# BIOGRAPHICAL SKETCH

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NAME: RABINOWITZ, JOSHUA D.

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

POSITION TITLE: Professor, Dept. of Chemistry & the Lewis-Sigler 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) | END DATE MM/YYYY | FIELD OF STUDY |
|---|---|---|---|
| University of North Carolina, Chapel Hill, NC | BA | 05/1994 | Chemistry |
| University of North Carolina, Chapel Hill, NC | BA | 05/1994 | Mathematics |
| Stanford University, Stanford, CA | PHD | 05/1999 | Biophysics |
| Stanford University, Stanford, CA | MD | 05/2001 | Medicine |

## A. Personal Statement

My research focuses on two broad questions: What is the quantitative flow (flux) through different metabolic pathways? How is this flux controlled? These questions go to the essence of how metabolism functions. To address these questions, my lab develops innovative technologies that blend mass spectrometry, isotope tracers, and computational data integration. Recently, we are pushing also into spatially resolved analyses through imaging mass spectrometry. We then apply these technologies to address major biomedical problems, including diabetes, infectious disease, and cancer.

In the area of cancer, we are deeply interested in the defining metabolic features of tumors. We contributed to the discoveries of the oncogenic metabolite 2-hydroxyglutarate and of autophagy and macropinocytosis as cancer nutrient acquisition routes. Recently, we figured out that tumors are metabolically thrifty: They grow despite making and using less energy than most healthy tissues of the body. We are also actively involved in clinical studies involving isotope tracing and mass spectrometry to probe human tumors.

We have also become deeply interested in the interplay among diet, metabolism, and cancer therapy. Based on striking preclinical results combining ketogenic diet with classical cytotoxic chemotherapy, we are contributing to a randomized clinical trial of ketogenic diet to augment chemotherapy in pancreatic ductal carcinoma, and are actively researching potential metabolic strategies to enhance immunotherapy.

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

SU2C Convergence31416 Honda (PI), Role: Co-PI 01/2021-12/2023 The Interplay of Diet, Microbiome, and Cancer Therapy

NIH R01CA163591 White (PI), Role: Co-PI 07/2017-06/2023 Tumor Cell Dependence on Host Metabolism

NIH DP1DK113643 Rabinowitz (PI) 09/2016-07/2021 Metabolism in Action: Quantitative Fluxes in Mammals

1. Bartman, C. R., Weilandt, D. R., Shen, Y., Lee, W. D., Han, Y., TeSlaa, T., Jankowski, C. S. R., Samarah, L., Park, N. R., da Silva-Diz, V., Aleksandrova, M., Gultekin, Y., Marishta, A., Wang, L., Yang, L., Roichman, A., Bhatt, V., Lan, T., Hu, Z., Xing, X., Lu, W., Davidson, S., Wühr, M., Vander Heiden, M. G., Herranz, D., Guo, J. Y., Kang, Y., Rabinowitz, J. D. (2023) Slow TCA flux and ATP production in primary solid tumours but not metastases. Nature, 614(7947): 349-357. PMC Journal – In Process

2. Ghergurovich JM, Lang JD, Levin MK, Briones N, Facista SJ, Mueller C, Cowan AJ, McBride MJ, Rodriguez ESR, Killian A, Dao T, Lamont J, Barron A, Su X, Hendricks WPD, Espina V, Von Hoff DD, O'Shaughnessy J, Rabinowitz JD. Local production of lactate, ribose phosphate, and amino acids

within human triple-negative breast cancer. Med (N Y). 2021 Jun 11;2(6):736-754. PubMed Central PMCID: PMC8248508.

3. Jang C, Chen L, Rabinowitz JD. Metabolomics and Isotope Tracing. Cell. 2018 May 3;173(4):822-837. PubMed Central PMCID: PMC6034115.
4. Hui S, Ghergurovich JM, Morscher RJ, Jang C, Teng X, Lu W, Esparza LA, Reya T, Le Zhan, Yanxiang Guo J, White E, Rabinowitz JD. Glucose feeds the TCA cycle via circulating lactate. Nature. 2017 Nov 2;551(7678):115-118. PubMed Central PMCID: PMC5898814.

