BIOGRAPHICAL SKETCH

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NAME: Zachary J. Reitman MD, PhD

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

POSITION TITLE: Assistant Professor of Radiation Oncology, Pathology, and Neurosurgery

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
Penn State, University Park, PA	B.S.	05/2006	Biochemistry and Molecular Biology
Duke University School of Medicine, Durham, NC	M.D./Ph.D.	05/2014	Pathology
Union Memorial Hospital, Baltimore, MD	Internship	06/2015	Internal Medicine
Harvard Radiation Oncology Program, Boston, MA	Research pathway residency	06/2019	Radiation Oncology
Duke University School of Medicine, Durham, NC	Postdoc	06/2021	Genetic mouse models

A. Personal Statement

I am a physician-scientist (80% research, 20% clinic) interested in identifying new diagnostic and therapeutic strategies for patients with brain tumors. To this end, my research group is pursuing three major areas of investigation: (1) To identify creative new approaches to target frequent somatic driver mutations in cancer; (2) To identify approaches that widen the therapeutic ratio of radiation therapy for brain tumor patients; and (3) To use genomics approaches to improve tumor detection, diagnosis, and monitoring and to understand and overcome therapeutic resistance. We use genetically engineered mouse models of brain tumors and expertise in genomic, metabolomic, and multi-omic approaches to carry out our work. I have independent laboratory space and am principal investigator on multiple basic science research projects which primarily use focal brain radiation therapy to treat small animal models of brain tumors.

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

NCI K08-CA256045-01A1 Clinician Scientist Mentored Career Development Award
Reitman, Zachary J. (PI)
8/1/2022 – 7/31/2027
Enhancing the efficacy of Radiation Therapy for brainstem glioma by targeting ATM

Alex's Lemonade Stand Foundation A Award
Reitman, Zachary J. (PI)
2/3/2024-2/7/2028 (pending)
Modulation of STING to enhance the efficacy of treatments for diffuse midline glioma

ChadTough Defeat DIPG New Investigator Award
Reitman, Zachary J. (PI)
7/1/2022-6/30/2024

Dissecting mechanisms of radioresistance associated with p53 mutations in DIPG

NCI U19-CA264385 Glioblastoma Therapeutics Network
Ashley, David M. (PI)
Role: Co-investigator to provide genetic mouse model expertise
9/13/2021-8/31/2026
6-thio-2'-deoxyguanosine in GBM: Pre-clinical Evaluation of Mechanism of action, Efficacy and Biomarker identification

NCI P50-CA190991
Sampson, John (PI)
9/1/2020-8/31/2024
Role: PI of Developmental Research Program project on investigation of FLASH-RT in preclinical models of brain tumors and on CRISPR-Cas9 based methods to develop mouse models of brain tumors
Duke SPORE in Brain Cancer

Pediatric Brain Tumor Foundation Early Career Development Award
Reitman, Zachary J. (PI)
9/15/2019 – 9/14/2023
Identifying brainstem glioma subtypes that can be radiosensitized by ATM inhibition

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2023	*Ad hoc* reviewer, NCI-J career development (K) applications study section
2023	*Ad hoc* reviewer, NIH Scientific Review Group ZCA1 RTRB-B M1 R, SEP-8: NCI Clinical and Translational Research R03 and R21 applications
2023-present	Duke Medical Scientist Training Program (MSTP) Interview Committee Member
2023-present	Full Membership of the Graduate Faculty at Duke
2022-present	Executive Committee Member, Duke Brain Tumor Omics Program
2022-present	Assistant Professor of Pathology, secondary, Duke University School of Medicine, Durham, NC
2022-present	Assistant Professor of Neurosurgery, secondary, Duke University School of Medicine
2022	Co-organizer, Inaugural Tisch Brain Tumor Center at Duke Scientific Retreat, Durham, NC
2021-present	Assistant Professor of Radiation Oncology, Duke University School of Medicine, Durham, NC
2019-present	Staff Radiation Oncologist at the Private Diagnostic Clinic
2019-present	Staff Radiation Oncologist at the Durham Veteran's Administration Hospital
2019-2021	Medical Instructor in Radiation Oncology, Duke University School of Medicine, Durham, NC
2017-2019	Affiliated Postdoctoral Scholar, The Broad Institute of Harvard and MIT, Cambridge, MA
2017-2019	Clinical Research Fellow, Dana-Farber Cancer Institute, Boston, MA
2015-2019	Resident, Harvard Radiation Oncology Program, Massachusetts General Hospital, Boston, MA
2014-2015	Internal Medicine Intern, Union Memorial Hospital, Baltimore, MD
2006-2014	M.D./Ph.D. Candidate, Medical Scientist Training Program, Duke University School of Medicine
2012-2014	Associate in Research, Department of Pathology, Duke Univ School of Medicine, Durham, NC
2008-2012	Graduate Assistant, Department of Pathology, Duke University School of Medicine, Durham, NC
2002-2006	Undergraduate Assistant, Department of Biochemistry, Penn State University, PA
2005	Homeland Security Summer Scholar, Lawrence Livermore National Laboratory, Livermore, CA
2004	Summer Intern, Molecular Biology Group, Cephalon Pharmaceuticals, Malvern, PA
2003	Summer Undergraduate Research Fellow, Wistar Institute, Philadelphia, PA

