BIOGRAPHICAL SKETCH

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NAME: Porter, Forbes Dennison

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

POSITION TITLE: Senior Investigator and Clinical 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
Washington University in St. Louis	B.A.	05/1982	Biology
Washington University in St. Louis	M.D., Ph.D.	05/1989	Medicine, Biology
St. Louis Children's Hospital	Residency	07/1992	Pediatrics
Washington University in St. Louis	Residency	07/1996	Clinical Genetics

A. Personal Statement

My research group investigates molecular, biochemical, cellular, and developmental processes that underlie genetic syndromes. Specifically, my research has focused on two rare genetic disorders, Smith-Lemli-Opitz syndrome, and Niemann-Pick Disease, type C1. Smith-Lemli-Opitz syndrome (SLOS) is an inborn error of cholesterol synthesis that results in birth defects and cognitive impairment. Niemann-Pick Disease, type C1 (NPC1) is a neurodegenerative, lysosomal storage disease due to impaired intracellular cholesterol transport. I have a clinical background in both Pediatrics and Medical Genetics, and my basic science training focused on using mouse models to study malformation syndromes. The goal of my research efforts is to combine both my basic science and clinical expertise to develop and test novel therapeutic interventions for SLOS and NPC1. My laboratory work has focused on development and characterization of mouse models to gain insight into pathological processes underlying these genetic disorders. This basic science work complements my clinical work in that we have built large cohorts of both SLOS and NPC1 subjects that span the clinical spectrum of both disorders. The combination of both basic and clinical science efforts in my research group truly allows for both an integrated bench-to-bedside and bedside-to-bench approach toward understanding the pathology of these disorders and developing therapeutic interventions.

B. Positions and Honors

Positions and Employment

1993-1996	Senior Staff Fellow, LMGD, NICHD, NIH
1996-2006	Investigator, HDB, NICHD, NIH
2006-present	Senior Investigator, PDEGEN, NICHD, NIH
2009-2011	Deputy Program Head, PDEGEN, NICHD, NIH
2010-present	Director, Molecular Genomics Laboratory, NICHD, NIH
2010-2011	Acting Clinical Director, NICHD, NIH
2011-present	Clinical Director, NICHD, NIH
2011-2013	Acting Program Head, PDEGEN, NICHD, NIH
2013-2015	Program Head, PDEGEN, NICHD, NIH
2015-present	Clinical Director, NCATS, NIH

Other Experience and Professional Memberships

1993-2014	Diplomat American Board of Pediatrics
1996-present	Diplomat American Board of Medical Genetics (Clinical Genetics)
2000-2003	Pharmacy and Therapeutics Committee, NIH Clinical Center
2002	Elected to the Society for Pediatric Research
2002-2007	NICHD Clinical Protocol Institutional Review Board
2005-present	Fellowship Executive Committee NIH Genetics Fellowship Program
2006-present	Smith-Lemli-Opitz/RSH Foundation Medical Advisory Board
2010-present	National Niemann-Pick Disease Foundation Scientific Advisory Board

Honors

1981	Phi Beta Kappa, Washington University in St. Louis
1982	Summa Cum Laude, Washington University in St. Louis
1989	Alpha Omega Alpha, Washington University Medical School
1995	Fellows Award for Research Excellence, NICHD, NIH
2013	National Institutes of Health Award of Merit
2013	National Institutes of Health Directors Award
2014	Dana Angles Research Trust, Guardian Angel Award
2015	National Center for Advancement of Translational Science Director's Award
2015	National Institutes of Health Award of Merit
2015	National Institutes of Health Directors Award

C. Contributions to Science

1. My research group has a longstanding interest in Smith-Lemli-Opitz syndrome (SLOS) and malformation/cognitive impairment syndromes due to inborn errors of cholesterol synthesis. My group initially cloned the DHCR7 gene and demonstrated that mutations of *DHCR7* underlie SLOS. We have also produced multiple mouse models corresponding to SLOS, lathosterolosis, desmosterolosis, and DHCR14 deficiency. Recent work has included producing an SLOS zebrafish model and induced Pluripotent Stem cells for both SLOS and lathosterolosis. These model systems are used to understand biological processes contributing to the malformations and cognitive dysfunction observed in these disorders and to develop potential therapies. This basic work complements a longstanding natural history trial of SLOS and placebo-controlled trials of dietary cholesterol supplementation and simvastatin.

