BIOGRAPHICAL SKETCH

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NAME: **McBrayer, Samuel Kent**

eRA COMMONS USER NAME (credential, e.g., agency login): **s-mcbrayer**

POSITION TITLE: **Assistant Professor, Children's Medical Center Research Institute and Dept. of Pediatrics at the University of Texas Southwestern Medical Center**

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
Baylor University, Waco, TX	B.S.	09/2002	05/2006	Biochemistry
Kellogg School of Management, Northwestern University, Evanston, IL	Certificate	06/2011	08/2011	Management
Feinberg School of Medicine, Northwestern University, Chicago, IL	Ph.D.	09/2006	03/2012	Cancer Biology
Cold Spring Harbor Laboratory Metabolomics Course, Cold Spring Harbor, NY	N/A	06/2018	06/2018	Metabolism
Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA	Postdoctoral Fellowship	07/2012	06/2019	Cancer Biology

A. Personal Statement

Metabolic reprogramming is a fundamental feature of malignancy. My laboratory aims to understand how metabolic changes drive cancer initiation, promote adaptation to oncogenic stress, and create targetable vulnerabilities. To do so, we predominantly study gliomas that are characterized by mutations in the genes encoding isocitrate dehydrogenase (IDH) metabolic enzymes. The molecular pathogenesis of these brain tumors offers a window onto oncogenic mechanisms that co-opt connections between metabolism and other facets of cell biology. We use a variety of tools and model systems to study the biology of this disease, including organoid and genetically engineered mouse models of glioma that we have developed. In addition to providing basic insights into metabolic reprogramming in cancer, we aim to address the paucity of effective therapies for glioma patients by using our findings to launch clinical trials of new treatment strategies.

1. Shi DD, Savani MR, Levitt MM, Wang AC, Endress JE, Bird CE, Buehler J, Stopka S, Regan MS, Lin Y-F, Puliyappadamba VT, Gao W, Khanal J, Evans L, Lee JH, Guo L, Xiao Y, Xu M, Huang B, Jennings RB, Bonal DM, Martin-Sandoval MS, Dang T, Gattie LC, Cameron AB, Lee S, Asara JM, Kornblum HI, Mak TW, Looper RE, Nguyen Q-D, Signoretti S, Gradl S, Sutter A, Jeffers M, Janzer A, Lehrman MA, Zacharias LG, Mathews TP, Losman JA, Richardson TE, Cahill DP, DeBerardinis RJ, Ligon KL, Xu L, Ly P, Agar NYR, Abdullah KG, Harris IS, Kaelin WG*, **McBrayer SK***. De Novo Pyrimidine Synthesis is a Targetable Vulnerability in IDH Mutant Glioma. ***Cancer Cell***, 2022. Accepted in Principle.
2. Abdullah KG*, Bird CE, Buehler JD, Gattie LC, Savani MR, Sternisha AC, Xiao Y, Levitt MM, Hicks WH, Li W, Ramirez DMO, Patel T, Garzon-Muvdi T, Barnett S, Zhang G, Ashley DM, Hatanpaa KJ, Richardson TE, **McBrayer SK***. Establishment of Patient-Derived Organoid Models of Lower-Grade Glioma. ***Neuro-Oncology***, 2022. 24(4):612-623. PMC8972292.
3. **McBrayer SK**, Mayers JR, DiNatale GJ, Shi DD, Khanal J, Chakraborty AA, Sarosiek KA, Briggs KJ, Robbins AK, Sewastianik T, Shareef SJ, Olenchock BA, Parker SJ, Tateishi K, Spinelli JB, Islam M,

Haigis MC, Looper RE, Ligon KL, Bernstein BE, Carrasco RD, Cahill DP, Asara JM, Metallo CM, Yennawar NH, Vander Heiden MG, Kaelin WG. Transaminase Inhibition by 2-Hydroxyglutarate Impairs Glutamate Biosynthesis and Redox Homeostasis in Glioma. ***Cell***, 2018. 175(1): 101-116. PMC6219629.

