BIOGRAPHICAL SKETCH

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NAME: Shawn M. Davidson , PhD

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POSITION TITLE: Lewis-Sigler Institute Fellow

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
Providence College, Providence, RI	B.S.	05/2010	Biology
Massachusetts Institute of Technology, Cambridge, MA	Ph.D.	02/2017	Biology, Biochemistry, Metabolism
Brigham and Women's of Harvard and Broad Institute of Harvard and MIT	Postdoctoral	06/2019	Biological Engineering

A. Personal Statement

I am appointed as a Lewis-Sigler Fellow at Princeton University. I have 10 years of experience in the area of cell metabolism and method development to study disease metabolism in the physiological setting. I received my Bachelor's Degree from Providence College in 2010 and my Ph.D. from the Massachusetts Institute of Technology in 2017, both in Biology. As a graduate student, I was the recipient of the National Science Foundation Graduate Research Fellowship to develop methodology for the study the metabolism of tumors in vivo in the lab of Dr. Matthew Vander Heiden, MD, PhD. My postdoctoral research was with Dr. Oliver Jonas at Brigham and Women's from 2017-2018, our research together focused on metabolism of tumor and immune cells using both imaging mass-spectrometry and an engineering approach to create metabolic perturbations in the tumor microenvironment in vivo.

My research as a Lewis-Sigler Institute Fellow is at the interface of biotechnology and genetics. Our work is in progress in the following areas: developing imaging mass spectrometry for analysis of stable-isotope tracers and metabolism; investigating the metabolic dysregulation that occurs in specific disease states with concomitant pathological assessment and mathematical modeling of metabolic fluxes; developing therapeutic strategies for metabolic targets; researching new ways to deliver metabolic therapeutics in vivo; and developing animal models that recapitulate genetic modifiers found in human disease states. My laboratory at Princeton University is equipped with state-of-the-art mass spectrometers and the biological tools needed for the proposed study to measure metabolism.

Current or recently completed research support to highlight:
Examining metabolic heterogeneity in cancer (Stand Up 2 Cancer) 09/2019-09/2022
Shawn M. Davidson (PI)
Enhancing multi-spatial-omics using Imaging-mass spectrometry (Allen Institute) 10/19 - 10/21
Shawn M. Davidson (PI), Role: Co-PI
Investigating ATG mutations in lung cancer (GO2 Lung Cancer Foundation) 10/19 - 10/22
Jessie Guo, Shawn M. Davidson (PI), Role: Co-PI

Positions, Scientific Appointments, and Honors

Positions and Employment
2020-pres Lewis-Sigler Institute Fellow, Princeton University, Princeton, NJ 08540

Honors and Awards
2008 National Science Foundation Research Experience for Undergraduates, Laboratory of Michael Sehorn, Department of Biochemistry, Clemson University
2008 Sigma Xi, Research Honor Society
2008 Pi Mu Epsilon, Mathematics Honor Society
2009-2010 Undergraduate Researcher, Laboratory of Leonard Guarente, Department of Biology, MIT
2010 Charles V. Reichart Award for dedication to the advancement of science, Providence College 2012-
2016 National Science Foundation Graduate Research Fellow, MIT
2017-2018 Post-doctoral Fellow, Brigham and Women's Hospital and Broad Institute, MIT and Harvard
2010-present Affiliate member, Broad Institute of MIT and Harvard
2017-present Affiliate member, Koch Institute of MIT
2018-present Lewis-Sigler Institute Experimental Fellow, Princeton University
2018-present Associate Member, Cancer Institute of New Jersey, Rutgers University
2022 Nominated for Scialog Fellowship

C. Contributions to Science
ORCID: 0000-0002-3475-0382.

The importance of metabolism to human health and disease has been a focus of scientific investigation since the birth of biochemistry in the nineteenth century. Many contemporary metabolism investigations have relied on studies of cells in tissue culture. Studies focused on understanding the nutrient requirements of cells in vitro have provided significant insight. The limitations of these systems, however, are numerous. They include the lack of relevant normal tissue controls; non-physiological oxygen, carbon dioxide, and bicarbonate levels; altered macro- and micro-environmental hormonal influences; altered spatial relationships to blood vessels and neighboring cells; lack of nervous innervation; and exhibit nutrient concentrations more than those found in vivo. Therefore, much of my work has focused on developing methods to study metabolic processes in the physiological setting using biochemical and bioengineering approaches.

