BIOGRAPHICAL SKETCH

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NAME: Sheffield, Val Cowley

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POSITION TITLE: Professor of Pediatrics, and Ophthalmology and Visual Sciences; Division of Medical Genetics and Genomics; Roy J. Carver Chair in Molecular Genetics; Carver College of Medicine, University of Iowa

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)*	Start Date MM/YYYY	Completion Date MM/YYYY	FIELD OF STUDY
Brigham Young University, Provo, Utah	B.S.	08/1971	08/1974	Zoology
Brigham Young University, Provo, Utah	M.S.	08/1974	08/1977	Developmental Biology
University of Chicago, Chicago, Illinois	Ph.D.	08/1978	12/1983	Developmental Biology
University of Chicago, Chicago, Illinois	M.D. (honors)	08/1979	06/1985	Medicine
University of California, San Francisco	Residency	08/1985	06/1987	Pediatrics
University of California, San Francisco	Fellowship	08/1987	06/1990	Medical Genetics

A. Personal Statement

Dr. Sheffield is a well-established physician-scientist and former Howard Hughes Medical Institute investigator (1997-2017) focused on understanding the pathophysiology and improving management of human genetic diseases including both Mendelian disorders and genetically complex diseases. His laboratory has contributed to a better understanding of hereditary blindness, obesity, diabetes and hypertension. This work includes (i) identifying the genes involved in specific hereditary diseases; (ii) determining the molecular functions of the genes/proteins associated with these disorders; (iii) determining genetic and protein interactions, as well as the protein complexes and networks involved; (iv) developing animal models of inherited diseases to aid in determining the disease-specific pathophysiology; and (v) utilizing animal models to develop interventions and treatments. His laboratory has made substantial contributions in all these areas and has extensive expertise in genetics, cell biology, pathophysiology, and animal models. Recently, his laboratory has developed a novel non-invasive treatment for oxidative stress-related disorders.

1. Carter CS, Huang SH, Searby CC, Cassaidy B, Miller MJ, Grzesik WJ, Piorczynski TB, Zhang Q, Bradberry K, Pak TK, Walsh SA, Dick DW, Akurathi V, Acevedo M, Mapuskar KA, Milne GL, Hinton A, Guo, DF, Hubert-Falls KC, Wagner BA, Carter WA, Wang K, Norris AW, Rahmouni K, Buettner GR, Hansen JM, Spitz DR, Abel ED, and **Sheffield VC**. Static magnetic and electric fields treat type 2 diabetes via redox dependent mechanisms. *Cell Metabolism*. 2020 32(4) 561-574.
2. Mykytyn K, Nishimura DY, Searby CC, Shastri M, Yen HJ, Beck JS, Braun T, Streb LM, Cornier AS, Cox GF, Fulton AB, Carmi R, Lüleci G, Chandrasekharappa SC, Collins FS, Jacobson SG, Heckenlively JR, Weleber RG, Stone EM, **Sheffield VC**. Identification of the gene (BBS1) most commonly involved in Bardet Biedl syndrome, a complex human obesity syndrome. Nat Genet 2002 4:435-8 PMID12118255 PMC37923
3. Seo S, Zhang Q, Bugge K, Breslow DK, Searby CC, Nachury MV, **Sheffield VC**. A novel protein LZTFL1 regulates ciliary trafficking of the BBSome and Smoothened. *PLoS Genet* 2011 7(11):e1002358 PMID 22072986 PMC3207910

4. Davis RE, Swiderski RE, Rahmouni K, Nishimura DY, Mullins RF. Agassandian K, Philp AR, Searby CC, Andrews MP, Thompson, S, Berry CJ, Thedens DR, Yang B, Weiss RM, Cassell MD, Stone EM, and **Sheffield VC**. A knock-in mouse model of the Bardet-Biedl syndrome 1 M390R mutation has cilia defects, ventriculomegaly, retinopathy and obesity. *Proc Natl Acad Sci* 2007 104 (49) 19422-7 PMID:18032602PMC2148305

B. Positions, Scientific Appointments and Honors

Positions

1998-	Professor, Department of Ophthalmology and Visual Sciences, University of Iowa
1998-	Professor, Department of Pediatrics, University of Iowa, Iowa City, Iowa
1997-2019	Director, Division of Medical Genetics, University of Iowa Carver College of Medicine
1997-2017	Investigator, Howard Hughes Medical Institute
1994-1998	Associate Professor, University of Iowa, Iowa City, Iowa
1990-1994	Assistant Professor, University of Iowa, Iowa City, Iowa
1978-1983	Graduate Assistant, Developmental Biology, University of Chicago
1974-1977	Graduate Assistant, Developmental Biology Program, Brigham Young University

