A. | A- | 2018 | RNA: The Real Secret of Life | A |
| 2016 | Slave Societies | A- | 2018 | Friendship in Italian Literature | A |
| 2016 | General Chemistry II | B- | 2018 | Molecular Basis of Cancer | A- |
| ICAHN SCHOOL OF MEDICINE – PREDOCTORAL | | | | | |
| 2020 | Structures (Gross Anatomy) | P | 2022 | Gastrointestinal and Liver Pathophysiology | P |
| 2020 | Journal Club in Cancer Biology | P | 2022 | Sexual and Reproductive Health | P |
| 2020 | Molecular, Cellular, and Genomic Foundations | P | 2022 | Renal Pathophysiology | P |
| 2020 | Biomedical Science for MDPhDs | A | 2022 | Musculoskeletal Pathophysiology | P |
| 2020 | Medical Scientist Grand Rounds | P | 2022 | Art and Science of Medicine II | P |
| 2021 | General Pathology | P | 2022 | Responsible Conduct of Research | P |
| 2021 | Immunology | P | 2022 | Journal Club in Pharmacological Sciences | P |
| 2021 | Physiology | P | 2022 | Medical Scientist Grand Rounds | P |
| 2021 | Medical Microbiology | P | 2022 | Seminar in Biophysics and Systems Pharmacology | P |
| 2021 | Biomedical Science for MDPhDs | A | 2022 | Introduction to Biostatistics | A |
| 2021 | Medical Scientist Grand Rounds | P | 2023 | Rigor and Reproducibility | P |
| 2021 | Brain and Behavior | P | 2023 | Journal Club in Pharmacological Sciences | P |
| 2021 | Pulmonary Pathophysiology | P | 2023 | Medical Scientist Grand Rounds | P |
| 2021 | Cardiovascular Pathophysiology | P | 2023 | Seminar Series in Oncological Sciences | P |
| 2022 | Hematology | P | 2023 | Principles of Scientific Proposals | P |

**Dartmouth College Grading:** Except for Organic Chemistry I, which is graded P (pass) or F (fail) where passing is 70% or better, all courses are graded on a traditional A-F scale.

**ISMMS Grading:** Except for Biomedical Sciences for MD/PhDs and Biostatistics, which are graded on a traditional A-F scale, graduate courses are graded P (pass) or F (fail). Passing is 70% or better.

## BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: JIAN JIN

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

POSITION TITLE: Mount Sinai Endowed Professor and Director

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)* | Start Date MM/YYYY | Completion Date MM/YYYY | FIELD OF STUDY |
|---|---|---|---|---|
| University of Science and Technology of China | BS | 09/1986 | 07/1991 | Chemistry |
| The Pennsylvania State University | PhD | 08/1992 | 01/1997 | Organic Chemistry |
| The Ohio State University | Post-doc | 01/1997 | 01/1998 | Organic Chemistry |

### A. Personal Statement

I am an internationally recognized medicinal chemist and chemical biologist with more than 25 years of experience in small-molecule drug discovery. My lab is a pioneer and leader in discovering novel small-molecule degraders of oncoproteins, selective inhibitors of protein methyltransferases (PMTs), and biased ligands of G protein-coupled receptors (GPCRs). As the Director of the Mount Sinai Center for Therapeutics Discovery and Co-Leader of the Cancer Clinical Investigation Program in the Tisch Cancer Institute, I am leading Mount Sinai's effort on discovering and developing novel therapeutics for the treatment of cancer. To date, I have published >200 peer-reviewed papers (h-index: 72; Google Scholar Citations: 18,376) and delivered >100 invited talks. I am also an inventor of >80 issued U.S. patents and published international patent applications. I have led multiple drug discovery programs that discovered and advanced 5 drug candidates to clinical development. In particular, I am an inventor of Daprodustat, a hypoxia-inducible factor (HIF) prolyl hydroxylase inhibitor, which has been approved in the United States and Japan as an oral medication for the treatment of anemia caused by chronic kidney disease. I have been inducted to the U.S. National Academy of Inventors.

My lab has made seminal contributions to the discovery of novel PROTAC degraders for oncoproteins, such as EZH2, WDR5 and AKT, and development of innovative technologies for advancing the heterobifunctional molecule-induced protein post-translational modification field, such as Bridged PROTAC, TF-PROTAC, TF-DUBTAC and AceTAC. For my detailed contributions to science, please see Section C.