1. ***Identifying therapeutic targets in neuro-related diseases***

Metabolic dysregulation is observed in neurodegenerative diseases and conditions of the brain. This dysregulation is frequently ascribed as epiphenomenal rather than causal. In both neurological and heart disease, we identify metabolic targets that are either causal for the pathology of the disease or actionable for therapeutic purposes. I have applied stable-isotope tracing and mass-spectrometry based methodology in animal models of these diseases, particularly looking at GPT2 mutations. GPT2 is a mitochondrial transaminase and together with Dr. Eric Morrow (Brown University) we identified this mutation as a causal genetic risk of postnatal microcephaly. Ongoing work in my laboratory is to examining the contributing genetic factors in Huntington's and Alzheimer's Disease to determine whether there are any actionable metabolic pathways that could be targeted for therapy.

1. Ouyang Q, Nakayama T, Baytas O, **Davidson SM**, Yang C, Schmidt M, Lizarraga SB, Mishra S, Ei-Quessny M, Niaz S, Gul Butt M, Imran Murtaza S, Javed A, Chaudhry HR, Vaughan DJ, Hill RS, Partlow JN, Yoo SY, Lam AT, Nasir R, Al-Saffar M, Barkovich AJ, Schwede M, Nagpal S, Rajab A, DeBerardinis RJ, Housman DE, Mochida GH, Morrow EM. Mutations in mitochondrial enzyme GPT2 cause metabolic dysfunction and neurological disease with developmental and progressive features. Proc Natl Acad Sci U S A. 2016 09 20; 113(38):E5598-607. PMID: 27601654.
2. Quaegebeur A, Segura I, Schmieder R, Verdegem D, Decimo I, Bifari F, Dresselaers T, Eelen G, Ghosh D, **Davidson SM**, Schoors S, Broekaert D, Cruys B, Govaerts K, De Legher C, Bouché A, Schoonjans L, Ramer MS, Hung G, Bossaert G, Cleveland DW, Himmelreich U, Voets T, Lemmens R,

Bennett CF, Robberecht W, De Bock K, Dewerchin M, Ghesquière B, Fendt SM, Carmeliet P. Deletion or Inhibition of the Oxygen Sensor PHD1 Protects against Ischemic Stroke via Reprogramming of Neuronal Metabolism. Cell Metab. 2016 Feb 09; 23(2):280-91. PMID: 26774962; PMCID: PMC4880550.

2. ***Personalized medicine for metabolic targets***

The nutrient requirements of different cancer types are distinct and therefore provide cancer-specific vulnerabilties. Identifying contexts where specific metabolic processes are essential to cellular function can enable the identification of novel targets for therapy or widen the therapeutic index.