Honors

2023	Early Career Investigator Award, International Congress of Radiation Research
2023	Clinical Resident Teaching Award, Department of Radiation Oncology
2020-2024	New Investigator Award, Michael Mosier Defeat DIPG SoSo Strong ChadTough Foundations
2020-2023	St. Baldrick's Foundation and Emily Beazley's Kures for Kids Fund Fellow
2019-2022	Early Career Development Award, Pediatric Brain Tumor Foundation
2018-2019	Conquer Cancer Foundation of ASCO Young Investigator Award

2018-2019 Defeat DIPG ChadTough Fellowship
2017-2019 American Board of Radiology B. Leonard Holman Research Pathway
2012-2013 Duke Cancer Biology NRSA Kirchstein Postdoctoral Training Grant (T32-CA059365-15)
2006-2010 Duke Medical Scientist Training Program NRSA Kirchstein Training Grant (T32-GM007171-35)
2009 Travel Award, Days of Molecular Medicine Conference, Boston, MA
2004-2006 Barry Goldwater Science Education Award
2004-2006 U.S. Department of Homeland Security Scholar
2006 Phi Beta Kappa
2004-2005 Thomas Bardos Science Education Award, American Association for Cancer Research
2003 Summer Undergraduate Research Fellowship, The Wistar Institute
2002 Valedictorian, Downingtown High School
2001 Eagle Scout, Boy Scouts of America

Professional memberships, clinical licensures, and specialty board certifications
2021-present Board Certified in Radiation Oncology, American Board of Radiology (ABR)
2020-present Medical License, Virginia Board of Medicine
2019-present Medical License, North Carolina Medical Board
2019-present Society for Neuro Oncology (SNO), member
2018-present Radiation Research Society (RRS), Early Career Investigator
2017-present American Society for Clinical Oncology (ASCO), Member
2016-present Radiosurgery Society (RSS), Member
2015-present American Society for Radiation Oncology (ASTRO), Member

C. Contributions to Science.

1. Genetically engineered mouse models and radiation biology of brain tumors. A major focus of my independent laboratory is on development of genetically engineered mouse models of brain tumors. Our work uses the Cre/loxP system and the RCAS/tv-a retroviral delivery system to edit genes in specific brain lineages, giving rise to tumors. Strengths of this approach include the ability to study tumorigenesis in primary, autochthonous models with intact immune systems. We used these approaches to show that targeting the Ataxia-telangiectasia mutated kinase (ATM), a master orchestrator of the DNA damage response to cytotoxic therapies, can enhance the efficacy of radiation therapy in specific genetic subtypes of glioma, but not others. This raised the question of whether patients with ATM-mutated tumors would have improved responses to radiotherapy and/or increased toxicity after radiotherapy; we showed was not the case using patient outcome and tumor molecular profiling data.