Other Experience and Professional Memberships

2014-2018	NIH NHGRI Advisory Council
2012-2018	NIH NHGRI H3Africa Expert Panel
2010-2015	NIH NHGRI Undiagnosed Disease Program Advisory Panel
2006-2010	NIH National Advisory Eye Council
2002	NHGRI Genetics Disease Research Branch Review Panel
2002-2005	Board of Directors of the American Society of Human Genetics
2000-2002	Program Committee for American Society of Human Genetics
2000	NHGRI Blue Ribbon Review Panel
1999-2003	Member NIH Genome Research Review Committee
1999-2002	Council Member of Society for Pediatric Research
1999	Member of Special NIH Panel to review sequencing centers
1997-2002	Member of NIH Center for Inherited Disease Research (CIDR) grant review panel
1995-2000	Member of NIH Genetic Determinants of High Blood Pressure Data Safety Monitoring Board
1994-1999	Member of NIH Marshfield Clinic Genotyping Center Review Committee
1993	Retinitis Pigmentosa Foundation Grant Review Study Section (Co-Chairman)

Honors

2021	Presidential Award for Outstanding Merit from Iowa Wesleyan University
2020	Elected Member, American Academy of Arts and Sciences
2019	Lewis Rudin Glaucoma Prize, New York Academy of Medicine
2014-present	Roy J. Carver Chair in Molecular Genetics, University of Iowa
2010	Honored Alumni Award, College of Life Sciences, Brigham Young University
2006-2014	Martin and Ruth Carver Chair in Genetics, University of Iowa
2005	Elected Member, National Academy of Medicine (formerly Institute of Medicine)
2004	Elected Member, American Association of Physicians
2003	E. Mead-Johnson Award for Pediatric Research from the Society for Pediatric Research
1998	Lewis Rudin Glaucoma Prize, New York Academy of Medicine
1990	Melvin Grumbach Pediatric Research Award, University of California, San Francisco
1988	Young Alumnus Achievement Award, Brigham Young University
1985	Graduated with Honors from University of Chicago, Pritzker School of Medicine
1985	F. Howell Wright Award for Outstanding Promise in Pediatrics, University of Chicago

C. Contributions to Science

1. Development of efficient disease gene discovery approaches. Work in my laboratory played a major role in the development of methods and improved approaches to facilitate human genetic disease mapping. This work includes major contributions to the completion of a high resolution polymorphic genetic map of the human genome (the first completed goal of the Human Genome Project). The genetic markers developed in my laboratory were highly informative and readily assayable using PCR. This contribution allowed for the efficient identification of disease genes, and the novel use of inbred populations for the mapping and identification of human disease genes. Polymorphic markers and genetic mapping methods developed in my laboratory have contributed to human disease gene identification by numerous laboratories around the world

a. **Sheffield VC**, Carmi R, Kwitek-Black A, Rokhlina T, Nishimura D, Duyk GM, Elbedour K, Sunden SL, Stone EM. Identification of a Bardet-Biedl syndrome locus on chromosome 3 and evaluation of an efficient approachto homozygosity mapping. *Hum Mol Genet* 1994 3(8):1331-1335 PMID 7987310

b. Murray, JC, Buetow KH, Weber JL, Ludwigsen S, Scherpbier-Heddema T, Manion F, Quillen J, **Sheffield VC**, Sunden S, Duyk GM, Weissenbach J, Gyapay G, Dib C, Morrissette J, Lathrop GM, Vignal A, White R,Matsunami N, Gerken S, Melis R, Albertsen H, Plaetke R, Odelberg S, Ward D, Dausset J, Cohen D, Cann H. A comprehensive human linkage map with centimorgan density. *Science* 1994 265:2049-2054 PMID 8091227

c. **Sheffield VC,** Weber JL, Buetow KH, Murray JC, Even DA, Wiles K, Gastier JM, Pulido JC, Yandava C, Sunden SL, Mattes G, Businga T, McClain A, Beck J, Scherpier T, Gilliam J, Zhong J, Duyk G. A collection of tri- and tetranucleotide repeat markers used to generate high quality, high resolution human genome-widelinkage maps. *Hum Mol Genet* 1995 4(10):1837-1844 PMID 8786107

d. **Sheffield VC**, Stone EM, Carmi R. Use of isolated inbred human populations for identification of disease genes. *Trends Genet* 1998 14(10):391-6 PMID 9820027