1. Romero R, Sayin VI, **Davidson SM**, Bauer MR, Singh SX, LeBoeuf SE, Karakousi TR, Ellis DC, Bhutkar A, Sánchez-Rivera FJ, Subbaraj L, Martinez B, Bronson RT, Prigge JR, Schmidt EE, Thomas CJ, Goparaju C, Davies A, Dolgalev I, Heguy A, Allaj V, Poirier JT, Moreira AL, Rudin CM, Pass HI, Vander Heiden MG, Jacks T, Papagiannakopoulos T. Keap1 loss promotes Kras-driven lung cancer and results in dependence on glutaminolysis. Nat Med. 2017 Nov; 23(11):1362-1368. PMID: 28967920.
2. Grassian AR, Parker SJ, **Davidson SM**, Divakaruni AS, Green CR, Zhang X, Slocum KL, Pu M, Lin F, Vickers C, Joud-Caldwell C, Chung F, Yin H, Handly ED, Straub C, Growney JD, Vander Heiden MG, Murphy AN, Pagliarini R, Metallo CM. IDH1 mutations alter citric acid cycle metabolism and increase dependence on oxidative mitochondrial metabolism. Cancer Res. 2014 Jun 15; 74(12):3317-31. PMID: 24755473; PMCID: PMC4885639.
3. Fendt SM, Bell EL, Keibler MA, **Davidson SM**, Wirth GJ, Fiske B, Mayers JR, Schwab M, Bellinger G, Csibi A, Patnaik A, Blouin MJ, Cantley LC, Guarente L, Blenis J, Pollak MN, Olumi AF, Vander Heiden MG, Stephanopoulos G. Metformin decreases glucose oxidation and increases the dependency of prostate cancer cells on reductive glutamine metabolism. Cancer Res. 2013 Jul 15; 73(14):4429-38. PMID: 23687346.
4. Anastasiou D, Yu Y, Israelsen WJ, Jiang JK, Boxer MB, Hong BS, Tempel W, Dimov S, Shen M, Jha A, Yang H, Mattaini KR, Metallo CM, Fiske BP, Courtney KD, Malstrom S, Khan TM, Kung C, Skoumbourdis AP, Veith H, Southall N, Walsh MJ, Brimacombe KR, Leister W, Lunt SY, Johnson ZR, Yen KE, Kunii K, **Davidson SM**, Christofk HR, et al. Pyruvate kinase M2 activators promote tetramer formation and suppress tumorigenesis. Nat Chem Biol. 2012 Oct; 8(10):839-47. PMID: 22922757; PMCID: PMC3711671.

3. ***Intracellular/extracellular protein as a nutrient source for cancer cells***

Amino acids are also important for cancer cell metabolism. These can come from exogenous sources (e.g., diet), are synthesized by the cell, or are acquired from intracellular and extracellular protein catabolism. We originally described an endocytic pathway called macropinocytosis to be a novel nutrient supply route by which tumors acquire amino acids and other nutrients in Kras-driven pancreatic cancer in cell lines in vitro and in vivo. These findings have therapeutic implications which are an active area of investigation.

1. **Davidson SM**, Jonas O, Keibler MA, Hou HW, Luengo A, Mayers JR, Wyckoff J, Del Rosario AM, Whitman M, Chin CR, Condon KJ, et al. Direct evidence for cancer-cell-autonomous extracellular protein catabolism in pancreatic tumors. Nat Med. 2017 Feb; 23(2):235-241. PMID: 28024083.
2. Mayers JR, Wu C, Clish CB, Kraft P, Torrence ME, Fiske BP, Yuan C, Bao Y, Townsend MK, Tworoger SS, **Davidson SM**, et al. Elevation of circulating branched-chain amino acids is an early event in human pancreatic adenocarcinoma development. Nat Med. 2014 Oct; 20(10):1193-1198. PMID: 25261994; PMCID: PMC4191991.
3. Commisso C, **Davidson SM**, Soydaner-Azeloglu RG, Parker SJ, Kamphorst JJ, Hackett S, Grabocka E, Nofal M, Drebin JA, Thompson CB, et al. Macropinocytosis of protein is an amino acid supply route in Ras-transformed cells. Nature. 2013 May 30; 497(7451):633-7. PMID: 23665962; PMCID: PMC3810415.

4. ***Environment influences cancer cell metabolism in cancer***

Limited studies of tumor metabolism have suggested the driver mutation, tissue of origin, and microenvironment all can impact metabolic phenotypes, highlighting the need to understand metabolism in spontaneously arising tumors. Discrepancies found between cancer cell metabolism in vitro compared to in vivo highlights the importance of considering environmental context in addition to genetics in metabolism studies, particularly in considering how best to target cancer metabolism.

