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: **Associate Professor, Children's Medical Center Research Institute (CRI), 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)*	Completion Date MM/YYYY	FIELD OF STUDY
St. Joseph's University	BS	05/1992	Biology
University of Pennsylvania	PhD	06/1999	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

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. Over the past few years, 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 in culture. 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 in human 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*. My trainee history includes undergraduates, pre-doctoral students and post-doctoral scientists, most of whom have remained engaged in research after moving on from my lab.

1. 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).
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. 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).

4. 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. In press, *Nature* (2017).

B. Positions and Honors

Positions and Employment

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

Other Experience and Professional Memberships

2000 – present	Member, American Academy of Pediatrics
2002 – present	Member, American Society of Human Genetics
2004 – present	Member, United Mitochondrial Disease Foundation
2007 – present	Member, Society for Inherited Metabolic Disorders
2009 – present	Member, American Association for Cancer Research
2009 – present	Member, Society for Pediatric Research
2009 – present	Faculty, Genetics and Development Graduate Group, UT Southwestern
2009 – present	Faculty, Cancer Biology Graduate Group, UT Southwestern
2011 – present	Program Committee (Cellular and Molecular Biology Section, Metabolism and Cancer Subcommittee), American Association for Cancer Research
2012 – 2016	Editorial Board, *Oncogene*
2014 – present	Editorial Board, *Cancer Discovery*
2014 – present	Editorial Board, *EMBO Molecular Medicine*
2014 – present	Senior Editor, *Cancer & Metabolism*
2016 – present	Board of Reviewing Editors, *eLife*
2014 – present	Deputy Editor, *Molecular Case Studies*, Cold Spring Harbor Press
2016	Steering Committee, American Association for Cancer Research Cancer Progress Report

Honors

1994-2000	University of Pennsylvania Franklin Scholar (MD/PhD support)
1998	Roy G. Williams Award for research in the basic sciences, University of Pennsylvania
2003	Senior Resident Clinician Award, Children's Hospital of Philadelphia
2004-2006	University of Pennsylvania Medical Genetics T32
2007	Children's Hospital of Philadelphia Faculty Honor Roll
2008	Society for Inherited Metabolic Disorders, Neil Buist Award
2008	William K. Bowes, Jr. Award in Medical Genetics, Harvard-Partners Center
2008	President's Research Council Young Researcher Award, UT Southwestern
2008	Sowell Family Scholar in Medical Research, UT Southwestern
2011	Damon Runyon Cancer Research Foundation Clinical Investigator Award
2012	American Society for Clinical Investigation
2013	Joel B. Steinberg, M.D. Chair in Pediatrics
2015 – 2016	Chair, Metabolism and Cancer Section, 2016 American Association for Cancer Research Program Committee
2016	Faculty Scholar, Howard Hughes Medical Institute

C. Contribution 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 nearly ten years, my research has focused on how mitochondrial metabolism supports cell 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. 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). PMID 18032601 PMC 2148292.
    b. Cheng T, Sudderth J, Yang C, Mullen AR, Jin ES and DeBerardinis RJ. Pyruvate carboxylase catalyzes an alternative metabolic strategy allowing tumor cells to escape glutamine dependence. *PNAS USA* 108: 8674-8679 (2011). PMID 21555572 PMC 3102381.
    c. 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.
    d. 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).
    e. 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. In press, *Nature* (2017).
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. Maher EA, Marin-Valencia I, Bachoo RM, Mashimo T, Raisanen J, Hatanpaa KJ, Jindal A, Choi C, Jeffrey FM, Madden C, Mathews D, Pascual JM, Mickey BE, Malloy CR and DeBerardinis RJ. Metabolism of [U-^{13}C]glucose in Human Brain Tumors In Vivo. *NMR in Biomedicine* 25: 1234-1244 (2012). PMID: 22419606

c. 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. **Novel methods in non-invasive assessment of metabolism.** Although ^{18}FDG-PET is widely used to assess tumor glucose uptake, this technique provides at best a pinhole view of the metabolic network and provides no information about either downstream metabolic of glucose or of the role of alternative nutrients. Many other metabolic imaging techniques, including proton magnetic resonance spectroscopy ^{13}C hyperpolarization and the use of alternative PET agents are potentially available to interrogate the metabolic state in cancer and other diseases. We have been highly engaged in developing and deploying new technologies to answer pressing questions in cancer biology and clinical oncology. Ongoing work demonstrates that multi-parametric MRI can be used to predict metabolic activity in intact human tumors. Key advancements from prior work are reported in:
    a. Choi C, Ganji SK, DeBerardinis RJ, Hatanpaa KJ, Rakheja D, Kovacs Z, Yang X-L, Mashimo T, Raisanen JM, Marin-Valencia I, Pascual JM, Madden CJ, Mickey BE, Malloy CR, Bachoo R and Maher EA. Noninvasive detection of 2-hydroxyglutarate by magnetic resonance spectroscopy in patients with IDH-mutated malignant gliomas. *Nat Med* 18: 624-629 (2012). PMID: 22281806
    b. Yang C, Harrison C, Jin ES, Chuang DT, Sherry AD, Malloy CR, Merritt ME and DeBerardinis RJ. Simultaneous steady-state and dynamic ^{13}C NMR can differentiate alternative routes of pyruvate metabolism in living cancer cells. *J Biol Chem* 289:6212-6224 (2014).
    c. Yang C, Ko B, Hensley CT, Jiang L, Wasti AT, Lumata L, Mitsche M, Merritt ME and DeBerardinis RJ. Glutamine oxidation maintains the TCA cycle and cell survival during impaired mitochondrial pyruvate transport. *Molecular Cell* 56:414-424 (2014).