2. Identification of genes and mechanisms involved in a syndromic blindness disorder. In the early 1990's, my laboratory began studying a rare pleiotropic autosomal recessive disorder known as Bardet-Biedl syndrome (BBS), which has major features including blindness, obesity, diabetes and hypertension. My laboratory identified the first BBS locus and demonstrated that the disorder is genetically heterogeneous. Wehave been a leader in the identification of numerous genes involved in this syndrome. These gene discoveries have led to the understanding of the role of primary cilia and intracellular trafficking in several phenotypes including retinopathy, obesity, hypertension, and diabetes. We have created and utilized null BBS mouse models to dissect the mechanisms involved in abnormalities associated with BBS. For example, we demonstrated that obesity in BBS null mice is associated with leptin resistance by showing an attenuated effect of exogenous systemic and central leptin on body weight and food intake, even when endogenous leptin levels are normalized. Our studies demonstrate selective leptin resistance in that the BBS mice are resistant to the metabolic action of leptin. We also showed that BBS proteins regulate insulin receptor trafficking, explaining insulin resistance.

a. Kwitek-Black AE, Carmi R, Duyk GM, Buetow KH, Elbedour K, Parvari R, Yandava CN, Stone EM, **SheffieldVC**. Linkage of Bardet-Biedl syndrome to chromosome 16q and evidence for non-allelic genetic heterogeneity.*Nature Genet* 1993 5(4):392-396 PMID 8298649

b. Mykytyn K, Braun T, Carmi R, Haider NB, Searby CC, Shastri M, Beck G, Wright AF, Iannaccone A, ElbedourK, Riise R, Baldi A, Raas-Rothschild A, Gorman SW, Duyk DM, Jacobson SG, Casavant T, Stone EM, **Sheffield VC**. Identification of the gene that, when mutated, causes the human obesity syndrome BBS4. *Nature Genet* 2001 28(2):188-91 PMID 11381270

c. Rahmouni K, Fath MA, Seo S, Thedens DR, Berry CJ, Weiss R, Nishimura DY, **Sheffield VC** Leptin resistancecontributes to obesity and hypertension in mouse models of Bardet-Biedl syndrome. *J Clin Invest* 2008 118(4):1458-67 PMID:18317583 PMC2259435

d. Stark RD, Beyer AM, Guo DF, Boland L, Zhang Q, **Sheffield VC**, Rahomouni K. Regulation of insulin receptortrafficking by BBS Proteins. *PLoS Genet*. 2015 11(6):1005311 PMID 26103456 PMC4478011

3. The discovery of novel cellular protein complexes that play a role in intracellular trafficking and intraflagellar trafficking (IFT). By studying BBS and identifying numerous BBS genes, my laboratory played amajor role in identifying two protein complexes that are important to ciliogenesis, intraflagellar

trafficking and intracellular trafficking. In addition, we have worked out the assembly pathway of these complexes known as theBBSome and BBS chaperonin complex, which are important in many organ systems. Mutation of the proteins involved in these complexes lead to diverse phenotypes including retinopathy, diabetes, obesity, hypertension, renal anomalies, and others.

a. Nachury MV, Loktev AV, Zhang Q, Westlake CJ, Peranen J, Merdes A, Slusarski DC, Scheller RH, Bazan JF,**Sheffield VC**, Jackson PK. A core complex of BBS proteins cooperates with the GTPase Rab8 to promote ciliary membrane biogenesis. *Cell* 2007 15:129(6):1041-3 PMID 17574030
b. Seo S, Baye LM, Schulz NP, Beck JS, Zhang Q, Slusarski DC, **Sheffield VC**. BBS6, BBS10 and BBS12 forma complex with CCT/TRIC family chaperonins and mediate BBSome assembly. Proc Natl Acad Sci USA. 2010107(4): 1488-1493. PMID 20080638 PMC2814390
c. Zhang Q, Yu D, Seo S, Stone E, **Sheffield V**. Intrinsic protein-protein interaction mediated and chaperonin assisted sequential assembly of a stable Bardet Biedl syndrome protein complex, the BBSome. *J Biol Chem*2012 287(24):20625-35 PMID 22500027 PMC3370246
d. Hsu Y, Garrison JE, Kim G, Schmitz AR, Searby CC, Zhang Q, Datta P, Nishimura DY, Seo S, **Sheffield VC**.BBSome function is required for both the morphogenesis and maintenance of the photoreceptor outer segment. PLos Genet 2017 19;13(10):31007057 doi: 10.1371/journal.pgen 1007057 eCollection 2017 PMID29049287 PMC5663628

4. Identification of the first glaucoma gene and elucidation of the disease pathophysiology. Although there was evidence that glaucoma, the second leading cause of blindness, had inherited components, prior to our work there were no glaucoma loci or genes identified. My laboratory played a key role in the mapping and Identification of the first gene (*MYOC*) known to cause glaucoma, thus conclusively demonstrating that glaucomais a hereditary disease. In addition, we developed the first mouse model of glaucoma based on mutation of the discovered gene contributing to the elucidation of the pathophysiological mechanisms causing glaucoma. Our work has led to extensive research into the genetics and molecular mechanisms of glaucoma including the identification of other genes by our and other laboratories.