## B. Positions, Scientific Appointments and Honors

### Positions and Scientific Appointments

| | |
|---|---|
| 2011 - | Professor, Dept. of Chemistry & the Lewis-Sigler Institute, Princeton University |
| 2021 - | Director, Ludwig Princeton Branch |
| 2008 - | Member, Rutgers Cancer Institute of NJ |
| 2005 - | Associated Faculty, Dept. of Molecular Biology, Princeton University |
| 2023 - | Scientific Advisor Board, Faeth Therapeutics |
| 2021 - | Scientific Advisory Board, Empress Therapeutics |
| 2020 - 2022 | Scientific Advisor and Consulting Principal Scientist, Rafael Holdings |
| 2020 - | Board of Directors, Raze Therapeutics |
| 2020 - | Co-Founder and Board of Directors, Farber Partners |
| 2020 - 2021 | Scientific Advisory Board, Empress Therapeutics |
| 2020 - 2021 | Consultant, Montai Health |
| 2019 - | Scientific Advisory Board, Bantam Pharmaceuticals |
| 2019 - | Scientific Advisory Board, Barer Institute |
| 2018 - | Director for Princeton University-PKU-Shenzhen Collaboration, Princeton University |
| 2018 - | Scientific Advisor, L. E. A. F. Pharmaceuticals |
| 2018 - | Scientific Advisor, Colorado Research Partners |
| 2018 - 2021 | Consultant, Pfizer |
| 2017 - | Founder and Board of Directors, Sofro Pharmaceuticals |
| 2010 - 2021 | Scientific Advisory Board, Kadmon Pharmaceuticals |
| 2009 - 2011 | Associate Professor, Dept. of Chemistry & the Lewis-Sigler Institute, Princeton University |
| 2004 - 2009 | Assistant Professor, Dept. of Chemistry & the Lewis-Sigler Institute, Princeton University |
| 2000 - 2004 | Co-founder and Vice President for Research, Alexza Pharmaceuticals |

### Honors

| | |
|---|---|
| 2019 | Allen Distinguished Investigator, The Paul G. Allen Frontiers Group |
| 2016 | NIH Pioneer Award, National Institutes of Health |
| 2013 | Agilent Thought Leader Award, Agilent Technologies, Inc. |
| 2007 - 2013 | CAREER Award, National Science Foundation |
| 2005 - 2009 | Beckman Young Investigator Award, Arnold and Mabel Beckman Foundation |
| 2008 | Kavli Frontiers of Science Scholar, Kavli Foundation and National Academy of Sciences |
| 2004 | Inventor, 100+ Issued US Patents |
| 1994 - 2001 | Medical Scientist Training Program (MSTP) Trainee, National Institutes of Health |
| 1993 - 1994 | President, Phi Beta Kappa, University of North Carolina |
| 1994 | Highest Honors in Mathematics, University of North Carolina |

## C. Contribution to Science

1. Metabolomic technology

   My lab has played a central role in the development of the field of metabolomics. We were among the first to develop LC-MS methods and integrate them into an effective workflow that enabled facile quantitation of

important known metabolites. Building from this metabolomics pipeline, I recognized that complete characterization of the metabolism involves knowing both metabolite concentrations and fluxes. Unlike metabolites themselves, however, fluxes cannot be measured in a mass spectrometer. To quantitative fluxes, my lab developed methods involving feeding isotope tracers and measuring the kinetics and extent of intracellular metabolite labeling. Labeling patterns are then computationally integrated to yield fluxes. Recently, we have expanded our toolbox for flux quantitation from cultured cell to mammals. Both our metabolite concentration and flux measurement methods have been widely adopted. Together, they provide a powerful toolset for revealing metabolic activity and its regulation.

a. Lu W, Su X, Klein MS, Lewis IA, Fiehn O, Rabinowitz JD. Metabolite Measurement: Pitfalls to Avoid and Practices to Follow. Annu Rev Biochem. 2017 Jun 20;86:277-304. PubMed Central PMCID: PMC5734093.
b. Park JO, Rubin SA, Xu YF, Amador-Noguez D, Fan J, Shlomi T, Rabinowitz JD. Metabolite concentrations, fluxes and free energies imply efficient enzyme usage. Nat Chem Biol. 2016 Jul;12(7):482-9. PubMed Central PMCID: PMC4912430.
c. Su X, Lu W, Rabinowitz JD. Metabolite Spectral Accuracy on Orbitraps. Anal Chem. 2017 Jun 6;89(11):5940-5948. PubMed Central PMCID: PMC5748891.
d. Bartman CR, TeSlaa T, Rabinowitz JD. Quantitative flux analysis in mammals. Nat Metab. 2021 Jul;3(7):896-908. PubMed Central PMCID: PMC9289955.