I have mentored 39 postdoctoral fellows and 10 MD/PhD and PhD students in my lab and had also served as a co-director of the Multidisciplinary Training Area in Pharmacology and Therapeutics Discovery for the Graduate School of Biomedical Sciences at Mount Sinai.

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

**Ongoing:**

**NIH / R01CA268384** PIs: Jin and Wang; Role: contact PI 5/1/2022 – 4/30/2027
*Discovery of First-in-class WDR5 PROTACs as a Novel Therapeutic Strategy for MLL-rearranged Leukemias*
The objective of this project is to develop first-in-class WDR5 PROTACs for treating *MLL*-r leukemias.

**NIH / R01CA268519** PIs: Wang and Jin; Role: MPI 1/1/2022 – 12/31/2026
*Dissecting and Targeting Canonical and Non-canonical Oncogenic Functions of EZH2 in Cancer*
The objectives of this project are to define noncanonical and canonical oncogenic functions of EZH2 and to optimize and determine therapeutic effects of EZH2 PROTACs in *MLL*-rearranged leukemias.

**NIH / R01CA260666** PIs: Jin and Wen; Role: contact PI 4/1/2021 – 3/31/2026
*Development of Novel PROTACs Targeting the ENL YEATS Domain for Treating MLL-rearranged Leukemias*
The objective of this project is to develop first-in-class ENL PROTACs for treating *MLL*-r leukemias.

**NIH / R01CA230854** PIs: Jin and Parsons; Role: contact PI 9/10/2018 – 8/31/2024

*(PQ9) Developing EZH2 Degraders for Treating Triple-Negative Breast Cancer*
The objective of this project is to evaluate EZH2 degraders in TNBC cellular and mouse models.

**NIH / R01AG084184** PI: Jin; Role: PI 9/15/2023 – 6/30/2028
*Novel Inhibitors of Lysine Methyltransferases G9a and GLP for the Treatment of Alzheimer's Disease*
The objective of this project is to optimize G9a/GLP inhibitors into a drug candidate for the treatment of AD.

**Recently completed (within last 3 years):**

**NIH / R01CA218600** PIs: Jin and Wang; Role: contact PI 6/8/2017 – 5/31/2023
*Targeting Lysine Methyltransferases EZH2 and EZH1 for Treating MLL-rearranged Leukemias*
Goal: Optimize bivalent inhibitors of EZH2 and EZH1 into a drug candidate for treating *MLL*-r leukemias.

**NIH / R01HD088626** PIs: Jiang and Jin; Role: MPI 9/1/2017 – 5/31/2022
*Epigenetic Therapy and Prader-Willi Syndrome*
Goal: Optimize UNC0642 into a drug candidate for treating Prader-Willi Syndrome.

**NIH / R01GM122749** PI: Jin; Role: PI 4/1/2017 – 1/31/2022
*Discovery of Selective Inhibitors for Histone Methyltransferases*
Goal: Develop histone methyltransferase selective inhibitors as chemical probes.

**Four representative peer-reviewed publications (* corresponding author(s)):**

1. Vedadi, M.; Barsyte-Lovejoy, D.; Liu, F. et al; Arrowsmith, C. H.*; **Jin, J.*** "A Chemical Probe Selectively Inhibits G9a and GLP Methyltransferase Activity in Cells" **Nature Chemical Biology**, 2011, 7, 566-574. PMCID: PMC3184254. Google Scholar Citations: **546** (as of 3/1/2024).
2. Ma, A.; Stratikopoulos, E.; Park, K. et al; Guccione, E.; Parekh, S.; Parsons, R.*; **Jin, J.*** "Discovery of a First-in-class EZH2 Selective Degrader" **Nature Chemical Biology**, 2020, 16, 214-222. PMCID: PMC6982609. Google Scholar Citations: **161** (as of 3/1/2024).
3. Yu, X.; Li, D.; Kottur, J. et al; Liu, J.; Aggarwal, A. K.; Wang, G. G.*; **Jin, J.*** "A Selective WDR5 Degrader Inhibits Acute Myeloid Leukemia in Patient-Derived Mouse Models" **Science Translational Medicine**, 2021, 13, eabj1578. PMCID: PMC8500670. Google Scholar Citations: **68** (as of 3/1/2024).
4. Wei, J.; Meng, F. et al, Wang, G. G.; Chen, X.; Kaniskan, H. U.; **Jin, J.*** "Harnessing the E3 Ligase KEAP1 for Targeted Protein Degradation" **Journal of the American Chemical Society**, 2021, 143, 15073-15083. PMCID: PMC8480205. Google Scholar Citations: **73** (as of 3/1/2024).