a. **Sheffield VC**, Stone EM, Alward WLM, Drack AV, Johnson AT, Streb LM, Nichols BE. Genetic linkage of familial open angle glaucoma to chromosome 1q21-q31. *Nature Genet* 1993 4:47-50 PMID 8513321
b. Stone EM, Fingert JH, Alward WLM, Nguyen TD, Polansky JR, Sunden SLF, Nishimura D, Clark AF, NystuenA, Nichols BE, Mackey DA, Ritch R, Kalenak JW, Craven ER, **Sheffield VC**. Identification of a gene that causes primary open angle glaucoma (GLC1A). *Science* 1997 275:668-670 PMID 9005853
c. Nishimura DY, Swiderski RE, Alward WLM, Searby CC, Patil SR, Bennett SR, Kanis AB, Gastier JM, Stone EM **Sheffield VC**. The forkhead transcription factor gene FKHL7 is responsible for glaucoma phenotypes which map to 6q25. *Nature Genet* 1998 19(2):140-147 PMID 9620769
d. Zode GS, Kuehn MH, Nishimura DY, Searby CC, Mohan K, Grozdanic SD, Bugge K, Anderson MG, Clark AF, Stone EM, **Sheffield VC**. Reduction in ER stress via a chemical chaperone prevents disease phenotypesin a mouse model of primary open angle glaucoma. *J. Clin. Invest.* 2011 121(9): 3542-3553 PMID 26237042PMC4563763

5. The discovery of novel mechanisms of genetic diseases leading to therapeutic modalities including genome editing. Our laboratory's work on genetic disorders has led to the understanding of several disease mechanisms for which we can now develop therapies based on the specific pathophysiology. For example, hydrocephalus is a common neurological disorder leading to enlargement of the cerebral ventricles. We employed a hydrocephalic mouse model of the human cilia-related disorder BBS and identified a major role for neural progenitor cells in the pathogenesis of neonatal hydrocephalus. We found that hydrocephalus is caused by aberrant PDGFRα signaling, resulting in increased apoptosis and impaired proliferation of NG2 $^{+}$PDGFRα^{+} neural progenitor cells. Targeting this pathway with lithium treatment rescued NG2 $^{+}$PDGFRα^{+} progenitor cell proliferation in BBS mutant mice, reducing the abnormal ventricular volume. In addition, we have been able to develop gene therapy for retinal diseases, and pharmacological therapy and gene editing therapy using CRISPR-Cas9 for the treatment of glaucoma, all based on the pathophysiology mechanisms discovered in our laboratory. Recently, the lab has developed a novel non-invasive **treatment for oxidative stress-related disorders including diabetes and cancer.**

a. Carter CS, Vogel TW, Zhang Q, Seo S, Swiderski RE, Moninger TO, Cassell MD, Thedens DR, Keppler- Noreuil KM, Nopoulos P, Nishimura DY, Searby CC, Bugge K, **Sheffield VC**. Abnormal development of NG2+PDGFR-a+ neural progenitor cells leads to neonatal hydrocephalus in a ciliopathy mouse model. *Nature Medicine* 2012 18(12):1797-804 PMID 23160237 PMC3684048

b. Seo S, Mullins RF, Dumitrescu AV, Bhattarrai S, Gratie D, Wong K, Stone EM, **Sheffield VC**, Drack AV. Subretinal gene therapy of mice with Bardet-Biedl Syndrome type 1. *Invest Ophthalmol Vis Sci* 2013 11;54(9):6118-32 PMID 23900607 PMC3771708

c. Jain A, Zode G, Kasetti RB, Ran FA, Yan W, Sharma TP, Bugge K, Searby CC, Fingert JH, Zhang F, Clark AF, **Sheffield VC**. CRISPR-Cas9-based treatment of myocilin-associated glaucoma. *Proc Natl Acad Sci USA*.2017 114(42):11199-11204 PMID 28973933 PMC5651749

d. Carter CS, Huang SH, Searby CC, Cassaidy B, Miller MJ, Grzesik WJ, Piorczynski TB, Zhang Q, Bradberry K, Pak TK, Walsh SA, Dick DW, Akurathi V, Acevedo M, Mapuskar KA, Milne GL, Hinton A, Guo, DF, Hubert- Falls KC, Wagner BA, Carter WA, Wang K, Norris AW, Rahmouni K, Buettner GR, Hansen JM, Spitz DR,Abel ED, and **Sheffield VC**. Static magnetic and electric fields treat type 2 diabetes via redox dependent mechanisms. *Cell Metabolism*. 2020 32(4) 561-574.

Complete List of Published Works:
http://www.ncbi.nlm.nih.gov/sites/myncbi/val.sheffield.1/bibliography/40873823/public/?sort=date&direction=ascending