Complete List of Published Work in MyBibliography (Over 145 publications in press or print; h-index 53; total citations > 17,000):
http://www.ncbi.nlm.nih.gov/sites/myncbi/ralph.deberardinis.1/bibliography/41156995/public/?sort=date&direction=ascending

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

Howard Hughes Medical Institute — DeBerardinis (PI) — 11/01/2016 – 10/31/2021
Faculty Scholars Program
The major goals are to further our understanding of metabolic fuels and regulation in human tumors in vivo.

1R01 CA157996 06 — DeBerardinis (PI) — 04/01/16 – 03/31/21
Metabolic regulators of tumor cell growth
The major goals of this project are to identify mitochondrial activities that are essential for the growth of cancer cells in vitro and in vivo.

V Foundation Translational Research Award — DeBerardinis (PI) — 11/01/13 – 10/31/17
Translational studies in lung cancer metabolism: creating new paradigms in diagnosis and therapy.
The major goals are to identify metabolic pathways operating in human lung tumors in vivo.

RP160089 (CPRIT) — DeBerardinis (PI) — 03/01/2016 – 02/28/2019
Carbamoyl Phosphate Synthase-1: A new metabolic liability in non-small cell lung cancers
The major goa is to understand how CPS-1 supports tumor growth in non-small cell lung cancer

Grant I-1733 (Welch Foundation) — DeBerardinis (PI) — 07/01/16 – 06/30/19
Compartmentation of a redox-balancing metabolic activity in the cancer cell perox
The goal is to produce a detailed understanding of the biochemical basis of the GDRC pathway.

W81XWH-12-1-0464 (DOD) — Semenza (PI) — 09/30/12 – 09/29/17
Oxygen-Regulated Metabolic Homeostasis: Therapeutic Implications of Paradigm Shift
The major goals are to identify metabolic changes that accompany hypoxia and the inhibition of HIF-1 signaling. Role: PI of Metabolomics sub-contract.

R01 CA168815 03 (NCI) Plas (PI) 04/01/13–03/31/18
Metabolic Adaptive Responses in Cancer
The goal is to identify metabolic mechanisms of survival during therapies directed against oncogenic signaling in cancer. Role: PI of Metabolomics sub-contract.

UL1TR001105 03 Toto (PI) 07/01/13–06/30/18
UT Southwestern Center for Translational Medicine
Goal is to oversee Core 1, in particular the development of high-throughput screening assays for disease detection and treatment in large patient cohorts. Role: Co-Director of Core 1.

5 R01 CA174786 02 (Chen) Chen (PI) 04/15/14- 02/28/19
Signaling and Targeting of 6-Phosphogluconate Dehydrogenase in Human Cancers
The goal is to perform isotope labeling and metabolomics experiments to determine the role of the pentose phosphate pathway in cancer.
Role: PI of Metabolomics sub-contract

P50 CA175754 Brugarolas (PI) 11/1/2016 – 10/31/2021
UTSW SPORE in Kidney Cancer
Goal of Project 3 is to identify metabolomic biomarkers to predict the oncological behavior of small renal masses.
Role: PI of Project 3 (Clinically Actionable Biomarkers from Renal Cell Carcinoma Metabolism and Imaging.

Completed Research Support

RP130272 (CPRIT) DeBerardinis (PI) 06/01/13 – 05/31/16
The metabolic phenome of human lung cancer
The major goal is to profile all of the metabolic phenotypes of non-small cell lung cancer cell lines, in culture and in orthotopic tumors.

RP101243 (CPRIT) Sherry (PI) 09/01/10 – 08/31/15
Metabolic Imaging of Hyperpolarized ^{13}C Substrates in Animal Models of Cancer
This project is a component of a multi-investigator grant to develop a center of excellence for research in cancer imaging. It proposes to use hyperpolarized nutrients as metabolic probes in animal models of cancer.
Role: PI of sub-project.

1R01 CA157996 05 S1 DeBerardinis (PI) 06/30/2014 – 07/01/2015
Metabolic regulators of tumor cell growth – Administrative supplement
The major goals of this project are to identify mitochondrial activities that are essential for the growth of glioblastoma cells in vitro and in vivo. This supplement supported the training of an under-represented minority student, Mr. Christopher Hensley.

Clinical Investigator Award (Damon Runyon) DeBerardinis (PI) 07/01/11 – 06/30/14
Translational Studies in Cancer Metabolism
The major goals of this grant are to perform targeted metabolomics and quantitative metabolic flux analysis on intact tumors.

Sponsored Research 101371-01 (Janssen) DeBerardinis (PI) 05/01/11-04/30/13
Identification and Validation of Novel Tumor Metabolism Targets in Glutaminolysis
The major goal is to identify chemical inhibitors of glutaminolysis and to characterize their effect on 3-dimensional models of cancer cell growth.

1 R21 CA159128-01 (NIH/NCI) Choi (PI) 09/20/11 - 08/31/13
In vivo detection of 2-hydroxyglutarate in gliomas by spectroscopic MRI
The goals are to develop a 1H MRS tool for measuring 2-hydroxyglutarate in gliomas with mutated IDH at 3.0 T and to carry out a study in 50 brain tumor patients. Role: Co-Investigator.