I confirm that I have not published under a different name.

## B. Positions, Scientific Appointments, and Honors

**Positions and Employment**

2020-present Professor with tenure, Department of Neuroscience (secondary appointment)
Icahn School of Medicine at Mount Sinai (ISMMS), New York, NY
2018-present Mount Sinai Endowed Professor in Therapeutics Discovery, ISMMS, New York, NY
2018-present Director, Mount Sinai Center for Therapeutics Discovery, ISMMS, New York, NY
2018-present Co-Leader, Cancer Clinical Investigation Program, Tisch Cancer Institute, ISMMS, New York
2017-2019 Co-Director, PTD MTA, Graduate School of Biomedical Sciences, ISMMS, New York, NY
2016-2018 Director, Center for Chemical Biology and Drug Discovery, ISMMS, New York, NY
2014-present Professor with tenure, Departments of Pharmacological Sciences and Oncological Sciences (primary appointment), Icahn School of Medicine at Mount Sinai (ISMMS), New York, NY
2013-2014 Associate Professor (joint appointment), Department of Pharmacology, UNC, Chapel Hill, NC
2008-2014 Associate Professor, Division of Chemical Biology and Medicinal Chemistry
Associate Director, Medicinal Chemistry, Center for Integrative Chemical Biology and Drug Discovery, Eshelman School of Pharmacy, University of North Carolina (UNC), Chapel Hill, NC
2003-2008 Manager, Medicinal Chemistry, GlaxoSmithKline, Collegeville/King of Prussia, PA
2000-2003 Senior Investigator, Medicinal Chemistry, GlaxoSmithKline, King of Prussia, PA
1998-2000 Investigator, Medicinal Chemistry, SmithKline Beecham Pharmaceuticals, King of Prussia, PA

**Other Professional Experience**

2023-present Member, National Academy of Inventors (elected in 2022)
2019-present External Scientific Advisory Committee member, U54 FusOnC2 "Center for Therapeutic Targeting of EWS-oncoproteins", Dana-Farber Cancer Institute
2018-present Cofounder and consultant for Cullgen, Inc. (San Diego, CA)
2018-2023 Appointed member, NIH DMPB (formerly DDNS) Study Section
2017-present SAB member for Onsero Therapeutics (Boston, MA) and Petra Pharma (New York, NY)

2014-present Adjunct Professor, University of North Carolina – Chapel Hill (UNC), Chapel Hill, NC
2013-present Consultant for BVF Partners, Epizyme, Boehringer Ingelheim Pharmaceuticals, FutuRx, Fulcrum Therapeutics, Accutar Biotechnology, Accent Therapeutics, and EpiCypher
2012-present Ad hoc grant reviewer: NCI P01 review panel, NIH Synthetic and Biological Chemistry B (SBCB), NIDDK Special Emphasis Panel, NSF Chemistry of Life Processes program, Wellcome Trust, etc.
2011-2014 Panelist, NIH MLPCN Chemical Probe Reports/Proposals Evaluation Panel

**Recent Honors**

2023 Inducted to the National Academy of Inventors
2023 GlaxoSmithKline Inventor Award (for inventing Daprodustat)
2020 Mount Sinai Faculty Council Award for Academic Excellence by Senior Faculty
2018 Mount Sinai 4D Technology Development Award
2018 Mount Sinai Endowed Professorship