4. **McBrayer SK**, Olenchock BA, DiNatale GJ, Shi DD, Khanal J, Jennings RB, Novak JS, Oser MG, Robbins AK, Modiste R, Bonal D, Moslehi J, Bronson RT, Neuberg D, Nguyen QD, Signoretti S, Losman JA, Kaelin WG. Autochthonous Tumors Driven by *Rb1* Loss Have an Ongoing Requirement for the RBP2 Histone Demethylase. ***PNAS***, 2018. 115(16): E3741-E3748. PMC5910822.
*****denotes co-corresponding author

B. Positions, Scientific Appointments and Honors

Positions and Employment

2019- Member, Simmons Comprehensive Cancer Center, UT Southwestern Medical Center
2019- Assistant Professor, Children's Medical Center Research Institute and Dept. of Pediatrics, UT Southwestern Medical Center, Dallas, TX
2012-19 Postdoctoral Fellow, Laboratory of William Kaelin, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA
2006-12 Ph.D. Candidate, Laboratory of Steven Rosen, Northwestern University, Chicago IL
2005-06 Undergraduate Researcher, Laboratory of Robert Kane, Baylor University, Waco, TX

Other Experience and Professional Memberships

2022 Invited member, Oligodendroglioma Think Tank, Oligo Nation Foundation
2021- Co-Chair, Society for Neuro-Oncology Young Investigators Committee
2021- Active Member, Society for Neuro-Oncology
2021- Active Member, American Association for Cancer Research
2021- Reviewer, *Nature Communications*
2021- Reviewer*, Molecular Cell*
2021- Reviewer, *Communications Biology*
2021- Reviewer, *Med*
2021- Reviewer, *Cell Press Community Review*
2021- Reviewer, *Trends in Endocrinology and Metabolism*
2020- Reviewer, *Trends in Cell Biology*
2020- Reviewer, *Science Advances*
2020- Reviewer, *iScience*
2019- Reviewer, *Cancer Research*
2018- Reviewer, *Cancer & Metabolism*

Honors and Awards

2021 Distinguished Scientist Award, Sontag Foundation
2021 Early Career Reviewer program, Center for Scientific Review, NIH
2021 "Rising Stars of Cancer Metabolism" Runner-Up, New York Academy of Sciences
2020 Abeloff V Scholar Award, The V Foundation for Cancer Research
2019 NIH/NCI K22 Career Transition Award
2019 CPRIT Scholar in Cancer Research
2018 Cold Spring Harbor Laboratory Young Scholars Symposium
2017 Aspen Cancer Conference Fellow
2017 Dana-Farber/Harvard Cancer Center Brain SPORE Career Enhancement Program Award
2014 American Cancer Society postdoctoral fellowship (*accepted*)
2014 NIH/NCI Ruth L. Kirschstein F32 NRSA postdoctoral fellowship (*declined*)
2011 Katten Muchin Rosenman, LLP Travel Scholarship
2008 NIH/NCI T32 Fellowship, Northwestern University
2006 *Phi Beta Kappa*
2006 Magna Cum Laude, Baylor University
2002 President's Gold Scholarship, Baylor University
2002 Fred T. and Gladys V. Hawley Scholarship, Community Foundation for Muskegon County
2002 Robert C. Byrd Honors Scholarship, U.S. Dept. of Education

2002 Valedictorian, North Muskegon High School, North Muskegon, MI

C. Contributions to Science

1. **Elucidating metabolic reprogramming by cancer-associated Isocitrate Dehydrogenase (IDH) mutations.** As a postdoctoral fellow in William Kaelin's lab at the Dana-Farber Cancer Institute, I explored how IDH mutations reshape the glial cell metabolome. I discovered that IDH mutations impair nitrogen metabolism by inhibiting the branched chain amino acid transaminases, which increases compensatory glutamine catabolism. Importantly, I found that inhibiting glutamine use by IDH mutant glioma cells causes tumor-selective radiosensitization. These findings informed a novel treatment approach for IDH mutant glioma: combining a glutamine metabolism inhibitor, CB-839, with radiation and temozolomide therapies. This strategy is now being tested in an ongoing phase I clinical trial (NCT03528642). I also collaborated with Christian Metallo at UCSD to evaluate the impact of IDH mutations on NADPH homeostasis.

