

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors.  
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Joseph T. Nickels, Jr

eRA COMMONS USER NAME (credential, e.g., agency login): nickels1

POSITION TITLE: Director

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
Rider University, Lawrenceville, NJ	B.S.	1988	Biochemistry
UMDNJ/Rutgers University, New Brunswick, NJ	Ph.D.	1993	Microbiology and Molecular Genetics
Princeton University, Princeton, NJ	Postdoc	1993-1997	Molecular Biology/Genetics

**A. Personal Statement**

Research at the Institute of Metabolic Disorders focuses on drug discovery for treating hyperlipidemia as a therapeutic approach for atherosclerosis, non-alcoholic fatty liver disease (NAFLD), and non-alcoholic steatohepatitis (NASH). These diseases have many common factors contributing to their initiation and progression, where our drug discovery efforts are targeting reducing lipid overload and inflammation. In addition to our small molecule identification of SREBP inhibitors, we are in mouse efficacy studies for inhibitors of the monoacylglycerol acyltransferase 2 enzyme for reducing dietary fat intake, have initiated a program for inhibitors of the Arv1 protein based on our knockout studies showing that loss of Arv1 in mice results in a drastic reduction in blood cholesterol and triacylglycerol levels. An inhibitor program that is entering initial screening will identify inhibitors of the CD36 fatty acid transport, which has been shown to have a major role in atherosclerosis. There are two additional programs for (1) identifying inhibitors of the innate immune pattern recognition receptors, nod-like receptor 3 (NLRP3) and (2) inhibitors for the RIG-1-like receptor 1 (RIG1) protein for reducing the inflammatory process that is associated with lipotoxicity.

I have combined academic and industrial experience rising to the ranks of Associate Professor at Drexel University College of Medicine (DUCOM) and Director of the Institute of Metabolic Disorders (IMD) at Genesis Research and Development, L.L.C.. While I was at DUCOM, I made the decision that I wanted to translate my yeast work into human translational studies. Genesis Biotech gave me the opportunity to move my research into mammalian cell culture systems and mouse efficacy research that was designed to initiate drug discovery efforts focusing on treatments for metabolic diseases.

## B. Positions and Honors

### PROFESSIONAL POSITIONS:

1993-1997	Postdoctoral Fellow, Department of Molecular Biology, Princeton University
1997-2004	Assistant Professor, Department of Biochemistry, Drexel University College of Medicine
2005-2007	Associate Professor, Department of Biochemistry and Molecular Biology, Drexel University College of Medicine
2007-2010	Research Team Leader, Division of Pharmacogenomics, Medical Diagnostic Laboratories, Hamilton, NJ 08690
2007-	Adjunct Associate Professor, Department of Biochemistry, Drexel University College of Medicine
2008-2013	Volunteer Professor, Department of Molecular Biology, UMDNJ-School of Osteopathic Medicine
2009-2010	Scientific Director, Venenum BioDesign L.L.C., Hamilton, NJ 08691
2010-2012	Director, Target Biology, Venenum BioDesign L.L.C., Hamilton, NJ 08691
2012-	Member, Rutgers University Center for Lipid Research
2013-	Director, IMD, The Institute of Metabolic Disorders, Hamilton, NJ 08691
2013-	Volunteer Professor, Department of Molecular Biology, Rowan University School of Medicine
2015-	Member, Rutgers University Institute for Food, Nutrition, and Health
2015-	Member, Rutgers Center for Lipid Research

### PROFESSIONAL AWARDS AND HONORS:

1994-1997	New Jersey Commission on Cancer Research Postdoctoral Fellow
2000-2002	Basil O'Connor Scholar, March of Dimes Foundation Award
2002-2005	NIH RO1 (#HL067401)
2006-	Editorial Board, Analytical Biochemistry
2011-2018	Editorial Board, Journal of Biological Chemistry
2011-	Ad hoc reviewer, Fungal Genetics and Biology
2011-	Ad hoc reviewer, Journal of Medical Microbiology
2011-	Ad hoc reviewer, Journal of Eukaryotic Microbiology
2012-	Ad hoc reviewer, Nature
2012-	Reviewer, Health Research Council of New Zealand
2013-	Ad hoc reviewer, PLOS One
2013-	Ad hoc reviewer, Nature Chemical Biology
2015-	Editorial Board, PLoS one
2015-	Editorial Board, Nutrition and Metabolism
2019-	Editorial Board, Journal of Lipid Research

