## BIOGRAPHICAL SKETCH

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NAME: Zachary Levi Watson

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

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 |
|---|---|---|---|
| University of North Florida, Jacksonville, FL | BS | 07/2006 | Biology |
| University of Florida, Gainesville, FL | PhD | 11/2013 | Virology |
| University of Colorado, Aurora, CO | Postdoctoral | 12/2016 | HPV-Associated Cancer |
| University of Colorado, Aurora, CO | Postdoctoral | 01/2019 | Ovarian Cancer |

### A. Personal Statement

My work focuses on the adipose environment of ovarian cancers, particularly the influence of inflammatory adipose cells of non-mesenchymal origin. This project is the first to study hematopoietic stem cell derived adipocytes (HSCDAs) in the context of ovarian cancer and their effects on signaling, metabolism, inflammation, and immunity. I have led this project from a small pilot grant from the Colorado Clinical & Translational Sciences Institute (CCTSI) to a highly competitive Department of Defense Pilot Award. I have also received other awards including an NCI R03 and a Rivkin/OCRA pilot award, and I have published on the topics of ovarian cancer epigenetics, Wnt signaling, therapy resistance, tumor metabolism, autophagy, and the immune microenvironment. With our latest findings, my team is excited to expand into studies of dietary interventions. My publication record shows that I am proficient with *in vitro* and *in vivo* ovarian cancer models and I am confident in my ability to lead these novel studies. I have assembled a team of experts in nutrition, metabolism, adipose biology, and ovarian cancer that will ensure the success of the proposed studies, which will integrate animal models, human derived primary cultures, and cutting-edge computational methods to advance our knowledge of the tumor microenvironment. The proposed studies include mechanistic aims, as well as translational aims intended to directly support future human clinical studies and trials. Ongoing and recently completed projects that I would like to highlight include:

Department of Defense OCRP Pilot Award OC210257
Watson (PI)
09/01/2022 – 08/31/2025
Identifying targetable vulnerabilities of bone marrow-derived adipocytes in the ovarian cancer tumor microenvironment

NIH/NCI R03CA249571
Watson (PI)
12/16/2020 – 06/15/2023
Targeting histone methyltransferases EHMT1 and EHMT2 to sensitize PARP inhibitor-resistant ovarian cancer

## B. Positions, Scientific Appointments, and Honors

### Positions and Employment

2023-current Assistant Professor, Obstetrics & Gynecology, University of Colorado (CU OB-GYN)
2019-2023 Instructor, CU OB-GYN
2017-2018 Postdoctoral Fellow, CU OB-GYN
2014-2016 Postdoctoral Fellow, Immunology & Microbiology, University of Colorado
2006-2013 Graduate Student, Molecular Genetics & Microbiology, University of Florida

### Other Experience and Professional Membership

2025 Early Career Reviewer, NIH/NCI BCIB Study Section
2025 Course Director, CU OB-GYN Fellows Research Intro Course
2025 Reviewer, CU Cancer Center – Cancer Research Experience for Undergraduates (CREU)
2024-current Reviewer, Department of Defense OCRP Pilot Study Section
2024-current Reviewer, Colorado Clinical & Translational Sciences Institute (CCTSI) Study Section
2024-current Co-Director, CU OB-GYN Research Seminar Series
2023 Cancer League of Colorado Scientific Advisory Board
2023 Ad-Hoc Member, University of Colorado OB-GYN CURE Grant Review Panel
2023-current Member, University of Colorado Cancer Biology NRSA Fellows Mock Review Panel
2022-current Member, Society for Reproductive Investigation (SRI)
2021-2024 Lecturer, CU OB-GYN Fellows Research Intro Course
2021-2022 Member, CU OB-GYN Research Retreat Organizing Committee
2019-2021 Lecturer, BSBT 6074 Foundation in Cell Biology, University of Colorado
2019-current Mentored Member, CU Cancer Center
2018-current Member, CCTSI
2018-current Member, American Association for Cancer Research (AACR)
2011-2016 Associate Member, American Society for Virology (ASV)
2010 BSL3 Science and Safety Course, Emory University, Atlanta, GA

