BIOGRAPHICAL SKETCH

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NAME: **Ralph J. DeBerardinis, M.D., Ph.D.**

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

POSITION TITLE: **Professor, Children's Medical Center Research Institute (CRI), University of Texas Southwestern Medical Center, and Investigator, Howard Hughes Medical Institute**

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
St. Joseph's University	BS	05/1992	Biology
University of Pennsylvania	PHD	06/1998	Cell & Molecular Biology
University of Pennsylvania	MD	05/2000	Medicine
Children's Hospital of Philadelphia	Residency	06/2005	Pediatrics & Medical Genetics
Children's Hospital of Philadelphia	Fellowship	06/2007	Biochemical Genetics
University of Pennsylvania	Post-doc	12/2007	Cancer biology (mentor Craig Thompson)

A. Personal Statement

The primary research interest of the DeBerardinis laboratory is the role of altered metabolic states in human diseases, including cancer and inborn metabolic diseases in children. We have extensive experience measuring metabolic flux in vitro, in vivo and ex vivo. By using a combination of mass spectrometry and NMR spectroscopy, we have developed the ability to provide extremely sensitive, specific and comprehensive views of intermediary metabolism in biological systems. We have used these approaches to identify a number of novel regulatory mechanisms, and novel metabolic pathways that support the ability of tumor cells to produce macromolecules and sustain proliferation and viability. We are now using metabolic flux analysis to understand the full breadth of metabolic diversity in cancer, and are applying these data sets to understand the molecular determinants of metabolic pathway choice and metabolic vulnerabilities. These studies are complemented by in vivo analysis of metabolism in mice and patients, and by translational efforts designed to understand and exploit metabolic idiosyncrasies of tumor cells. Emerging work explores the utility of combining metabolic analysis with molecular imaging techniques to monitor metabolic states non-invasively and to discover the drivers of metabolic phenotypes in vivo. In inborn errors of metabolism, we use genomics and metabolomics to identify novel disease genes and develop therapies, including dietary modifications, to treat these conditions.

Training and mentoring are essential and rewarding aspects of my position as a lab head, research program director and clinical Division Chief. My trainee history includes undergraduates, pre-doctoral students, postdoctoral scientists and junior faculty. I make it a priority to help all my trainees find positions that best suit their goals and talents, including positions in academia, industry and clinical practice. I cultivate an atmosphere of inclusion, collegiality and collaboration within my lab, and do my best to teach trainees how to be members of the scientific community. My efforts in diversity, equity and inclusion include serving as an advisor in UT Southwestern's Provost's Initiative for Diverse Emerging Scholars (PROVIDES) program, which seeks to identify and support postdoctoral trainees from traditionally underrepresented groups.

1. DeBerardinis RJ, Mancuso A, Daikhin E, Nissim I, Yudkoff M, Wehrli S and Thompson CB. Beyond aerobic glycolysis: Transformed cells can engage in glutamine metabolism that exceeds the requirement for protein and nucleotide synthesis. *PNAS USA* 104:19345-19350 (2007).

2. Hensley CT, Faubert B, Yuan Q, Lev-Cohain N, Jin E, Kim J, Jiang L, Ko B, Skelton R, Loudat L, Wodzak M, Klimko C, McMillan E, Butt Y, Ni M, Oliver D, Torrealba J, Malloy CR, Kernstine K, Lenkinski RE and DeBerardinis RJ. Metabolic heterogeneity in human lung tumors. *Cell* 164: 681-694 (2016).
3. Kim J, Hu Z, Cai L, Li K, Choi E, Faubert B, Bezwada D, Rodriguez-Canales J, Villalobos P, Lin Y-F, Ni M, Huffman KE, Girard L, Byers LA, Unsal-Kacmaz K, Peña CG, Heymach JV, Wauters E, Vansteenkiste J, Castrillon DH, Chen BPC, Wistuba I, Lambrechts D, Xu J, Minna JD and DeBerardinis RJ. CPS1 maintains pyrimidine pools and DNA synthesis is KRAS/LKB1-mutant lung cancer cells. *Nature* 546:168-172 (2017).
4. Solmonson A, Faubert B, Gu W, Rao A, Cowdin MA, Menendez-Montes I, Kelekar S, Rogers TJ, Pan C, Guevara G, Tarangelo A, Zacharias LG, Martin-Sandoval MS, Do D, Pachnis P, Dumesnil D, Mathews TP, Tasdogan A, Pham A, Cai L, Zhao Z, Ni M, Cleaver O, Sadek HA, Morrison SJ and DeBerardinis RJ. Compartmentalized metabolism supports midgestation mammalian development. *Nature* 604:349-353 (2022).