a. Wassif, C.A., Maslen, C., Kachilele-Linjewile, S., Lin, D., Linck, L.M., Connor, W.E., Steiner, R.D., **Porter, F.D.** (1998) Mutations in the Human Sterol Δ^7-Reductase Gene at 11q12-13 Cause Smith-Lemli- Opitz Syndrome. Am. J. Hum. Genet. 63, 55-62. PMID: 9634533
b. Correa-Cerro, L.S., Wassif, C.A., Kratz, L., Miller, G.F., Munasinghe, J.P., Grinberg, A., Fliesler, S.J., **Porter, F.D.** (2006) Development and Characterization of a Hypomorphic Smith-Lemli-Opitz Syndrome Mouse Model and Efficacy of Simvastatin Therapy. Hum. Mol. Genet. 15: 839-851. PMID 16446309
c. Jiang, X-S, Wassif, C.A., Backlund, P.S., Song, L., Holtzclaw, L.A., Li, Z., Yergey, A.L., **Porter, F.D.** (2010) Activation of Rho GTPases in Smith-Lemli-Opitz Syndrome: Pathophysiological and Clinical Implications. Hum. Mol. Genet. 19: 1347-1357. PMID: 20067919
d. Francis KR*, Ton AN*, Xin Y, O'Halloran PE, Wassif CA*, Malik N, Williams IM*, Cluzeau CV*, Trivedi NS, Pavan WJ, Cho W, Westphal H, **Porter FD**. Modeling Smith-Lemli-Opitz Syndrome with Induced Pluripotent Stem Cells Reveals a Causal Role for Wnt/Beta-Catenin Defects in Neuronal Cholesterol Synthesis Phenotypes. Nature Medicine. 2016. PubMed PMID: 26998835.

2. My research group studies basic, translational, and clinical aspects of Niemann-Pick disease, type C1 (NPC1). NPC1 is a lysosomal storage disorder of cholesterol that is phenotypically characterized by progressive neurodegeneration. As part of a longitudinal Natural History/Observational study (06-CH-0186) we have developed a neurological severity scale to delineate disease progression and have collaborated to develop a sensitive and specific blood-based diagnostic test. This Natural History study has also supported biomarker development by both my laboratory and collaborating groups. Building on collaboration with multiple extramural groups and NCATS, my group is completing a Phase 1/2a trial of intrathecal 2-hydroxypropyl-β-cyclodextrin therapy for NPC1. This later work has transitioned to a Phase 2b/3 multicenter, multinational trial

for which I am a co-principal investigator. My research group is also engaged in a Phase 1/2a trial of vorinostat therapy for NPC1.

a. Yanjanin, N.M., Vélez, J.I., Gropman, A., King, K., Bianconi, S.E., Conley, S.K., Brewer, C.C., Solomon, B., Pavan, W.J., Arcos-Burgos, M., Patterson, M.C., **Porter, F.D.** (2010) Linear Clinical Progression, Independent of Age of Onset, in Niemann-Pick Disease, type C. Am. J. Med. Genet. Part B: Neuropsychiatric Genetics. 153B: 132-140. PMID 19415691
b. **Porter, F.D**., Scherrer, D.E., Lanier, M.H., Langmade, S.J., Molugu, V., Gale, S.E., Olzeski, D., Sidhu, R., Dietzen, D.J., Fu, R., Wassif, C.A., Yanjanin, N.M., Marso, S.P., House, J., Vite, C., Schaffer, J.E., Ory, D.S. (2010) Cholesterol oxidation producs are sensitive and specific blood-based biomarkers for Niemann-Pick C1 disease. Science Translational Medicine. 2: 56ra81. PMID: 21048217
c. Wassif, C.A., Cross, J.L., Iben, J. Sanchez-Pulido, L., Cougnoux, A., Platt, F.M., Ory, D.S., Ponting, C.P., Bailey-Wilson, J.E., Biesecker, L.G., **Porter, F.D.** (2015) High Incidence of Unrecognized Visceral/Neurological Late-onset Niemann-Pick Disease, type C1 Predicted by Analysis of Massively Parallel Sequencing Data Sets. Genetics in Medicine. Epub ahead of print PMID: 25764212
d. Cougnoux A*, Cluzeau C*, Mitra S, Li R, Williams I*, Burkert K*, Xu X, Wassif CA*, Zheng W, Porter FD. Necroptosis in Niemann-Pick Disease, Type C1: A Potential Therapeutic Target. Cell death & Disease. 2016;7:e2147. PubMed PMID: 26986514.