### Honors

2024-2026 Colorado SCORE Scholar (early career investigator supported by U54AG062319)
2024-2026 Rivkin Center/OCRA Pilot Study Award RPG-R-2024-2-1269446
2024 CU Cancer Center / American Cancer Society Institutional Research Grant 22-154-59
2022-2025 Department of Defense Ovarian Cancer Research Program Pilot Award OC210257
2020-2023 National Cancer Institute R03CA249571
2020-2022 CCTSI Co-Pilot Award CO-J-20-006
2019-2020 Cancer League of Colorado Research Grant 193527-ZW
2019 CU OB-GYN Research Retreat – Best Faculty Poster
2018 University of Colorado Cancer Biology Postdoc Symposium – Best Oral Presentation
2018 University of Colorado Postdoctoral Association Travel Award
2014-2016 NRSA Postdoctoral T32 – Lung Head & Neck Cancer
2012 NIH Chromatin Control of Viral Infection Travel Award
2011 36th Annual Herpesvirus Workshop Travel Award
2010 35th Annual Herpesvirus Workshop Travel Award
2008-2010 NRSA Predoctoral T32 – Biodefense & Emerging Infectious Disease
2006-2008 University of Florida Grinter Fellowship

## C. Contributions to Science

**1.** The primary cause of death from HGSC is metastatic disease within the peritoneal cavity. There is a significant knowledge gap as to how HGSC cells gain the ability to exfoliate from the fallopian tube, survive in suspension, and metastasize to the peritoneum. To address this gap, I have contributed to several studies of ovarian cancer dissemination and identified epigenetic factors, metabolic adaptations, and autophagy regulators as contributing to anoikis resistance and survival in suspension. Ongoing and future work includes highly innovative studies examining adipocytes and the tumor microenvironment as factors contributing to ovarian cancer progression, immune evasion, and therapy response.

a. Woodruff ER, Bailey CA, To F, Manda V, Maltzahn JK, Sullivan TM, Boorgula MP, Recouvreux MS, Vianzon R, Conrad B, Gavin KM, Jordan KR, Klemm DJ, Bitler BG, **Watson ZL***. Ablation of hematopoietic stem cell derived adipocytes reduces tumor burden in a syngeneic mouse model of high grade serous ovarian carcinoma. *2025. Life Science Alliance.**(In Revision) *Corresponding author.***
b. Bapat J, Yamamoto TM, Woodruff ER, Qamar L, Mikeska RG, Aird KM, **Watson ZL**, Brubaker LW, Bitler BG. CASC4/GOLM2 drives high grade serous carcinoma anoikis resistance through recycling of EGFR. *2024. Cancer Gene Ther. DOI: 10.1038/s41417-023-00703-1*
c. Wheeler LJ*, **Watson ZL***, Qamar L, Yamamoto TM, Sawyer BT, Sullivan KD, Khanal S, Joshi M, Ferchaud-Roucher V, Smith H, Vanderlindent LA, Brubaker SW, Caino CM, Kim H, Espinosa JM, Richer JK, Bitler BG. Multi-omic approaches identify metabolic and autophagy regulators important in ovarian cancer dissemination. *2019. iScience. DOI: 10.1016/j.isci.2019.07.049.* ***Co-first authors.***
d. Wheeler LJ*, **Watson ZL***, Qamar L, Yamamoto TM, Post MD, Berning AA, Spillman MA, Behbakht K, Bitler BG. CBX2 Identified as Driver of Anoikis Escape and Dissemination in High Grade Serous Ovarian Cancer. *2018. Oncogenesis. DOI: 10.1038/s41389-018-0103-1.* ***Co-first authors.***

**2.** Poly ADP-ribose polymerase inhibitor (PARPi) resistance is a major obstacle to elimination of recurrent ovarian cancer. My goal is to examine epigenetic mechanisms of PARPi resistance and to identify novel biomarkers and druggable targets. Using multiple PARPi-resistant cell lines and mouse models, I have observed upregulation of H3K9me2 and the histone methyltransferases EHMT1 and EHMT2. Targeting EHMT1/2 sensitizes PARPi-resistant cells to treatment and ablates DNA damage repair. In syngeneic mouse models, targeting EHMT1/2 with a novel orally-available compound sharply decreases tumor burden. *In vivo* antitumor response is at least partially due to reactivation of transposable elements and recognition of dsRNA by MDA5/RIG-I, which induces IFN pathways, “viral mimicry,” and a CD8+ T-cell response.

