BIOGRAPHICAL SKETCH

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NAME: Bruce A. Barshop, M.D., Ph.D.

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

POSITION TITLE: Professor

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)*	YEAR(s)	FIELD OF STUDY
Brandeis University, Waltham, MA	A.B.	1976	Biochemistry
Washington University, St. Louis, MO	M.D.	1984	Medicine
Washington University, St. Louis, MO	Ph.D.	1984	Molecular Biology

A. Personal Statement

A major focus of my career has been in chemometrics and numerical modeling, and my laboratory has focused on large-scale quantitative clinical metabolomic measurements. My background is in metabolic regulation and control, and I direct the William L. Nyhan Biochemical Genetics and Metabolomics Laboratory at UCSD, a CLIA-compliant, CAP-certified facility which processes large numbers of clinical samples. I have served on the CAP-ACMG Genetics Resource Committee charged with designing and evaluating proficiency testing in Biochemical Genetics. I am clinically active in the practice of Biochemical Genetics and am Clinical Chief of Genetics at Rady Children's Hospital San Diego. I have experience in clinical trials and have been involved in many investigator-initiated and sponsored studies.

B. Positions and Honors.

PROFESSIONAL EXPERIENCE

1984-1986: Intern and Resident in Pediatrics (PL-1,-2), University of California San Diego
1986-1988: Clinical Fellow, Human Genetics, Department of Pediatrics, UCSD: Dr. William Nyhan.
1988-1990: Research Fellow, Department of Medicine, UCSD: Dr. J. Seegmiller.
1990-1991: Assistant Research Scientist, Department of Pediatrics, UCSD
1991-1992: Senior Resident in Pediatrics (PL-3), UCSD
1992-1998: Assistant Professor in Residence, Department of Pediatrics, UCSD
1998-2004: Associate Clinical Professor, Department of Pediatrics, UCSD
2004-: Professor of Clinical Pediatrics, Department of Pediatrics, UCSD

HONORS AND AWARDS

High honors in Biochemistry, Brandeis University (1976); Aaron B. Chausmer Prize in Biomedical Computing, National Student Research Forum (1982); Outstanding Resident Teaching Award, UCSD Department of Pediatrics (1992); Best Doctors in America (2003-2011). Benard L. Maas Chair in Inherited Metabolic Disease, UCSD (2007-present). Co-chair, session on Metabolic Diseases, 2014 meeting of the American Society of Human Genetics. Opening talk at the 2014 SIMD meeting on "Metabolomic Approaches to Metabolic Testing."

SERVICE APPOINTMENTS

Director, Biochemical Genetics Laboratory, Department of Pediatrics, UCSD (1994-); Assistant Director, UCSD Pediatric Pharmacology Research Unit (1996-2003); Chair, UCSD Clinical Research Center Advisory Committee (1997-2001); Research Safety Advisor, UCSD General Clinical Research Center (2001-2010); Chief Medical Consultant, California Newborn Screening, Region V (2002-present)

REGIONAL, NATIONAL AND INTERNATIONAL COMMITTEE SERVICE

Board of Directors, Society for Inherited Metabolic Diseases (2000-); Steering Committee, Mitochondrial Medicine Society (2001-3); Advisory Committee, Expanded Newborn Screening Project, California Department of Health Services, Genetic Disease Branch (2002-); Item Writer, American Board of Medical Genetics, Section on Biochemical Genetics (2001-); American College of Medical Genetics, Web Site Oversight Committee, 2006-2009; College of American Pathologists, Biochemical and Molecular Genetics

Resource Committee 2007-2013; Data Safety Monitoring Boards, StemCells, Inc. Phase I trial of neuronal stem cell therapy in a) neuronal ceroid lipofuscinosis, 2007-present, b) Pelizaeus-Merzbacher disease, 2010-present; Communicating Editor, Journal of Inherited Metabolic Disease (2005-present). Subcommittee on Biochemical Genetics Testing, CDC/CLIA, 2009-2010.

C. Contributions to Science

1) Kinetic studies of enzyme reactions and biomedical processes

My earliest work involved development of a computational method for pre-steady state simulation of chemical kinetics and enzyme reactions. The 1982 publication describing the KINSIM system for solution of simultaneous differential equations has been widely cited, is still in use, and has served as the basis for other chemical simulation programs. I have applied the approach to describe protein-protein interactions and kinetic processes using stable isotope tracers *in vivo*.