Complete List of Published Work in My Bibliography:

http://www.ncbi.nlm.nih.gov/sites/myncbi/forbes.porter.1/bibliograpahy/47421977/public/?sort=date&direction=ascending

3. The following Clinical Protocols and IND's have supported my research groups clinical work:

a. Investigational New Drug Applications

2003-2010	Simvastatin suspension for treatment of Smith-Lemli-Opitz syndrome IND 67,321 Holder and Sponsor
2009-2011	N-acetyl cysteine for treatment of Niemann-Pick Disease, type C IND 106,112 Holder and Sponsor
2012-2014	Intraventricular 2-hydroxypropyl-β-cyclodextrin for treatment of Niemann-Pick Disease, type C1 IND 113,273 Holder and Sponsor (Transferred to Vtesse Inc.)

b. Clinical Protocols

1998-present	Clinical and Basic Investigations into Smith-Lemli-Opitz Syndrome (98-CH-0081) Principal and Accountable Investigator
2001-2003	Carrier Frequency and Incidence of Smith-Lemli-Opitz Syndrome in African Americans (01-CH-0191) Principal and Accountable Investigator
2002-present	Investigations into Inborn Errors of Cholesterol Synthesis and Related Disorders (02-CH-0311) Principal and Accountable Investigator
2003-present	Investigations of Simvastatin Therapy in Smith-Lemli-Opitz Syndrome (03-CH-0225) Principal and Accountable Investigator
2005-2009	Short-term Behavioral Effects of Cholesterol Therapy in Smith-Lemli-Opitz Syndrome (05-CH-0168) Principal and Accountable Investigator
2006-present	Evaluation of Biochemical Markers and Clinical Investigation of Niemann-Pick Disease, Type C (06-CH-0186) Principal and Accountable Investigator
2009-2014	Biomarker Validation for Niemann-Pick Disease, type C: Safety and Efficacy of N-Acetyl Cysteine (09-CH-0185) Principal and Accountable Investigator

2009-2014 Cholesterol in Autism Spectrum Disorder (ASD): Characterization and Treatment (09-CH-0203)
Principal and Accountable Investigator

2009-present Exome Sequencing in Autistic Spectrum Disorder Patients with Altered Cholesterol Homeostasis (10-CH-0022)
Principal and Accountable Investigator

2012-present Intrathecal 2-Hydroxypropyl-β-cyclodextrin in patients with Niemann-Pick Disease type C (13-CH-0001)
Principal and Accountable Investigator

2014-present Phase I/II study of Vorinostat Therapy in Niemann-Pick Disease, type C1 (14-CH-0102)
Principal and Accountable Investigator

2015-present A Phase 2b/3 Prospective, Randomized, Double-Blind, Sham-Controlled Trial of VTS270 (2-hydroxypropyl-β-cyclodextrin) in Subjects with Neurologic Manifestations of Niemann-Pick Type C1 (NPC1) Disease (16-CH-0016)
Principal and Accountable Investigator

D. Research Support

Ongoing Research Support

1996-present NICHD Intramural Research Program
2014-2017 OU1HD079065 Phase 1 Vorinostat Trial in NPC1
2015 Ara Parseghian Medical Research Foundation (Vorinostat trial support)
2015 Ara Parseghian Medical Research Foundation (Necroptosis)

Completed Research Support related to NPC1

2009-2012 Ara Parseghian Medical Research Foundation (NPC1 Natural History Study)
2010-2011 NIH Bench-to-Bedside Award
2010-2011 Therapeutics for Rare and Neglected Diseases (HPβCD development)
2011-2012 NIH Bench-to-Bedside Award
2012-2013 National Niemann Pick Disease Foundation (NPC CSF Proteomics)
2014-2015 NICHD Director's Award Grant