B. Positions, Scientific Appointments, and Honors

Positions and Employment

09/2018-present	Investigator, Howard Hughes Medical Institute
09/2017-present	Professor with tenure, CRI, UT Southwestern
09/2013-present	Director, Genetic and Metabolic Disease Program, CRI, UT Southwestern
09/2013-present	Division Chief, Pediatric Genetics and Metabolism, Dept. of Pediatrics, UT Southwestern
09/2013-08/2017	Associate Professor with tenure, CRI, UT Southwestern
12/2011-08/2013	Assistant Professor, CRI, UT Southwestern
07/2011-2014	Director, Medical Genetics Residency Program, UT Southwestern
01/2008-08/2013	Assistant Professor of Pediatrics and Genetics, UT Southwestern
07/2005-2007	Instructor and Attending Physician, Children's Hospital of Philadelphia
06/2000-06/2005	Resident, Pediatrics/Medical Genetics Program, The Children's Hospital of Philadelphia
09/1992-05/2000	MD/PhD student, The University of Pennsylvania, Combined-Degree Program

Other Experience and Professional Memberships

2022 – present	Editorial Committee, *Annual Reviews in Cancer Biology*
2021 – present	National Cancer Institute, Board of Scientific Counselors
2021 – present	Founder and Advisor, Atavistic Biosciences
2019 – present	Selection Committee, Damon Runyon Cancer Research Foundation Clinician Investigator Award
2019 – present	External Advisory Board, Rutgers Comprehensive Cancer Center
2016	Steering Committee, AACR Cancer Progress Report
2015 – present	Keystone Symposia Study Group
2014 – 2018	Deputy Editor, *Molecular Case Studies*, Cold Spring Harbor Press
2016 – 2021	Board of Reviewing Editors, *eLife*
2014 – present	Editorial Board, *EMBO Molecular Medicine*
2014 – present	Editorial Board, *Cancer Discovery*
2013 – present	Scientific Advisory Board, Agios Pharmaceuticals
2011 – present	Program Committee (Cellular and Molecular Biology Section, Metabolism and Cancer Subcommittee), American Association for Cancer Research
2009 – present	Faculty, Cancer Biology Graduate Group, UT Southwestern
2009 – present	Faculty, Genetics and Development Graduate Group, UT Southwestern
2009 – present	Member, Society for Pediatric Research
2009 – present	Member, American Association for Cancer Research
2007 – present	Member, Society for Inherited Metabolic Disorders
2004 – present	Member, United Mitochondrial Disease Foundation
2002 – present	Member, American Society of Human Genetics
2000 – present	Member, American Academy of Pediatrics

Honors

2021	Paul Marks Prize for Cancer Research, Memorial Sloan Kettering Cancer Center
2021	The Academy of Medicine, Engineering and Science of Texas
2020	National Academy of Medicine
2020	Association of American Physicians

2019	Post-doctoral mentoring award, UT Southwestern Medical Center
2018	Edith and Peter O'Donnell Award in Medicine, The Academy of Medicine, Engineering and Science of Texas
2018	Investigator, Howard Hughes Medical Institute
2017	Outstanding Investigator Award, National Cancer Institute, NIH
2017	Inaugural Robert L. Moody, Sr. Faculty Scholar
2016 – 2020	*D Magazine*, Best Doctors and Pediatric Subspecialists
2016	Faculty Scholar, Howard Hughes Medical Institute
2015 – 2016	Chair, Metabolism and Cancer Section, 2016 American Association for Cancer Research Program Committee
2013	Joel B. Steinberg, M.D. Distinguished Chair in Pediatrics
2012	American Society for Clinical Investigation
2011	Damon Runyon Cancer Research Foundation Clinical Investigator Award
2008	Sowell Family Scholar in Medical Research, UT Southwestern
2008	President's Research Council Young Researcher Award, UT Southwestern
2008	William K. Bowes, Jr. Award in Medical Genetics, Harvard-Partners Center
2008	Society for Inherited Metabolic Disorders, Neil Buist Award
2007	Children's Hospital of Philadelphia Faculty Honor Roll
2004 – 2006	University of Pennsylvania Medical Genetics T32
2003	Senior Resident Clinician Award, Children's Hospital of Philadelphia
1998	Roy G. Williams Award for research in the basic sciences, University of Pennsylvania
1994 – 2000	University of Pennsylvania Franklin Scholar (MD/PhD support)