## C. Contributions to Science

Early in my career as a doctoral student in the laboratory of Dr. George Carman at Rutgers University, I purified and characterized a novel 55 kDa membrane-bound phosphatidylinositol 4-kinase (PI-4 kinase) from *Saccharomyces cerevisiae*. I was the first investigator to show ADP levels and CTP-diacylglycerol regulated PI-4 kinase. This work resulted in 3 first author and 4 co-author publications.

1. Nickels, Jr., J.T., Buxeda, R.J., and Carman, G.M. (1992). Purification, characterization, and kinetic analysis of a 55-kDa form of phosphatidylinositol 4-kinase from *Saccharomyces cerevisiae*. *J. Biol. Chem.* **267**: 16297-16304

2. Nickels, Jr., J.T. and Carman, G.M. (1993). Photoaffinity labeling of the 45-kDa and 55-kDa forms of phosphatidylinositol 4-kinase from the yeast *Saccharomyces cerevisiae*. *J. Biol. Chem.* **268**: 24083-24088.
3. Nickels, Jr., J.T., Buxeda, R.J., and Carman, G.M. (1994). Regulation of phosphatidylinositol 4-kinase from the yeast *Saccharomyces cerevisiae* by CDP-diacylglycerol. *J. Biol. Chem.* **269**: 11018-11024

As a postdoctoral fellow in the laboratory of Dr. Jim Broach at Princeton University, I was the first investigator to determine the protein subunit make up of the heterotrimeric ceramide-activated protein kinase (CAPP) from *S. cerevisiae* and show that it was necessary for cell cycle arrest under stress conditions. This work helped Dr. Broach in receiving an award from the American Cancer Society. I followed up this work by being a part of a team from Merck that discovered the long chain base phosphate phosphatases, *LBP1/2*, and characterized the essential role of Lbp1 for maintaining cell viability under stress conditions.

1. Nickels, Jr., J.T., and Broach, J.R. (1996). A ceramide-activated protein phosphatase mediates ceramide-induced G1 arrest of *Saccharomyces cerevisiae*. *Genes & Dev.* **10**: 382-394.
2. Mandala, S., Thornton, R., Tu, Z., Kurtz, M., Nickels, Jr., J.T., Broach, J.R., Mendelev, R., and Spiegel, S. (1998) Sphingosine 1-phosphate phosphatase, a key regulator of sphingoid metabolism and stress response. *Proc. Natl. Acad. Sci.* **95**: 150-155

I then moved to Drexel University College of Medicine (DUCOM) and started an independent laboratory focusing on the interplay between sphingolipid and sterol biosynthesis in *S. cerevisiae*. My laboratory demonstrated that recessive mutations in either sphingolipid or sterol genes resulted in defects in the synthesis of both sterol and sphingolipid biosynthesis. My laboratory went on to characterize the role of the lipid transporter, Arv1, in sphingolipid biosynthesis and sterol trafficking. We showed that loss of Arv1 caused defects in sphingolipid biosynthesis - ceramide accumulation and a reduction in complex sphingolipid levels- and sterol trafficking and distribution defects. We determined the membrane topology of Arv1 from *S. cerevisiae*, and showed its role in maintaining virulence during *C. albicans* infection.

My laboratory also continued to work on the CAPP protein and showed that it regulated the cell cycle through regulating cyclin levels. We also showed that CAPP was necessary for proper DNA replication during meiosis. Loss of the Cdc55 subunit of CAPP resulted in re-replication and increased tetrad formation. In addition, we found that Cdc55 was required for restoring endocytosis in endocytosis-defective mutants and that it was necessary for glucose transporter trafficking.