    a. Kizilbash SH, **McBrayer SK**, Port J, Reid JM, Lanza I, Allred JB, Chakravarti A, Kunos C, Adjei AA. A Phase Ib Trial of CB-839 (Telaglenastat) in Combination with Radiation Therapy and Temozolomide in Patients with IDH-Mutated Diffuse Astrocytoma and Anaplastic Astrocytoma (NCT03528642) [abstract]. In: Proceedings of the American Society of Clinical Oncology Annual Meeting 2019; 2019 May 31-June 4; Chicago, IL. Alexandria (VA): ASCO; ***Journal of Clinical Oncology***, 2019. 37(15 Suppl): Abstract nr 2075. DOI: 10.1200/JCO.2019.37.15_suppl.TPS2075.
    b. Kizilbash SH, Burgenske DM, **McBrayer SK**, Devarajan S, Gupta SK, Hitosugi T, He L, Schroeder MA, Carlson BL, Gelman M, Kunos CA, Reid JM, Adjei AA, Sarkaria JN. The addition of CB-839 to temozolomide significantly reduces glioma aspartate and glutamate in an IDH mutated patient derived glioma xenograft model [abstract]. In: Proceedings of the American Association for Cancer Research Annual Meeting 2019; 2019 Mar 29-Apr 3; Atlanta, GA. Philadelphia (PA): AACR; ***Cancer Research***, 2019. 79(13 Suppl): Abstract nr 3870. DOI: 10.1158/1538-7445.Am2019-3870.
    c. **McBrayer SK**, Mayers JR, DiNatale GJ, Shi DD, Khanal J, Chakraborty AA, Sarosiek KA, Briggs KJ, Robbins AK, Sewastianik T, Shareef SJ, Olenchock BA, Parker SJ, Tateishi K, Spinelli JB, Islam M, Haigis MC, Looper RE, Ligon KL, Bernstein BE, Carrasco RD, Cahill DP, Asara JM, Metallo CM, Yennawar NH, Vander Heiden MG, Kaelin WG. Transaminase Inhibition by 2-Hydroxyglutarate Impairs Glutamate Biosynthesis and Redox Homeostasis in Glioma. ***Cell***, 2018. 175(1): 101-116. PMC6219629.
    d. Badur MG, Muthusamy T, Parker SJ, Ma S, **McBrayer SK**, Cordes T, Magana JH, Guan KL, Metallo CM. Oncogenic R132 IDH1 Mutations Limit NADPH for *De Novo* Lipogenesis through (D)2-hydroxyglutarate Production in Fibrosarcoma Cells. ***Cell Reports***, 2018. 25(4): 1018-1026. PMC6613636.

2. **Identifying and therapeutically exploiting novel cancer dependencies.** My work has defined oncogene-induced vulnerabilities, particularly those driven by synthetic lethality, in a variety of cancer contexts. For example, my lab has identified synthetic lethal relationships between genes encoding enzymes in the de novo pyrimidine synthesis pathway and IDH oncogenes in glioma. Additionally, my work has revealed metabolic liabilities in aggressive breast cancers, pancreatic cancer dependence on the GOT1 transaminase for ferroptosis suppression, and a requirement for the RBP2/KDM5A histone demethylase in neuroendocrine tumors harboring inactivating *RB1* mutations.

    a. Shi DD, Savani MR, Levitt MM, Wang AC, Endress JE, Bird CE, Buehler J, Stopka S, Regan MS, Lin Y-F, Puliyappadamba VT, Gao W, Khanal J, Evans L, Lee JH, Guo L, Xiao Y, Xu M, Huang B, Jennings RB, Bonal DM, Martin-Sandoval MS, Dang T, Gattie LC, Cameron AB, Lee S, Asara JM, Kornblum HI, Mak TW, Looper RE, Nguyen Q-D, Signoretti S, Gradl S, Sutter A, Jeffers M, Janzer A, Lehrman MA, Zacharias LG, Mathews TP, Losman JA, Richardson TE, Cahill DP, DeBerardinis RJ, Ligon KL, Xu L, Ly P, Agar NYR, Abdullah KG, Harris IS, Kaelin WG*, **McBrayer SK***. De Novo Pyrimidine Synthesis is a Targetable Vulnerability in IDH Mutant Glioma. ***Cancer Cell***, 2022. Accepted in Principle.
    b. Pal S, Kaplan JP, Nguyen H, Stopka SA, Savani MR, Regan MS, Nguyen Q-D, Jones KL, Moreau LA, Peng J, Dipiazza MG, Perciaccante AJ, Zhu X, Hunsel BR, Liu KX, Alexandrescu S, Drissi R, Filbin MG, **McBrayer SK**, Agar NYR, Chowdhury D, Haas-Kogan D. A Druggable Addiction to De Novo Pyrimidine Biosynthesis in Diffuse Midline Glioma. ***Cancer Cell***, 2022. Accepted in Principle.