a) Tu KJ, Stewart CE, Williams NT, Ma Y, Luo L, Ghosh D, Weidenhammer LB, Floyd SR, Fan Y, Kirsch DG, Oldham M, **Reitman ZJ**. Single-fraction Radiation Treatment Dose Response in a Genetically Engineered Mouse Model of Medulloblastoma. Radiat Res. 2023 Nov 22. Epub ahead of print. PMID: 37990957.
b) Stewart CE, Guerra-García ME, Luo L, Williams NT, Ma Y, Regal JA, Ghosh D, Sansone P, Oldham M, Deland K, Becher OJ, Kirsch DG, **Reitman ZJ.** The Effect of *Atm* Loss on Radiosensitivity of a Primary Mouse Model of *Pten*-Deleted Brainstem Glioma. Cancers (Basel). 2022 Sep 17;14(18):4506. doi: 10.3390/cancers14184506. PMID: 36139666; PMCID: PMC9496888.
c) Floyd W, Carpenter D, Vaios E, Shenker R, Hendrickson P, Adamson JD, Giles WM, Wang C, Allen K, Mullikin T, Floyd SR, Kirkpatrick JP, Green M, **Reitman ZJ** (in press). Impact of ATM Variants on Radionecrosis and Local Control after Stereotactic Radiosurgery for Non Small Cell Lung Cancer Brain Metastases. Adv Radiat Oncol. (accepted July 2023)
d) Weidenhammer LB, Liu HQ, Luo L, Williams NT, Deland K, Kirsch DG, **Reitman ZJ.** Inducing primary brainstem gliomas in genetically engineered mice using RCAS/TVA retroviruses and Cre/loxP recombination. STAR Protoc. 2023 Mar 17;4(1):102094. doi: 10.1016/j.xpro.2023.102094. Epub 2023 Feb 13. PMID: 36853662; PMCID: PMC9950926.

2. Discovery and targeting of brain tumor driver mutations, including oncogenic phosphatase PPM1D mutations and TERT promoter mutations. I the co-led the discovery of ultra-frequent TERT promoter mutations in brain tumors which are now used for brain tumor classification according to the World Health Organization 2021 guidelines. I also co-led the discovery of mutations in the oncogenic phosphatase PPM1D

in brainstem and thalamus gliomas (reported in *Nature Genetics* below). I have carried on this work more recently by identifying oncogenic functions of these important brain tumor-derived mutations. For instance, I characterized the oncogenic functions of PPM1D mutations (Khadka, Reitman et al., below). In my independent lab we used CRISPR/Cas9 pooled screening approaches to identify genetic dependencies associated with TERT promoter mutations (Tu et al., below).

a) Tu KJ, Stewart CE, Hendrickson PG, Regal JA, Kim SY, Ashley DM, Waitkus MS, **Reitman ZJ.** Pooled genetic screens to identify vulnerabilities in TERT-promoter-mutant glioblastoma. Oncogene. 2023 Oct;42(44):3274-3286. Epub 2023 Sep 23. PMID: 37741952; PMCID: PMC10615780.
b) Khadka P*, **Reitman ZJ***, Lu S, Buchan G, Gionet G, Dubois F, Carvalho DM, Shih J, Zhang S, Greenwald NF, Zack T, Shapira O, Pelton K, Hartley R, Bear H, Georgis Y, Jarmale S, Schoolcraft K, Miller PG, Condurat AL, Gonzalez E, Qian K, Morin E, Langhnoja J, Lupien L, Rendo V, Digiacomo J, Wang D, Zhou K, Kumbhani R, Guerra Garcia ME, Sinai CE, Becker S, Schneider R, Vogelzhang J, Melanson R, Keshishian H, Goodale A, Abid T, Kalani Z, Persky NS, Piccioni F, Root DE, Carcaboso AM, Carr SA, Ebert BL, Fuller C, Kieran MW, Jones C, Ligon KL, Beroukhim R, Phoenix TN, Bandopadhayay P. *PPM1D* mutations are oncogenic drivers of *de novo* Diffuse Midline Glioma formation (2022). Nat Commun. 13(1):604 PMID: 35105861 ***Equal contributor**
c) Zhang L, Chen LH, Wan H, Yang R, Wang Z, Feng J, Yang S, Jones S, Wang S, Zhou W, Zhu H, Killela PJ, Zhang J, Wu Z, Li G, Hao S, Wang Y, Webb JB, Friedman HS, Friedman AH, McLendon RE, He Y, **Reitman ZJ†**, Bigner DD, Yan H†. Exome sequencing identifies somatic gain-of-function PPM1D mutations in brainstem gliomas (2014). Nat Genetics. 46(7):726-30 PMID: 24880341. PMCID: PMC4073211. **†Corresponding author**
d) Killela PJ*, **Reitman ZJ***, Jiao Y*, Bettegowda C*, Agrawal N, Diaz LA Jr., Friedman AH, Friedman H, Gallia GL, Giovanella BC, Grollman AP, He TC, He Y, Hruban RH, Jallo GI, Mandahl N, Meeker AK, Mertens F, Netto GJ, Rasheed BA, Riggins GJ, Rosenquist TA, Schiffman M, Shih IM, Theodorescu D, Torbenson MS, Velculescu VE, Wang TL, Wentzensen N, Wood LD, Zhang M, McLendon RE, Bigner DD, Kinzler KW, Vogelstein B, Papadopoulos N, Yan H. TERT promoter mutations occur frequently in gliomas and a subset of tumors derived from cells with low rates of self-renewal (2013). Proc Natl Acad Sci (USA). 110(15):6021-6 PMID: 23530248. PMCID: PMC3625331. ***Equal contributor**