2. Novel metabolites and reactions

Metabolism is the best mapped major biochemical network. Nevertheless, new reactions remain to be discovered. To this end, we are advancing new machine learning approaches for accelerating the discovery of new metabolites from LC-MS data. This builds on our history of discovering important metabolites and pathways. We have identified a new route in yeast to the key nucleic acid precursor ribose-5-phosphate, riboneogenesis. We discovered folate-dependent tRNA methylation that is critical to mitochondrial translation and thus respiration. We helped to identify itaconate as a mammalian metabolite. Most importantly, we contributed to the discovery that oncogenic mutant versions of the TCA cycle enzyme isocitrate dehydrogenase (IDH) produces the oncometabolite 2-hydroxyglutarate (2HG), explaining how this mutation cause cancer. Mutant IDH inhibitors are now FDA-approved for treatment of acute myeloid leukemia.

a. Clasquin MF, Melamud E, Singer A, Gooding JR, Xu X, Dong A, Cui H, Campagna SR, Savchenko A, Yakunin AF, Rabinowitz JD, Caudy AA. Riboneogenesis in yeast. Cell. 2011 Jun 10;145(6):969-80. PubMed Central PMCID: PMC3163394.
b. Dang L, White DW, Gross S, Bennett BD, Bittinger MA, Driggers EM, Fantin VR, Jang HG, Jin S, Keenan MC, Marks KM, Prins RM, Ward PS, Yen KE, Liau LM, Rabinowitz JD, Cantley LC, Thompson CB, Vander Heiden MG, Su SM. Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. Nature. 2009 Dec 10;462(7274):739-44. PubMed Central PMCID: PMC2818760.
c. Morscher RJ, Ducker GS, Li SH, Mayer JA, Gitai Z, Sperl W, Rabinowitz JD. Mitochondrial translation requires folate-dependent tRNA methylation. Nature. 2018 Feb 1;554(7690):128-132. PubMed Central PMCID: PMC6020024.
d. Chen, L, Lu, W, Wang, L, Xing, X, Chen, Z, Teng, X, Zeng, X, Muscarella, AD, Shen, Y, Cowan, A, McReynolds, MR, Kennedy, BJ, Lato, AM, Campagna, SR, Singh, M, Rabinowitz, JD. Metabolite discovery through global annotation of untargeted metabolomics data. Nature Methods. 2021 Nov;18(11):1377-1385. PubMed Central PMCID: PMC8733904.

3. Nutrient scavenging in cancer

Cancer requires a steady stream of nutrients to feed cell survival and growth. Enhanced glucose catabolism has been recognized as a hallmark of cancer for now more than 90 years and underlies sensitive cancer detection by PET imaging. More recently, glutamine and other monomeric amino acids have been identified as additional critical nutrients for cancer growth. Through a combination of cell culture studies and analyses of primary human tumor specimens, we have identified an alternative mode of

nutrient acquisition that supports some of the nastiest tumors: scavenging of protein and lipids. Scavenged nutrients constitute essential metabolic inputs of cancers driven by the Ras oncogene. This scavenger lifestyle contributes to the resistance of Ras-driven tumors to current therapies but may open the door to novel approaches that target the recycling mechanisms.

a. Commisso C, Davidson SM, Soydaner-Azeloglu RG, Parker SJ, Kamphorst JJ, Hackett S, Grabocka E, Nofal M, Drebin JA, Thompson CB, Rabinowitz JD, Metallo CM, Vander Heiden MG, Bar-Sagi D. Macropinocytosis of protein is an amino acid supply route in Ras-transformed cells. Nature. 2013 May 30;497(7451):633-7. PubMed Central PMCID: PMC3810415.
b. Kamphorst JJ, Nofal M, Commisso C, Hackett SR, Lu W, Grabocka E, Vander Heiden MG, Miller G, Drebin JA, Bar-Sagi D, Thompson CB, Rabinowitz JD. Human pancreatic cancer tumors are nutrient poor and tumor cells actively scavenge extracellular protein. Cancer Res. 2015 Feb 1;75(3):544-53. PubMed Central PMCID: PMC4316379.
c. Kamphorst JJ, Cross JR, Fan J, de Stanchina E, Mathew R, White EP, Thompson CB, Rabinowitz JD. Hypoxic and Ras-transformed cells support growth by scavenging unsaturated fatty acids from lysophospholipids. Proc Natl Acad Sci U S A. 2013 May 28;110(22):8882-7. PubMed Central PMCID: PMC3670379.
d. Rabinowitz JD, White E. Autophagy and metabolism. Science. 2010 Dec 3;330(6009):1344-8. PubMed Central PMCID: PMC3010857.