1. **Davidson SM**, Papagiannakopoulos T, Olenchock BA, Heyman JE, Keibler MA, Luengo A, Bauer MR, Jha AK, O'Brien JP, Pierce KA, Gui DY, Sullivan LB, Wasylenko TM, Subbaraj L, Chin CR, Stephanopolous G, Mott BT, Jacks T, Clish CB, Vander Heiden MG. Environment Impacts the Metabolic Dependencies of Ras-Driven Non-Small Cell Lung Cancer. Cell Metab. 2016 Mar 08; 23(3):517-28. PMID: 26853747; PMCID: PMC4785096.
2. Mayers JR, Torrence ME, Danai LV, Papagiannakopoulos T, **Davidson SM**, Bauer MR, Lau AN, Ji BW, Dixit PD, Hosios AM, Muir A, Chin CR, Freinkman E, Jacks T, Wolpin BM, Vitkup D, Vander Heiden MG. Tissue of origin dictates branched-chain amino acid metabolism in mutant Kras-driven cancers. Science. 2016 09 09; 353(6304):1161-5. PMID: 27609895.
3. Gui DY, Sullivan LB, Luengo A, Hosios AM, Bush LN, Gitego N, **Davidson SM**, Freinkman E, Thomas CJ, Vander Heiden MG. Environment Dictates Dependence on Mitochondrial Complex I for NAD+ and Aspartate Production and Determines Cancer Cell Sensitivity to Metformin. Cell Metab. 2016 Nov 08; 24(5):716-727. PMID: 27746050.
4. d. Papagiannakopoulos T, Bauer MR, **Davidson SM**, Heimann M, Subbaraj L, Bhutkar A, Bartlebaugh J, Vander Heiden MG, Jacks T. Circadian Rhythm Disruption Promotes Lung Tumorigenesis. Cell Metab. 2016 Aug 09; 24(2):324-31. PMID: 27476975.

5. Identification and development of new therapeutic strategies and methods

Drug resistance in cancers, both acquired and de novo, presents a major challenge towards achieving durable treatment responses in patients. In this context, identifying tumor vulnerabilities dynamically and developing novel treatment strategies that maximize treatment efficacy are major research interests of mine. My lab has also pioneered cutting-edge technology, such as imaging-mass spectrometry, to better understand metabolism at near single-cell level.

1. *Wang L, Xing X, Zeng X, Jackson SR, TeSlaa T, Yang L, McReynolds M, Li X, Wolff J, Rabinowitz JR,* ***Davidson SM****. Spatially resolved stable-isotope tracing reveals regional metabolic activity. Nat. Methods. Feb;19(2):223-230. PMID: 35132243.*
2. Pacold ME, Brimacombe KR, Chan SH, Rohde JM, Lewis CA, Swier LJ, Possemato R, Chen WW, Sullivan LB, Fiske BP, Cho S, Freinkman E, Birsoy K, Abu-Remaileh M, Shaul YD, Liu CM, Zhou M, Koh MJ, Chung H, **Davidson SM**, Luengo A, Wang AQ, Xu X, Yasgar A, Liu L, Rai G, Westover KD, Vander Heiden MG, Shen M, Gray NS, Boxer MB, Sabatini DM. A PHGDH inhibitor reveals coordination of serine synthesis and one-carbon unit fate. Nat Chem Biol. 2016 06; 12(6):452-8. PMID: 27110680; PMCID: PMC4871733.
3. Sayin VI, LeBoeuf SE, Singh SX, **Davidson SM**, Biancur D, Guzelhan BS, Alvarez SW, Wu WL, Karakousi TR, Zavitsanou AM, Ubriaco J, Muir A, Karagiannis D, Morris PJ, Thomas CJ, Possemato R, Vander Heiden MG, Papagiannakopoulos T. Activation of the NRF2 antioxidant program generates an imbalance in central carbon metabolism in cancer. Elife. 2017 Oct 02; 6. PMID: 28967864. s