a. Nguyen LL*, **Watson ZL***, Ortega R, Woodruff ER, Jordan KR, Iwanaga R, Yamamoto TM, Bailey CA, To F, Lin S, Villagomez FR, Jeong, AD, Guntupalli SR, Behbakht K, Gibaja V, Arnoult N, Chuong EB, Bitler BG. EHMT/G9A inhibition promotes regression of therapy-resistant ovarian cancer tumors in a CD8 T cell-dependent manner. *2024. Mol Cancer Res. DOI: 10.1158/1541-7786.MCR-24-0067* ***Co-first authors.***
b. Nguyen LL*, **Watson ZL***, Ortega R, Woodruff ER, Jordan KR, Iwanaga R, Yamamoto TM, Bailey CA, To F, Jeong AD, Guntupalli SR, Behbakht K, Gbaja V, Arnoult N, Cocozaki A, Chuong EB, Bitler BG. Combining EHMT and PARP Inhibition: A Strategy to Diminish Therapy-Resistant Ovarian Cancer Tumor Growth while Stimulating Immune Activation. *2024. Mol Cancer Ther. DOI: 10.1158/1535-7163.MCT-23-0613.* ***Co-first authors.***
c. Bitler BG, Bailey CA, Yamamoto TM, McMellen A, Kim H, **Watson ZL***. Targeting BRPF3 moderately reverses olaparib resistance in high grade serous ovarian carcinoma. *2023. Mol Carcinog. DOI: 10.1002/mc.23610.* ***Corresponding author.***
d. **Watson ZL**, Yamamoto TM, McMellen A, Kim H, Hughes CJ, Wheeler LJ, Post MD, Behbakht K, Bitler BG. Histone methyltransferases EHMT1 and EHMT2 (GLP/G9A) maintain PARP inhibitor resistance in high grade serous ovarian carcinoma. *2019. Clin Epigenetics. DOI:10.1186/s13148-019-0758-2.*

**3.** Herpes simplex virus type 1 (HSV-1) establishes latency within trigeminal ganglia (TG), and reactivation from the ophthalmic branch leads to recurrent corneal scarring and blindness. I demonstrated that the viral noncoding latency-associated transcript (LAT) epigenetically promotes reactivation by disrupting heterochromatin deposition on viral genomes. In an innovative translational study, I designed a ribozyme targeting the LAT and delivered it into rabbit TG using an AAV vector, which I had previously demonstrated to transduce >90% of sensory neurons. The ribozyme knocked down LAT RNA levels and reduced HSV-1 reactivation by over 50%. This result represents an entirely novel therapeutic approach against previously untreatable HSV-1 reactivation.

a. **Watson Z**, Dhummakupt A, Messer H, Phelan D, and D Bloom. 2013. Role of Polycomb Proteins in Regulating HSV-1 Latency. *2013. Viruses. DOI: 10.3390/v5071740*
b. **Watson ZL**, Ertel MK, Lewin AS, Tuli SS, Schultz GS, Neumann DM, and DC Bloom. 2016. Adeno-Associated Virus Vectors Efficiently Transduce Mouse and Rabbit Sensory Neurons Coinfected With Herpes Simplex Virus 1 Following Peripheral Inoculation. *2016. J Virol. DOI: 10.1128/JVI.01028-16*

c. **Watson ZL**, Washington SD, Phelan DM, Lewin AS, Tuli SS, Schultz GS, Neumann DM, Bloom DC. 2018. In Vivo Knockdown of the Herpes Simplex Virus 1 Latency-Associated Transcript Reduces Reactivation from Latency. *J Virol. DOI: 10.1128/JVI.00812-18.*
d. Washington SD, Edenfield SI, Lieux C, **Watson ZL**, Taasan SM, Dhummakupt A, Bloom DC, Neumann DM. Depletion of the insulator protein CTCF results in HSV-1 reactivation in vivo. *2018. J Virol. DOI: 10.1128/jvi.00173-18.*

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