**C. Contributions to Science**

1. My lab has made seminal contributions to discovery and development of novel small-molecule degraders including proteolysis targeting chimeras (PROTACs) (Nature Reviews Cancer (2021)). Since 2014, we have generated numerous first-in-class degraders targeting oncoproteins and characterized their antitumor activities. We discovered novel, potent and selective WDR5 PROTACs with robust in vivo antitumor activities via structure-based design and solved two high-resolution crystal structures of WDR5-PROTAC-E3 ligase ternary complexes (Science Translational Medicine (2021), Oncogene (2022), eLIFE (2022), Cell Chemical Biology (2023), Journal of Medicinal Chemistry (2023)). We also discovered novel degraders of EZH2 (Nature Chemical Biology (2020), Nature Cell Biology (2022), ACS P & TS (2022), Nucleic Acids Research (2022), Oncogene (2023), European Journal of Medicinal Chemistry (2024)), AKT (Cancer Discovery (2021), Journal of Medicinal Chemistry (2021a, 2022a & 2022b)) and CDK4/6 (Nature Cancer (2021)), which displayed robust in vivo antitumor activities. Moreover, we developed novel PROTACs of ALK (European Journal of Medicinal Chemistry (2018)), MEK1/2 (Journal of Medicinal Chemistry (2019 & 2020a), Science Signaling (2022)), EGFR (Journal of Medicinal Chemistry (2020b & 2022c)), PRMT5 (Journal of Medicinal Chemistry (2020c)), NSD3 (Cell Chemical Biology (2022)), NSD2 (Journal of Medicinal Chemistry (2022d)), MDM2 (Leukemia (2023)), LDH (Journal of Medicinal Chemistry (2023)), USP7 (Cell Death and Differentiation (2023)) and GSPT1 (Cell Host and Microbe (2023)). Using these degraders, we have developed novel therapeutic strategies and demonstrated that pharmacological degradation is superior to pharmacological inhibition of these oncoproteins for treating cancer. In addition to the 2020 NCB and 2021 STM papers listed in Section A, our representative papers (*corresponding author(s)) in this area include:
   a. Chiarella, A. M. et al; **Jin, J.***; Hathaway, N. A.* "Dose-dependent Activation of Gene Expression Is Achieved Using CRISPR and Small Molecules That Recruit Endogenous Chromatin Machinery" **Nature Biotechnology**, 2020, 38, 50-55. Google Scholar Citations: **56** (as of 3/1/2024).
   b. Xu, J.; Yu, X.; et al, **Jin, J.***; Parsons, R.* "AKT Degradation Selectively Inhibits the Growth of PI3K/PTEN Pathway Mutant Cancers with Wild Type KRAS and BRAF by Destabilizing Aurora Kinase B" **Cancer Discovery**, 2021, 11, 3064-3089. Google Scholar Citations: **33** (as of 3/1/2024).
   c. Wang, J.; Yu, X. et al; **Jin, J.***; Wang, G. G.* "EZH2 Noncanonically Binds cMyc and p300 Through a Cryptic Transactivation Domain to Mediate Gene Activation and Promote Oncogenesis" **Nature Cell Biology**, 2022, 24, 384-399. Google Scholar Citations: **83** (as of 3/1/2024).
   d. Park, K.-S.; Qin, L.; Kabir, M.; Luo, K.; Dale, B.; Zhong, Y.; Kim, A.; Wang, G. G.; Kaniskan, H. Ü.; **Jin, J.*** "Targeted Degradation of PRC1 Components, BMI1 and RING1B, via a Novel Protein Complex Degrader Strategy" **Advanced Science**, 2023, 10, e2205573. PMCID: PMC10074066. Google Scholar Citations: **5** (as of 3/1/2024)
2. My lab has also made seminal contributions to development of novel technologies for advancing the heterobifunctional molecule-induced protein post-translational modification (PTM) field. We developed new technologies, termed opto-PROTAC (Science Advances, 2020) and folate-caged PROTACs (JACS, 2021a; Journal of Medicinal Chemistry 2021b), resulting in selective targeted protein degradation (TPD) in cancer over normal cells, which enables degraders to be precision cancer therapeutics. We demonstrated that the E3 ligase KEAP1 can be harnessed for PROTAC development using a selective KEAP1 ligand, thus expanding the toolbox for TPD (JACS, 2021b). To target undruggable transcription factors (TFs), we developed innovative technologies, termed TF-PROTAC (JACS, 2021c) and TF-DUBTAC (JACS, 2022a), which effectively degrade oncogenic TF and stabilize tumor-suppressive TF, respectively. Using the same oligonucleotide-based strategy, we developed the first-in class TeloTAC, Methyl-PROTAC and Z-DNA-based