3. Multi-omic analyses of brain tumors. I carried out post-doctoral research focusing on single cell RNA sequencing and functional genomics approaches in the Beroukhim and Bandopadhayay labs at the Dana-Farber Cancer Institute. The work also identified therapeutically actionable gene programs in pediatric low grade gliomas using single cell RNA sequencing approaches. I have now executed the first-ever single cell and spatially-resolved RNA-seq analysis of gangliogliomа, an important brain tumor of children and young adults. I have additional experience in executing genome-wide sequencing and studies to define the genetic landscape of other tumors such as pituitary adenoma.

a) Regal JA, Guerra García ME, Jain V, Chandramohan V, Ashley DM, Gregory SG, Thompson EM, López GY, **Reitman ZJ**. Ganglioglioma deep transcriptomics reveals primitive neuroectoderm neural precursor-like population. Acta Neuropathol Commun. 2023 Mar 25;11(1):50. doi: 10.1186/s40478-023-01548-3. PMID: 36966348; PMCID: PMC10039537.
b) **Reitman ZJ***, Paolella BR*, Bergthold G, Pelton K, Becker S, Jones R, Sinai CE, Malkin H, Huang Y, Grimmet L, Herbert ZT, Sun Y, Weatherbee JL, Alberta J, Daley JF, Rozenblatt-Rosen O, Condurat AL, Qian K, Khadka P, Segal RA, Haas-Kogan D, Filbin MG, Suva ML, Regev A , Stiles C, Kieran MW, Goumnerova L, Ligon KL, Shalek AK, Bandopadhayay P, Beroukhim R. Mitogenic and progenitor gene programs in single pilocytic astrocytoma cells (2019). Nat Commun. 10(1):3731. PMID: 31427603. PMCID: PMC6700116. ***Equal contributor**
c) Song ZJ*, **Reitman ZJ***, Ma ZY*, Chen JH*, Zhang QL*, Shou XF*, Huang CX, Wang YF, Li SQ, Mao Y, Zhou LF, Lian BF, Yan H, Shi YY, Zhao Y. The genome-wide mutational landscape of pituitary adenomas (2016). Cell Res. 26:1255–1259 PMID: 27670697. PMCID: PMC5099864. ***Equal contributor**

4. Identification of functions of IDH1 mutations in brain tumors. I led the development of a fruit fly model of cancer-derived isocitrate dehydrogenase 1 (IDH1) mutations, revealing effects of these mutations on apoptosis pathways. I also led the first metabolome-wide study of brain tumor-derived IDH1 mutations, revealing widespread changes enforced by IDH1 mutations on the cellular metabolome in cancer cell lines, and also revealed that IDH1 mutations stimulate glutamine metabolism in tumors and cell lines, with

therapeutic implications. This work was done during my PhD and post-doctoral studies. These findings generate therapeutic hypotheses to exploit unique features of tumor metabolism.