1. Barshop BA, Wrenn RF, Frieden C. Analysis of numerical methods in computer simulation of chemical kinetic processes: Development of KINSIM, a flexible, portable system. *Analytical Biochemistry* 1982; 130:134-145. PMID: 6688159
2. Barshop BA, Frieden C. Analysis of the interaction of rabbit skeletal muscle adenylate deaminase with myosin subfragments: A kinetically regulated system. *Journal of Biological Chemistry* 1983; 259:60-66. PMID: 6368542
3. Barshop BA, Breuer J, Holm J, Leslie J, Nyhan WL. Excretion of hippuric acid during sodium benzoate therapy in patients with hyperglycinaemia or hyperammonaemia. *Journal of Inherited Metabolic Disease* 1989; 12:72-79. PMID: 2501586
4. Barshop BA, Yoshida I, Ajami A, Sweetman L, Wolff J, Prodanos C, Sweetman FR, Smith M, Nyhan WL. Metabolism of 1-13C-propionate in patients with disorders of propionate metabolism. *Pediatric Research* 1991; 30:15-22. PMID: 1909779
5. Opladen T, Lindner M, Das AM, Marquardt T, Khan A, Emre SH, Burton BK, Barshop, BA, Böhm T, Meyburg J, Zangerl K, Mayorandan S, Burgard P, Dürr UH, Rosenkranz B, Rennecke J, Derbinski J, Yudkoff M, Hoffmann GF. In vivo monitoring of urea cycle activity with (13)C-acetate as a tracer of ureagenesis. Mol Genet Metab. [Epub ahead of print] PubMed PMID: 26597322.

2) Characterization of metabolic diseases and clinical trials for their treatment

Throughout my career, I have studied rare metabolic disorders, characterized them and worked on therapeutic approaches. In addition to the publications below, I have participated in several studies sponsored by pharmaceutical companies on enzyme replacement treatments for lysosomal storage disorders and cofactor treatments for phenylketonuria, etc. Other investigator-initiated studies include the works below, which center on disorders of purine metabolism (Lesch-Nyhan disease and adenylosuccinase deficiency), alkaptonuria, and mitochondrial disease, including a prior study treating lactic acidemia associated with mitochondrial disease using sodium dichloroacetate. A recent genome-wide sequencing study of methylcrotonyl-CoA carboxylase deficiency (MCCD) searching for genetic markers distinguishing symptomatic from asymptomatic cases found that most symptoms attributed to MCCD were related to unanticipated mutations at other loci, and pointed out the importance of assessing degree of homozygosity in populations used for characterization of autosomal recessive disease.

1. Barshop BA, Alberts AS, Gruber HE. Kinetic studies of mutant human adenylosuccinase. *Bioch Biophys Acta* 1989; 999:19-23. PMID: 280413
2. Wolff JA, Barshop BA, Nyhan WL, Leslie J, Seegmiller JE, Gruber HE, Garst M, Winter S, Michals K, Matalon R. Effects of ascorbic acid in alkaptonuria: Alterations in benzoquinone acetic acid and an ontogenic effect in infancy. *Pediatric Research* 1989; 26:140-144. PMID: 2771520
3. Page T, Barshop BA, Yu A, Nyhan WL. Treatment of Lesch-Nyhan syndrome with AICAR. *Adv Exp Med Biol* 1994; 370:353-6. PMID: 7660927
4. Haas RH, Barshop BA. Diet change in the management of metabolic encephalomyopathies. *BioFactors* 1998; 7:259-62. PMID: 9568263
5. Spruijt L, Naviaux RK, McGowan KA, Nyhan WL, Sheean G, Haas RH, Barshop BA. Nerve conduction changes in patients with mitochondrial diseases treated with dichloroacetate. *Muscle Nerve*. 2001; 24(7):916-24. PMID: 11410919.

6. Barshop BA, Naviaux RK, McGowan KA, Levine F, Nyhan WL, Loupis-Geller A, Haas RH. Chronic Treatment of mitochondrial disease patients with dichloroacetate. *Molec Genet Metab* 2004; 83(1-2):138-49. PMID: 15464428
7. Shepard PJ, Barshop BA, Baumgartner MR, Hansen JB, Jepsen K, Smith EN, Frazer KA. Consanguinity and rare mutations outside of MCCC genes underlie nonspecific phenotypes of MCCD. *Genet Med*. 2015 Aug;17(8):660-7. Epub 2014 Nov 6. PubMed PMID: 25356967

3) Pharmacokinetics and clinical trials of cystinosis

My lab performed the pharmacokinetic and pharmacodynamic studies related to cysteamine absorption of cysteamine, and the phase I/II study leading to the approval of the delayed release formulation eventually approved as Procysbi®. I have a particular ongoing interest in cystinosis.