1. Swain, E, Stukey, J, McDonough, V, Baudry, K, Germann, M, Allegood, J, Merrill, A, Mandala, S, Kurtz, M, and Nickels, Jr, J.T. (2002). Sterol-dependent regulation of sphingolipid biosynthesis in *Saccharomyces cerevisiae*. *J. Biol. Chem.* **277** 26177-26184.
2. Swain, E, Stukey, J, McDonough, V, Germann, M, Lui, L., Sturley, S. and Nickels, Jr, J.T. (2002). Yeast cells lacking the *ARV1* gene harbor defects in sphingolipid metabolism: Complementation by human *Arv1*. *J. Biol. Chem.* **277** 36152-36160.
3. Rice, L., Gallo, C., Plakas, C., and Nickels, Jr, J.T. (2005) The loss of re-replication block in yeast cells defective for Cdc28 regulation. *Eukaryot. Cell* **4** 55-62
4. McCourt, P., Morgan, J., and Nickels, Jr., J.T. (2009) Stress-induced ceramide-activated protein phosphatase can compensate for loss of amphiphysin-like activity in *Saccharomyces cerevisiae* and functions to reinitiate endocytosis. *J. Biol. Chem.* **284** 11930-11941

My work at DUCOM resulted in 15 senior author papers and 5 co-author papers.

At the Institute of Metabolic Disorders, my focus was to transition from budding yeast to human drug discovery targeting lipid metabolic diseases. My laboratory demonstrated that miR-185 negatively regulated *SREBP2F* expression through a feedback loop requiring SREBP1. We also found that miR-185 levels were decreased in patients with hyperlipidemia. This resulted in a patent award and a senior author publication. We went on to show that SREBP gene levels were regulated by protein phosphatase 2A (PP2A) through its negative regulation of AMP kinase (AMPK). We also found that the insulin growth factor mRNA binding protein 2 (IGF2BP2) was required for miR-33a/b-dependent regulation of *ABCA1* expression and that expression of human IGF2BP2 in mice lowered *ABCA1* expression and protein levels, and increased LDL-C levels. Our *in vivo* mouse studies using constitutive *Arv1*<sup>-/-</sup> null mice showed that these mice had drastically reduced cholesterol and triglyceride levels in the blood and liver, while showing no signs of hepatic steatosis. They also showed less fat accumulation in their aortas (*J. Nickels, personal communication*).

1. Yang, M., Liu, W., Pellicane, C., Sahyoun, C., Joseph, B., Gallo-Ebert, C., Donigan, M., Pandya, D., Giordano, C., Bata, A, and Nickels, Jr., J.T. (2014) Identification of miR-185 as a regulator of *de novo* cholesterol biosynthesis and low-density lipoprotein uptake. *J. Lipid Res.* **55** 226-238
2. Rice, L. M., Donigan, M., Yang M., Liu, W., Pandya, D., Joseph, B., Sodi, V., Gearhart, T. L., Yip, J., Bouchard, M. B., and Nickels, Jr., J. T. (2014) Protein phosphatase 2A regulates low-density lipoprotein uptake through regulating SREBP-2 DNA binding *J. Biol. Chem.* **289** 17268-17279
3. Joseph, B., Liu, H-Y., Francisco, J., Pandya, D., Donigan, M., Gallo-Ebert, C., Giordano, C., Bata, A., Nickels, Jr., J.T. (2015) Inhibition of AMP kinase by the protein phosphatase 2A heterotrimer, PP2A<sup>PPP2R2d</sup> *J. Biol. Chem.* **290** 10588-10598
4. Gallo-Ebert, C., Francisco, J., Liu, HY., Modi, K., Hayward, M.D., Jones, BK., Buiakova, O., McDonough, V, and Nickels, Jr., J.T. (2018) Mice lacking *ARV1* have reduced signs of metabolic syndrome and non-alcoholic fatty liver disease. *J. Biol. Chem.* **293** 5956-5974

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

Genesis Biotechnology Group has a Master's program that is affiliated with Rowan University College of Medicine (RUCOM). I am the Director of this program and have mentored 7 students through the program from the time it was initiated. I maintain academic positions at DUCOM and RUCOM. I mentored 7 PhD students and 2 MS students while at DUCOM. I am also a member of the Rutgers University Center for Lipid Research and The Institute of Food, Nutrition, and Health at Rutgers. Over the years, I have had over 50 undergraduate students come through my laboratory and several visiting scientists.

"Mechanisms regulating sterol metabolism"

NIH RO1-HL067401

2000-2004

\$800,000 direct costs