C. Contributions to Science

1. **Metabolic reprogramming in cancer cells**: Regulated alteration of metabolic pathways – also known as metabolic reprogramming – is considered to be a biological hallmark of malignancy, a consequence of tumorigenic mutations, and a source of novel therapeutic targets in cancer. The most commonly held view of cancer metabolism, inherited from nearly 100 years of research since the seminal work of Otto Warburg in the 1920s, is that cancer cells require elevated glycolysis and suppressed mitochondrial metabolism to achieve rapid proliferation. This view discounts the importance of mitochondrial metabolism in producing macromolecular precursors for biosynthesis and growth. For over ten years, my research has focused on how mitochondrial metabolism and other pathways support growth in both transformed and non-transformed cells. This has led to a renewed interest in the mitochondria as biosynthetic organelles, in the metabolic flexibility of the tricarboxylic acid cycle and other mitochondrial pathways to meet the biosynthetic demands of rapid cell proliferation, and the versatility of glutamine in providing carbon and nitrogen for growth and survival. I was the primary or corresponding author on the following papers:
   a. Mullen AR, Wheaton WW, Jin ES, Chen P-S, Sullivan LB, Cheng T, Yang Y, Linehan WM, Chandel NS and DeBerardinis RJ. Reductive carboxylation supports growth in tumour cells with defective mitochondria. *Nature* 481:385-388 (2011). PMID 22101431 PMC 3262117.
   b. Jiang L, Shestov A, Swain, P, Yang C, Parker SJ, Wang QA, Terada LS, Adams ND, McCabe MT, Pietrak B, Schmidt S, Metallo, CM, Dranka BP, Schwartz B and DeBerardinis RJ. Reductive carboxylation supports redox homeostasis during anchorage-independent growth. *Nature* 532:255-288 (2016).
   c. Kim J, Hu Z, Cai L, Li K, Choi E, Faubert B, Bezwada D, Rodriguez-Canales J, Villalobos P, Lin Y-F, Ni M, Huffman KE, Girard L, Byers LA, Unsal-Kacmaz K, Peña CG, Heymach JV, Wauters E, Vansteenkiste J, Castrillon DH, Chen BPC, Wistuba I, Lambrechts D, Xu J, Minna JD and DeBerardinis RJ. CPS1 maintains pyrimidine pools and DNA synthesis is KRAS/LKB1-mutant lung cancer cells. *Nature* 546:168-172 (2017).
   d. Huang F, Ni M, Chalishazar MD, Huffman KE, Kim J, Cai L, Shi X, Cai F, Zacharias LG, Ireland AS, Li K, Gu W, Kaushik AK, Liu X, Gazdar AF, Oliver TG, Minna JD, Hu Z, DeBerardinis RJ. Inosine monophosphate dehydrogenase dependence in a subset of small cell lung cancers. *Cell Metabolism* 28:369-382 (2018).
2. **Understanding the metabolism of intact tumors.** The vast majority of cancer metabolism research to date has focused on culture models of cancer cell growth rather than on intact tumors. Although research in cancer cell biology has produced a wealth of information about how metabolic pathways and dependencies are regulated, they have done little to answer what we consider to be the key question in this field: which metabolic pathways are at work in bona fide tumors in living subjects? We were among the first groups to

develop efficient methods to introduce intra-operative nutrient tracers (e.g. isotope-labeled glucose and glutamine) to mice and humans with cancer. Our work has led to the following major findings: *1*) intra-operative isotope infusions are safe, practical, and highly informative in mice and humans; *2*) as predicted from our work in cultured cancer cells, aggressive tumors display oxidative metabolism in their mitochondria; and *3*) glucose is only one of several nutrients oxidized in the tumor mitochondria. This latter observation has opened up several new avenues of investigation for us and others. Key findings are reported in:

a. Marin-Valencia I, Cho S, Yang C, Mashimo T, Yang X-L, Rajagopalan KN, Vemireddy V, Cai L, Good L, Tu BP, Hatanpaa K, Mickey BE, Pascual JM, Maher EA, Malloy CR, *DeBerardinis RJ and *Bachoo RM. Analysis of tumor metabolism reveals mitochondrial glucose oxidation in genetically diverse, human glioblastomas in the mouse brain in vivo. *Cell Metab* 15: 827-837 (2012).
b. Hensley CT, Faubert B, Yuan Q, Lev-Cohain N, Jin E, Kim J, Jiang L, Ko B, Skelton R, Loudat L, Wodzak M, Klimko C, McMillan E, Butt Y, Ni M, Oliver D, Torrealba J, Malloy CR, Kernstine K, Lenkinski RE and DeBerardinis RJ. Metabolic heterogeneity in human lung tumors. *Cell* 164: 681-694 (2016).
c. Faubert B, Li KY, Cai L, Hensley CT, Kim J, Zacharias LG, Yang C, Do Q, Doucette S, Burguete D, Li H, Huet G, Yuan Q, Wigal T, Butt Y, Ni M, Torrealba J, Oliver D, Lenkinski RE, Malloy CR, Wachsmann JW, Young JD, Kernstine K, DeBerardinis RJ. Lactate metabolism in human lung tumors. *Cell* 171:358-371 (2017).
d. Tasdogan A, Faubert B, Ramesh V, Ubellacker JM, Shen B, Solmonson A, Murphy MM, Gu Z, Gu W, Martin M, Kasitinon SY, Vandergriff T, Mathews TP, Zhao Z, Schadendorf D, DeBerardinis RJ, Morrison SJ. Metabolic heterogeneity confers differences in melanoma metastatic potential. *Nature* 577(7788):115-120 (2020).

3. **Monogenic metabolic diseases in children.** Inborn errors of metabolism (IEMs) comprise a large category of pediatric diseases, usually caused by loss-of-function mutations in metabolic enzymes and nutrient transporters. The clinical importance of these diseases relates to the fact that many are treatable if the underlying metabolic abnormalities and their relationship to the phenotype are thoroughly understood. In an effort to better understand the pathophysiology of IEMs and to identify new, potentially treatable diseases, we established a research program aligned with our clinical practice in Pediatric Genetics and Metabolism at UT Southwestern and with our collaborators at other centers around the world. We use genomics, unbiased metabolic profiling and functional studies in patient-derived cells and other experimental models to determine causality of rare variants.
   a. Ni M, Solmonson A, Pan C, Yang C, Li D, Notzon A, Cai L, Guevara G, Zacharias LG, Faubert B, Vu HS, Jiang L, Ko B, Morales NM, Pei J, Vale G, Rakheja D, Grishin NV, McDonald JG, Gotway GK, McNutt MC, Pascual JM, DeBerardinis RJ. Functional Assessment of Lipoyltransferase-1 Deficiency in Cells, Mice, and Humans. *Cell Reports* 27(5):1376-1386 (2019).
   b. Ni M, Afroze B, Xing C, Pan C, Shao Y, Cai L, Cantarel BL, Pei J, Grishin NV, Hewson S, Knight D, Mahida S, Michel D, Tarnopolsky M, Poduri A, Rotenberg A, Sondheimer N and DeBerardinis RJ. A pathogenic *UFSP2* variant in an autosomal recessive form of pediatric neurodevelopmental anomalies and epilepsy. *Genetics in Medicine* 23:900-908 (2021).
   c. Solmonson A, Faubert B, Gu W, Rao A, Cowdin MA, Menendez-Montes I, Kelekar S, Rogers TJ, Pan C, Guevara G, Tarangelo A, Zacharias LG, Martin-Sandoval MS, Do D, Pachnis P, Dumesnil D, Mathews TP, Tasdogan A, Pham A, Cai L, Zhao Z, Ni M, Cleaver O, Sadek HA, Morrison SJ and DeBerardinis RJ. Compartmentalized metabolism supports midgestation mammalian development. *Nature* 604:349-353 (2022).

Complete List of Published Work in MyBibliography (Over 260 publications in press or print; h-index 103; total citations > 64,000):

https://www.ncbi.nlm.nih.gov/myncbi/1joG72cV8NS5c/bibliography/public/