PROTAC (Z-PROTAC) for degrading telomeric repeat-binding factor proteins (JACS, 2023a), methyl-CpG-binding protein 2 (JACS, 2023b) and ADAR1 (JACS, 2024), respectively. We also developed a novel technology, termed Bridged PROTAC, to degrade undruggable proteins, which has been applied to generation of the first-in-class cyclin D1 (JACS, 2022b) and BMI1/RING1B (Advanced Science, 2023) PROTACs. Most recently, we developed another innovative technology, termed Acetylation Targeting Chimera (AceTAC), for inducing targeted protein acetylation (JACS, 2023c). Lastly, we developed new technologies to activate and silence target genes by hijacking acetyltransferases (Nature Biotechnology, 2020) and histone deacetylases (ACS Synthetic Biology, 2018), respectively. Overall, these innovative technologies as potentially generalizable platforms have significantly advanced the heterobifunctional small molecule-induced protein PTM field. In addition to the 2021 JACS paper listed in Section A, our representative papers (*corresponding author(s)) in this area include:

a. Liu, J.; Chen, H.; Kaniskan, H.; Xie, L.; Chen, X.; **Jin, J.***; Wei, W.* "TF-PROTACs Enable Targeted Degradation of Transcription Factors" **Journal of the American Chemical Society**, 2021, 143, 8902-8910. PMCID: PMC8225582. Google Scholar Citations: **117** (as of 3/1/2024).
b. Xiong, Y.; Zhong, Y.; Yim, H. et al; Chen, X.; Liu, J.; **Jin, J.*** "Bridged Proteolysis Targeting Chimera (PROTAC) Enables Degradation of Undruggable Targets" **Journal of the American Chemical Society**, 2022, 144, 22622–22632. PMCID: PMC9772293. Google Scholar Citations: **27** (as of 3/1/2024).
c. Liu, J.; Yu, X.; Chen, H. et al; Chen, X.; **Jin, J.***; Wei, W.* "TF-DUBTACs Stabilize Tumor Suppressor Transcription Factors" **Journal of the American Chemical Society**, 2022, 144, 12934-12941. Google Scholar Citations: **22** (as of 3/1/2024).
d. Kabir, M.; Sun, N.; Hu, X.; Martin, T. C.; Yi, J.; Zhong, Y.; Xiong, Y.; Kaniskan, H. Ü.; Gu, W.; Parsons, R.; **Jin, J.*** "Acetylation Targeting Chimera Enables Acetylation of the Tumor Suppressor p53" **Journal of the American Chemical Society**, 2023, 145, 14932–14944. PMCID: PMCID: PMC10040430. Google Scholar Citations: **8** (as of 3/1/2024).