a) **Reitman ZJ**, Sinenko SA, Spana EP, Yan H. Genetic dissection of leukemia-associated IDH1 and IDH2 mutants and D-2-hydroxyglutarate in Drosophila (2015). Blood. 125(2):336-45 PMID: 25398939. PMCID: PMC4287640.
b) **Reitman ZJ**, Duncan CG, Poteet E, Winters A, Yan LJ, Gooden DM, Spasojevic I, Boros LG, Yang SH, Yan H. Cancer-associated isocitrate dehydrogenase 1 (IDH1) R132H mutation and d-2-hydroxyglutarate stimulate glutamine metabolism under hypoxia (2014). J Biol Chem. 22;289(34):23318-28 PMID: 24986863. PMCID: PMC4156049.
c) **Reitman ZJ***, Jin G*, Karoly ED, Spasojevic I, Yang J, Kinzler KW, He Y, Bigner DD, Vogelstein B, Yan H. Profiling the effects of isocitrate dehydrogenase 1 and 2 mutations on the cellular metabolome (2011). Proc Natl Acad Sci (USA) 108(8):3270-5 PMID: 21289278. PMCID: PMC3044380. ***Equal contributor**
d) Jin G*, **Reitman ZJ***, Duncan CG, Spasojevic I, Gooden DM, Rasheed BA, Yang R, Lopez GY, He Y, McLendon RE, Bigner DD, Yan H. Disruption of wild type IDH1 suppresses D-2-hydroxyglutarate production in IDH1-mutated gliomas (2013). Cancer Res. 73(2):496-501 PMID: 23204232. PMCID: PMC3548957. ***Equal contributor**

5. Enzyme redesign guided by cancer mutations. New enzymes are needed to enable new chemical synthesis approaches. In a highly innovative study that combined cancer genomics with enzyme development, I designed and characterized a novel 2-hydroxyadipate dehydrogenase enzyme. This was done by applying mutations found in the active site of isocitrate dehydrogenase in human cancer to the active site of a distantly-related yeast enzyme (Reitman et al., featured on the cover of *Nature Chemical Biology*, below). This novel enzyme may be useful to enable a 100% bio-based method to produce the important chemical adipic acid which is used for nylon production. In my independent lab, we developed approaches to identify additional cancer-derived enzyme mutations. I also co-first-authored work that defined the effects of mutations on cancer- and virus-derived enzymes using enzyme biochemistry and metabolomic approaches.

a) Tu KJ, Diplas BH, Regal JA, Waitkus MS, Pirozzi CJ, **Reitman ZJ.** Mining cancer genomes for change-of-metabolic-function mutations. Commun Biol. 2023 Nov 10;6(1):1143. PMID: 37950065; PMCID: PMC10638295.
b) **Reitman ZJ,** Choi BD, Spasojevic IS, Sampson JH, Yan H. Enzyme redesign guided by cancer-derived IDH1 mutations (2012). Nat Chem Biol 8(11):887-9 PMID: 23001033. PMCID: PMC3487689. **Cover feature**
c) Jin G*, **Reitman ZJ***, Spasojevic I, Batinic-Haberle I, Yang J, Schmidt-Kittler O, Bigner DD, Yan H. 2-Hydroxyglutarate production, but not dominant negative function, is conferred by glioma-derived $NADP^+$-dependent isocitrate dehydrogenase mutations (2011). PLoS One 6(2):e16812 PMID: 21326614. PMCID: PMC3033901. ***Equal contributor**
d) Shen M*, **Reitman ZJ***, Zhao Y, Moustafa I, Wang Q, Arnold JJ, Pathak HB, Cameron CE. Picornavirus genome replication: Identification of the surface of the poliovirus (PV) 3C dimer that interacts with PV 3Dpol during VPg uridylylation and construction of a structural model for the PV $3C_2$-3Dpol complex (2008). J Biol Chem. 283(2):875–888 PMID: 17993457. PMCID: PMC2186065. ***Equal contributor**

Complete List of 50+ publications (15+ lead-authored original research publications) in MyBibliography: https://www.ncbi.nlm.nih.gov/myncbi/1LuR1s9uvwuQl/bibliography/public/