1. Fidler MC, Barshop BA, Gangoiti JA, Deutsch R, Martin M, Schneider JA, Dohil R. Pharmacokinetics of cysteamine bitartrate following gastrointestinal infusion. *Br J Clin Pharmacol* 2007; 63(1):36-40. PMID: 17229040
2. Fidler MC, Gangoiti JA, Schneider JA, Barshop BA. Time before isolating cystinotic leukocytes affects reliability of cystine determination. *Pediatr Nephrol* 2009;24(12):2465-6. PMID: 19396469
3. Dohil R, Fidler M, Gangoiti JA, Kaskel F, Schneider JA, Barshop BA. Twice-daily cysteamine bitartrate therapy for children with cystinosis. *J Pediatr* 2010;156(1):71-75. PMID: 19775699
4. Dohil R, Gangoiti JA, Cabrera BL, Fidler M, Schneider JA, Barshop BA. Long-term treatment of cystinosis in children with twice-daily cysteamine. *J Pediatr* 2010;156(5):823-7. PMID: 20138296
5. Gangoiti JA, Fidler M, Cabrera BL, Schneider JA, Barshop BA, Dohil R. Pharmacokinetics of enteric-coated cysteamine bitartrate in healthy adults: a pilot study. *Br J Clin Pharmacol* 2010; 70(3):376-82. PMID: 20716238
6. Okamura DM, Bahrami NM, Ren S, Pasichnyk K, Williams JM, Gangoiti JA, Lopez-Guisa JM, Yamaguchi I, Barshop BA, Duffield JS, Eddy AA. Cysteamine modulates oxidative stress and blocks myofibroblast activity in CKD. J Am Soc Nephrol. 25(1):43-54, 2014. PMID: 24009239
7. Dohil R, Cabrera BL, Gangoiti JA, Barshop BA, Rioux P. Pharmacokinetics of cysteamine bitartrate following intraduodenal delivery. *Fundam Clin Pharmacol* 2014; 28(2):136-43. PMID: 23113697.
8. Gertsman I, Johnson W, Nishikawa C, Gangoiti JA, Holmes B, Barshop BA. Diagnosis and monitoring of cystinosis using immunomagnetically purified granulocytes. *Clin Chem*, accepted

4) Domino liver transplantation in metabolic disease

Orthotopic liver transplantation may be life-saving controversial in metabolic disease, but since it may be less than completely curative, the procedure is controversial. Given that liver grafts are so precious and limited a resource, I we did the first domino transplantations in maple syrup urine disease and methylmalonic acidemia and showed that the explants from these patients may be used successfully used as grafts for other patients who would otherwise not be eligible to receive transplantation through conventional means.

1. Nyhan WL, Khanna A, Barshop BA, Naviaux RK, Precht AF, Lavine JE, Hart MA, Hainline BE, Wappner RS, Nichols S, Haas RH. Pyruvate carboxylase deficiency—insights from liver transplantation. *Molec Genet Metab* 2002; *77*(1): 143-149, PMID: 12359142
2. Barshop BA, Khanna A. Domino hepatic transplant in maple syrup urine disease. *New Engl J Med* 2005; 353(22): 2410-1. PMID: 16319396
3. Khanna A, Hart, M, Nyhan WL, Hassanein T, Panyard-Davis J, Barshop BA. Domino liver transplantation in maple syrup urine disease. *Liver Transplant* 2006; 12(5):876-82. PMID: 16628687
4. Khanna A, Gish R, Winter SC, Nyhan WL, Barshop BA. Successful Domino Liver Transplantation from a Patient with Methylmalonic Acidemia. JIMD Rep. 2015 Jul 29. PubMed PMID: 26219882.

5) Clinical metabolomics

My laboratory's major emphasis has been on metabolomics. Applications have included bacterial engineering, organic anon transporter systems, diabetic nephropathy, and human metabolic disorders, We developed a platform which combines targeted and discovery mode metabolomics.