3. My lab has made extensive contributions to discovering selective inhibitors of protein methyltransferases (PMTs) by targeting the substrate-binding groove, cofactor-binding site and allosteric binding sites of PMTs (Chemical Reviews (2018), Nature Reviews Drug Discovery (2021)). When my lab started working in this area in 2008, there was no evidence that the substrate binding grooves of PMTs could be exploited. We discovered highly potent, selective and cell-active G9a/GLP inhibitors including UNC0638 (Nature Chemical Biology (2011), Journal of Medicinal Chemistry (2009, 2010 & 2011), Genes & Development (2014), Chemistry & Biology (2009), Journal of Biological Chemistry (2015)) and UNC0642, which is efficacious in vivo (Journal of Medicinal Chemistry (2013), Nature Medicine (2017), Cancer Discovery (2020), Cell (2023)). We also discovered GLP selective inhibitors including MS012, which are highly selective for GLP over G9a (Journal of Medicinal Chemistry (2017), Bioorg. & Med. Chem. (2017)), and the first covalent G9a/GLP inhibitor MS8511 (Journal of Medicinal Chemistry (2022)). We also discovered the first SETD8 selective non-covalent and covalent inhibitors including UNC0379 and MS453 (Journal of Medicinal Chemistry (2014 & 2016), MedChemComm (2014), Cancer Cell (2017), JCI Insight (2019), eLIFE (2019), Clinical Epigenetics (2021)). Furthermore, my lab discovered MS023, a potent and selective inhibitor of type I protein arginine methyltransferases, which has displayed robust cellular and in vivo efficacy (ACS Chemical Biology (2016), Blood (2019a & 2019b), Cancer Cell (2019), Cell (2021), Cell Reports (2021), Nature Chemical Biology (2022)). We also discovered MS049, a cell-active dual inhibitor of PRMT4 and PRMT6 (Journal of Medicinal Chemistry (2016)), and MS117, a potent, selective and cell-active covalent inhibitor of PRMT6 (Journal of Medicinal Chemistry (2020)). <u>Together, these results have demonstrated that the PMT substrate binding groove can be targeted to yield potent, selective and in vivo efficacious inhibitors.</u> By targeting the EZH2-cofactor binding site, we discovered UNC1999, the first orally bioavailable EZH2 inhibitor (ACS Chemical Biology (2013), Journal of Medicinal Chemistry (2016)). It has high in vitro potency and selectivity, exhibits robust on-target activities in cells, and is efficacious in vivo (ACS Chemical Biology (2013), Blood (2015, 2017 & 2019), Cancer Biology & Therapy (2014), PLOS ONE (2015), Oncotarget (2016, 2017a & 2017b), Clinical Cancer Research (2017), Circulation Research (2018), Nature Communications (2019), Cancer Cell (2019), Cancer Discovery (2020), Nature Communications (2021)). In addition, we in collaboration with the Structure Genomics Consortium (SGC) discovered the first allosteric inhibitors of PRMT3 (Structure (2012), Angew. Chem. Int. Ed. (2015), Journal of Medicinal Chemistry (2013 & 2018)) and PRMT6 (Journal of Medicinal Chemistry (2021)). <u>These selective PMT inhibitors have been widely utilized by the research community, and the pharmaceutical industry has also advanced multiple optimized compounds into clinical development, which led to the approval of the EZH2 inhibitor Valemetostat in Japan.</u> Our representative papers (*corresponding author(s)) in this area include:

a. Vedadi, M.; Barsyte-Lovejoy, D.; Liu, F. et al; Arrowsmith, C. H.*; **Jin, J.*** "A Chemical Probe Selectively Inhibits G9a and GLP Methyltransferase Activity in Cells" **Nature Chemical Biology**, 2011, 7, 566-574. PMCID: PMC3184254. Google Scholar Citations: **546** (as of 3/1/2024).
b. Liu, F.; Barsyte-Lovejoy, D.; Li, F. et al; Arrowsmith, C. H.; Brown, P. J.; Vedadi, M.; **Jin, J.*** "Discovery of an *in vivo* Chemical Probe of the Lysine Methyltransferases G9a and GLP" **Journal of Medicinal Chemistry**, 2013, 56, 8931-8942. Google Scholar Citations: **265** (as of 3/1/2024).
c. Konze, K. D.; Ma, A.; Li, F. et al; Wang, G. G.; Vedadi, M.; **Jin, J.*** "An Orally Bioavailable Chemical Probe of the Lysine Methyltransferases EZH2 and EZH1" **ACS Chemical Biology**, 2013, 8, 1324-1334. PMCID: PMC3773059. Google Scholar Citations: **476** (as of 3/1/2024).
d. Eram, M. S.; Shen, Y.; Szewczyk, M. et al; Barsyte-Lovejoy, D.; Liu, J.*; Vedadi, M.*; **Jin, J.*** "A Potent, Selective and Cell-active Inhibitor of Human Type I Protein Arginine Methyltransferases" **ACS Chemical Biology**, 2016, 11, 772-781. Google Scholar Citations: **226** (as of 3/1/2024).