c. Liao C, Glodowski CR, Fan C, Liu J, Mott KR, Kaushik A, Vu H, Locasale JW, **McBrayer SK**, DeBerardinis RJ, Perou CM, Zhang Q. Integrated Metabolic Profiling and Transcriptional Analysis Reveals Therapeutic Modalities for Targeting Rapidly Proliferating Breast Cancers. ***Cancer Research***, 2022. 82(4): 665-680. PMC8857046.
d. **McBrayer SK**, Olenchock BA, DiNatale GJ, Shi DD, Khanal J, Jennings RB, Novak JS, Oser MG, Robbins AK, Modiste R, Bonal D, Moslehi J, Bronson RT, Neuberg D, Nguyen QD, Signoretti S, Losman JA, Kaelin WG. Autochthonous Tumors Driven by *Rb1* Loss Have an Ongoing Requirement for the RBP2 Histone Demethylase. ***PNAS***, 2018. 115(16): E3741-E3748. PMC5910822.

3. **Examining metabolic control of the epigenome.** We seek to understand how crosstalk between the metabolome and the epigenome controls gliomagenesis. To study this issue, my lab has created a genetically engineered mouse model of anaplastic astrocytoma driven by the *IDH1-R132H* oncogene. My previous work in this area contributed to identification of the dioxygenase KDM6A as a histone demethylase whose activity is regulated by oxygen abundance.

a. Shi DD, Savani MR, Levitt MM, Wang AC, Endress JE, Bird CE, Buehler J, Stopka S, Regan MS, Lin Y-F, Puliyappadamba VT, Gao W, Khanal J, Evans L, Lee JH, Guo L, Xiao Y, Xu M, Huang B, Jennings RB, Bonal DM, Martin-Sandoval MS, Dang T, Gattie LC, Cameron AB, Lee S, Asara JM, Kornblum HI, Mak TW, Looper RE, Nguyen Q-D, Signoretti S, Gradl S, Sutter A, Jeffers M, Janzer A, Lehrman MA, Zacharias LG, Mathews TP, Losman JA, Richardson TE, Cahill DP, DeBerardinis RJ, Ligon KL, Xu L, Ly P, Agar NYR, Abdullah KG, Harris IS, Kaelin WG*, **McBrayer SK***. De Novo Pyrimidine Synthesis is a Targetable Vulnerability in IDH Mutant Glioma. ***Cancer Cell***, 2022. Accepted in Principle.
b. Liu Y, Sathe AA, Abdullah KG, **McBrayer SK**, Adams SH, Brenner AJ, Hatanpaa KJ, Viapiano MS, Xing C, Walker JM, Richardson TE. Global DNA methylation profiling reveals chromosomal instability in IDH-mutant astrocytomas. ***Acta Neuropathologica Communications***, 2022. 10(1): 32. PMC8908645.
c. Shi DD, Wang AC, Gao W, Khanal J, Levitt MM, Jennings RB, Bonal D, Signoretti S, Nguyen QD, Cahill DP, Abdullah KG, Ligon KL, Kaelin WG, **McBrayer SK**. Creation of a Genetically Engineered Mouse Model of Anaplastic Astrocytoma Driven by the IDH1-R132H Oncogene [abstract]. In: Proceedings of the Society for Neuro-Oncology Annual Meeting 2020; 2020 Nov 19-22; Austin, TX. Houston (TX): SNO; ***Neuro-Oncology***, 2020. 22(2 Suppl): Abstract nr TMOD-14. DOI: 10.1093/neuonc/noaa215.965.
d. Chakraborty AA, Laukka T, Myllykoski M, Ringel AE, Booker MA, Tolstorukov MY, Meng YJ, Meier S, Jennings R, Creech A, Herbert ZT, Spinelli J, **McBrayer SK**, Olenchock BA, Looper RE, Jaffe JD, Haigis M, Beroukhim R, Signoretti S, Koivunen P, Kaelin WG. Histone Demethylase KDM6A Directly Senses Oxygen to Control Chromatin and Cell Fate. ***Science***, 2019. 363(6432): 1217-1222. PMC7336390.