1. Barshop BA. Metabolomic approaches to mitochondrial disease: correlation of urine organic acids. *Mitochondrion* 2004; 4/5-6:521-7. PMID: 16120410
2. Eraly SA, Vallon V, Vaughn DA, Gangoiti JA, Richter K, Nagle M, Monte JC, Rieg T, Truong DM, Long JM, Barshop BA, Kaler G, Nigam SK. Decreased renal organic anion secretion and plasma accumulation of endogenous organic anions in OAT1 knockout mice. *J Biol Chem* 2006; 281(8): 5072-83. PMID: 16354673
3. Wikoff WR, Gangoiti JA, Barshop BA, Siuzdak G. Metabolomics identifies perturbations in human disorders of propionate metabolism. *Clin Chem* 2007; 53(12):2169-76,. PMID: 17951291
4. Eraly SA, Vallon V, Rieg T, Gangoiti JA, Wikoff WR, Siuzdak G, Barshop BA, Nigam SK. Multiple organic anion transporters contribute to net renal excretion of uric acid. *Physiol Genomics*. 2008; 33(2):180-92. PMID: 18270321
5. Vallon V, Eraly SA, Wikoff WR, Rieg T, Kaler G, Truong DM, Ahn SY, Mahapatra NR, Mahata SK, Gangoiti JA, Wu W, Barshop BA, Siuzdak G, Nigam SK. Organic anion transporter 3 contributes to the regulation of blood pressure. *J Am Soc Nephrol* 2008; 19(9):1732-40. PMID: 18508962
6. Sharma K, Mathew AV, Gangoiti JA, Wassel CL, Saito R, Ix JH, Karl B, Sharma S, You Y, Wang L, Diamond-Stanic M, Ramachandra-Rao S, Lindenmeyer MT, Forsblom C, Ideker T, Cohen CD, Groop P-H, Barshop BA, Naviaux RK. Urine Metabolomics Reveals a Signature of Mitochondrial Dysfunction in Diabetic Kidney Disease. J Am Soc Nephrol 2013, 24(11):1901-12. PMID: 23949796.
7. McCloskey D, Gangoiti JA, King ZA, Naviaux RK, Barshop BA, Palsson BO, Feist AM. A model-driven quantitative metabolomics analysis of aerobic and anaerobic metabolism in E. coli K-12 MG1655 that is biochemically and thermodynamically consistent. Biotechnol Bioeng. Epub: doi: 10.1002/bit.25133, 2013. PMID: 24249002
8. Gertsman I, Gangoiti JA, Barshop BA. Validation of a dual LC–HRMS platform for clinical metabolic diagnosis in serum, bridging quantitative analysis and untargeted metabolomics. Metabolomics 10(2): 312-23, 2014, PMID: 25411574
9. Gertsman I, Barshop BA, Panyard-Davis J, Gangoiti JA, Nyhan WL. Metabolic Effects of Increasing doses of nitisinone in the treatment of alkaptonuria. *JIMD Rep*. 2015 Feb 10. [Epub] PMID: 25665838.
10. Gertsman I, Gangoiti JA, Nyhan WL, Barshop BA. Perturbations of tyrosine metabolism promote the indolepyruvate pathway via tryptophan in host and microbiome. *Mol Genet Metab*. 2015; 114(3):431-7. PMID: 2568092

List of Published Work in MyBibliography: http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/43215420

D. Research Support

Ongoing Research Support

R01 AG043120 (Schenk S, PI) 4/1/14 – 3/31/16
SIRT1 and muscle insulin sensitivity.
Goals: Apply metabolomics to determine mechanisms of insulin resistance; metabolomics instruction
Role: Project Director

DP3 DK094352-01: (Sharma K, PI) 9/30/11 – 6/30/16
Novel Paradigms in Diabetic Complications.
Goals: Correlate biomarkers and complications in lysosomal disease. Role: Co- Investigator

California Department of Public Health 7/1/14 – 6/30/17
Newborn Screening Metabolic Vendor Agreement.
Goals: Coordinate newborn screening follow-up, southernmost counties of California. Role: Project Director

U54 TR001339-01 (Firestein G, PI) 7/1/15 – 6/30/20
San Diego Clinical and Translational Research Institute.
Goals: Support clinical translational research. Role: Design, Biostatistics & Ethics Officer

R01 DK102813-01A1 (Purnell JQ, Gillingham M, PI) 4/1/15 – 3/31/20
Metabolomics of fatty acid oxidation effects on cataplerosis, metabolic control. Role: Co-Investigator.
Major Aim: Study metabolomics in animal models of fatty acid oxidation defects and effects of dietary odd-chain triglycerides.

Recently Completed Research Support

R03 HD069983: 8/15/11 – 7/31/13

Genetic factors involving expression of 3-methylcrotonyl-CoA carboxylase deficiency.

Goals: Correlate genome-wide associations with presence of symptoms in 3MCC-deficiency. Role: PI