4. My lab discovered the first β-arrestin-biased agonists of dopamine $D_2$ receptor ($D_2R$), which displayed robust antipsychotic drug-like activities in multiple animal models (PNAS (2011), Journal of Medicinal Chemistry (2012), Neuropsychopharmacology (2016), PNAS (2016)), and complementary G protein-biased $D_2R$ agonists (Journal of Medicinal Chemistry (2016 & 2019)). We developed a rational approach for translating GPCR structural data into β-arrestin-biased ligands at aminergic GPCRs (Nature Chemical Biology (2018)). We also developed biased agonists of dopamine $D_1$ receptor ($D_1R$) (Journal of Medicinal Chemistry (2019), ACS Chemical Neuroscience (2019)) and revealed structural determinants of 5-$HT_{2B}$ biased agonism using structural and chemical biology approaches (Nature Structural and Molecular Biology (2018)). My lab contributed to discovery of first-in-class positive allosteric modulators (PAMs) of GPR68 and GPR65 (Nature, 2015) and novel probes for the atypical opioid receptors MRGPRX2 (Nature Chemical Biology, 2017) and MRGPRX4 (Nature, 2021). We also developed improved GPR68 PAMs, which are suitable for in vivo studies (Journal of Medicinal Chemistry (2019)), and potent and selective antagonists of 5-$HT_{5A}$ via structure-based design (Nature Structural and Molecular Biology (2022)).
   a. Allen, J. A.; Yost, J. M. et al; Roth, B. L.*; **Jin, J.*** "Discovery of β-Arrestin-Biased Dopamine $D_2$ Ligands for Probing Signal Transduction Pathways Essential for Antipsychotic Efficacy" **PNAS***,* 2011, 108, 18488-18493. PMCID: PMC3215024. Google Scholar Citations: **372** (as of 3/1/2024).
   b. Chen, X.; Sassano, M. F. et al; Roth, B. L.*; **Jin, J.*** "Structure-Functional Selectivity Relationship Studies of Beta-arrestin-biased Dopamine $D_2$ Receptor Agonists" **Journal of Medicinal Chemistry**, 2012, 55, 7141-7153. PMCID: PMC3443605. Google Scholar Citations: **142** (as of 3/1/2024).
   c. McCorvy, J. D.; Butler, K. V. et al; Shoichet, B. K.; Dror, R. O.*; **Jin, J.***; Roth, B. L.* "Structure-inspired Design of β-arrestin-biased Ligands for Aminergic GPCRs" **Nature Chemical Biology**, 2018, 14, 126-134. PMCID: PMC5771956. Google Scholar Citations: **151** (as of 3/1/2024).
   d. Huang, X. P.; Karpiak, J.; Kroeze, W. K. et al; Penn, R. B.; **Jin, J.**; Koller, B. H.; Kenakin, T.; Shoichet, B. K.*; Roth, B. L.* "Allosteric Ligands for the Pharmacologically Dark Receptors GPR68 and GPR65" **Nature**, 2015, 527, 477-483. PMCID: PMC4796946. Google Scholar Citations: **245** (as of 3/1/2024).

5. I have led multiple small-molecule drug discovery programs that discovered and advanced 5 drug candidates to clinical development. Since 2008, my lab has contributed to many other drug discovery projects (Nature (2012), Cell (2012), Science (2016), Nature Biotechnology (2020), etc.) and we have written a number of high impact reviews (e.g., Nature Reviews Cancer (2021), Nature Reviews Drug Discovery (2021)).
   a. Duncan, J. S.; Whittle, M. C. et al; **Jin, J.** et al; Johnson, G. L.* "Dynamic Reprogramming of the Kinome In Response to Targeted MEK Inhibition In Triple Negative Breast Cancer" **Cell**, 2012, 149, 307-321. PMCID: PMC3328787. Google Scholar Citations: **822** (as of 3/1/2024).
   b. Huang, H.-S.; Allen, J. A. et al; Chen, X.; **Jin, J.**; Bridges, A. S.; Zylka, M. J.*; Roth, B. L.*; Philpot, B. D.* "Topoisomerase Inhibitors Unsilence the Dormant Allele of *Ube3a* in Neurons" **Nature**, 2012, 481, 185-189. PMCID: PMC3257422. Google Scholar Citations: **384** (as of 3/1/2024).
   c. Rialdi, A., Campisi, L., Zhao, N. et al; **Jin, J.**, Weirauch, M. et al; García-Sastre, A., Bukreyev, A., Marazzi, I.* "Topoisomerase 1 inhibition suppresses inflammatory genes and protects from death by inflammation" **Science**, 2016, 352, aad7993. Google Scholar Citations: **150** (as of 3/1/2024).
   d. Dale, B.; Cheng, M. et al; Xiong, Y.*; **Jin, J.*** "Advancing Targeted Protein Degradation for Cancer Therapy" **Nature Reviews Cancer**, 2021, 21, 638-654. PMCID: PMC8463487. Google Scholar Citations: **271** (as of 3/1/2024).

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