4. **Developing new tools and model systems to support preclinical studies of glioma biology and treatment response.** Together with my clinical research partner Kalil Abdullah, a neurosurgeon-scientist at the University of Pittsburgh, we have created organoid, xenograft, and genetically engineered mouse models of glioma that represent faithful experimental platforms to study this disease. We are using these models to 1) reveal metabolic mechanisms of brain tumor initiation, 2) study the glioma microenvironment, and 3) test experimental glioma therapies. Finally, I developed a target-agnostic approach to manipulating protein expression in brain tumors *in* vivo. This system supports evaluation of novel therapeutic targets for which pharmacological inhibitors do not exist.

a. Guo G, Gong K, Beckley N, Zhang Y, Yang X, Chkheidze R, Hatanpaa KJ, Garzon-Muvdi T, Koduru P, Nayab A, Jenks J, Sathe AA, Xing C, Wu SY, Chiang CM, Mukherjee B, Burma S, Wohlfeld B, Patel T, Mickey B, Abdullah KG, Youssef M, Pan E, Gerber DE, Tian S, Sarkaria JN, **McBrayer SK**, Zhao D, Habib AA. EGFR ligand shifts the role of EGFR from oncogene to tumor suppressor in EGFR amplified glioblastoma. ***Nature Cell Biology***, 2022. In Press.
b. Buehler JD, Bird CE, Savani MR, Gattie LC, Hicks WH, Levitt MM, El Shami M, Hatanpaa KJ, Richardson TE, **McBrayer SK***, Abdullah KG*. Semi-automated computational assessment of cancer organoid viability using rapid live-cell microscopy. ***Cancer Informatics***, 2022. 21:11769351221100754. PMC9150230.

c. Abdullah KG*, Bird CE, Buehler JD, Gattie LC, Savani MR, Sternisha AC, Xiao Y, Levitt MM, Hicks WH, Li W, Ramirez DMO, Patel T, Garzon-Muvdi T, Barnett S, Zhang G, Ashley DM, Hatanpaa KJ, Richardson TE, **McBrayer SK***. Establishment of Patient-Derived Organoid Models of Lower-Grade Glioma. ***Neuro-Oncology***, 2022. 24(4):612-623. PMC8972292.
d. Koduri V, **McBrayer SK**, Liberzon E, Wang AC, Briggs KJ, Cho H, Kaelin WG. Peptidic Degron for IMiD-Induced Degradation of Heterologous Proteins. ***PNAS***, 2019. 116(7): 2539-2544. PMC6377458.

5. **Determining the causes and consequences of elevated glucose metabolism in multiple myeloma.** As a graduate student in Steven Rosen's laboratory, I showed that aberrant plasma membrane localization, and hence activation, of the glucose transporter GLUT4 is a key mechanism driving glycolysis in myeloma. Furthermore, we found that novel RNA-directed nucleoside analogues being developed in the Rosen laboratory were able to reverse this phenotype, thus contributing to their antitumor activity.

a. Cheng JC, **McBrayer SK**, Coarfa C, Dalva-Aydemir S, Gunaratne PH, Keats J, Rosen ST, Shanmugam M. Expression and Phosphorylation of the AS160_v2 Splice Variant Supports GLUT4 Activation and the Warburg Effect in Multiple Myeloma. ***Cancer & Metabolism***, 2013. 1:14. PMC4718207.
b. **McBrayer SK**, Yarrington M, Qian J, Feng G, Shanmugam M, Gandhi V, Krett NL, Rosen ST. Integrative Gene Expression Profiling Reveals G6PD-mediated Resistance to RNA-directed Nucleoside Analogues in B Cell Neoplasms. ***PLOS One***, 2012. 7(7): e41455. PMC3407247.
c. **McBrayer SK**, Cheng JC, Singhal S, Krett NL, Rosen ST, Shanmugam M. Multiple Myeloma Exhibits Novel Dependence on GLUT4, GLUT8, and GLUT11: Implications for Glucose Transporter-directed Therapy. ***Blood***, 2012. 119(20): 4686-97. PMC3367873.
d. Shanmugam M, **McBrayer SK**, Qian J, Raikoff K, Avram MJ, Singhal S, Gandhi V, Schumacker PT, Krett NL, Rosen ST. Targeting Glucose Consumption and Autophagy in Myeloma with the Novel Nucleoside Analogue 8-aminoadenosine. ***Journal of Biological Chemistry***, 2009. 284(39): 26816-30. PMC2785370.

Complete List of Published Work in MyBibliography:
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