4. Metabolic pathway usage in mammals

My lab is actively applying isotope tracers to figure out how metabolic pathways are used in mammals. We developed the first methods to enable tracing of the redox active hydrogen of NADH and NADPH. Using these methods, we identified folate metabolism as an important NADPH source. This unexpected NADPH production route was then shown to drive cancer metastasis and liver fat synthesis. More recently, we have been examining metabolic pathway usage *in vivo*. This led to identification of circulating nicotinamide as the main source of tissue NAD. Other experiments, probing central carbon metabolism, led to a paradigm shift in understanding the catabolic pathway of glucose. Instead of cells directly taking up glucose when they need energy from carbohydrate, red muscle converts circulating glucose into lactate, with circulating lactate used as the main carbohydrate energy source for the rest of the body.

a. Fan J, Ye J, Kamphorst JJ, Shlomi T, Thompson CB, Rabinowitz JD. Quantitative flux analysis reveals folate-dependent NADPH production. Nature. 2014 Jun 12;510(7504):298-302. PubMed Central PMCID: PMC4104482.
b. Liu, L., Su, X., Quinn, W. J. 3rd, Hui, S., Krukenberg, K., Frederick, D. W., Redpath, P., Zhan, L., Chellappa, K., White, E., Migaud, M., Mitchison, T. J., Baur, J. A., Rabinowitz, J. D. (2018) Quantitative analysis of NAD synthesis-breakdown fluxes. Cell Metabolism 2018 May 1;27(5):1067-1080. PubMed Central PMCID: PMC5932087.
c. Hui S, Ghergurovich JM, Morscher RJ, Jang C, Teng X, Lu W, Esparza LA, Reya T, Le Zhan, Yanxiang Guo J, White E, Rabinowitz JD. Glucose feeds the TCA cycle via circulating lactate. Nature. 2017 Nov 2;551(7678):115-118. PubMed Central PMCID: PMC5898814.
d. TeSlaa T, Bartman CR, Jankowski CSR, Zhang Z, Xu X, Xing X, Wang L, Lu W, Hui S, Rabinowitz JD. The Source of Glycolytic Intermediates in Mammalian Tissues. Cell Metab. 2021 Feb 2;33(2):367-378.e5. PubMed Central PMCID: PMC8088818.

5. Quantitative analysis of metabolic regulation

How are concentrations and fluxes controlled? Using a combination of theory and experiment, we have identified novel metabolic regulatory mechanisms in E. coli, such as control of pyrimidine end product levels through directed overflow metabolism, a previously undescribed mode of regulation. We have also developed a general method for integrating fluxomics, metabolomics, and proteomics to identify metabolic regulation: systematic identification of meaningful metabolic enzyme regulation (SIMMER). Its application to yeast identified several new physiologically important allosteric regulatory interactions, as well as a general propensity for metabolites to exert more control over physiological fluxes than enzymes. More

recently, we have quantitatively tackled metabolic pathways in intact mammals. One striking observation is that the small intestine effectively yields the liver from modest (but not large) loads in ingested fructose, thereby protecting against fatty liver disease. We have also developed methods to understand metabolic interplay between host and microbiome quantitatively, mapping the nutrient sources used by the microbiome and showing that dietary changes lead to outgrowth of bacteria that prefer the incoming nutrients.


a. Reaves ML, Young BD, Hosios AM, Xu YF, Rabinowitz JD. Pyrimidine homeostasis is accomplished by directed overflow metabolism. Nature. 2013 Aug 8;500(7461):237-41. PubMed Central PMCID: PMC4470420.

b. Hackett SR, Zanotelli VR, Xu W, Goya J, Park JO, Perlman DH, Gibney PA, Botstein D, Storey JD, Rabinowitz JD. Systems-level analysis of mechanisms regulating yeast metabolic flux. Science. 2016 Oct 28;354(6311) PubMed Central PMCID: PMC5414049.

c. Jang C, Wada S, Yang S, Gosis B, Zeng X, Zhang Z, Shen Y, Lee G, Arany Z, Rabinowitz JD. The small intestine shields the liver from fructose-induced steatosis. Nat Metab. 2020 Jul;2(7):586-593. PubMed Central PMCID: PMC8020332.

d. Zeng X, Xing X, Gupta M, Keber FC, Lopez JG, Lee YJ, Roichman A, Wang L, Neinast MD, Donia MS, Wühr M, Jang C, Rabinowitz JD. Gut bacterial nutrient preferences quantified in vivo. Cell. 2022 Sep 1;185(18):3441-3456. PubMed Central PMCID: PMC9450212


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