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: Diane L. Barber, PhD

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

POSITION TITLE: Endowed Professor and Department Chair

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
University of California, Davis	BS	06/1975	Biological Sciences
University of California, Davis	MS	06/1977	Physiology
University of California, Los Angeles	PhD	03/1985	Anatomy
University of Massachusetts Medical Center	Postdoc	06/1987	Physiology

A. Personal Statement

A major aspect our research program is determining in molecular detail how intracellular (cytoplasmic) pH (pHi) dynamics regulates cell behaviors, with a focus on cancers. Although pHi was previously thought to be relatively constant as a homeostatic mechanism, we now know that pHi changes during normal cell cycle progression, cell migration, and cell differentiation. Moreover, pHi is dysregulated in diseases, including being constitutively increased in cancers. Our previous review on pHi and cancer (Webb et al., Nature Rev Cancer, 2011) has been cited by > 2300 publications. The molecular mechanisms mediating pHi-regulated cancer cell behaviors, however, remain understudied and largely unknown. Our work bridges protein structure and electrostatics with cell biology to reveal how pHi dynamics regulates cell behaviors through protonation of titrating amino acids as a posttranslational modification to regulate protein functions (Schönichen et al., 2013 Ann Rev Biophys. 42:289). We revealed the design principles and functions of “pH sensors” described as endogenous proteins regulated within the cellular pH range, including guanine nucleotide exchange factors regulating cell polarity (Frantz et al., 2007 J Cell Biol. 179:403), cofilin controlling actin assemblies (Frantz et al., 2008 J Cell Biol.183:865), β-catenin regulating tumorigenesis (White et al., 2018 J Cell Biol. 217:3965), talin (Srivastava et al., 2008 Proc Natl Acad Sci. 105:14436) and the focal adhesion kinase FAK (Choi et al., 2013 J Cell Biol. 202:849) controlling cell-substrate adhesion, and FOX family transcription factors regulating gene expression (Kisor et al., 2025 Nucleic Acids Res). We also found that increased pHi is necessary for adult and embryonic stem cell differentiation as well as lineage specification (Ulmschneider et al., 2016 J Cell Biol. 215:345-355; Benitez et al., 2019 Dev Biol. 452:127s, Liu et al., 2023 Nat Commun 14:3745). Through our work we developed new genetically encoded pHi biosensors that we used in clonal cells (Choi et al., 2013 J Cell Biol. 202:849; Webb et al., Mol Biol Cell 32:131; Infante and Barber, 2025 Mol Biol Cell 36:ar145) as well as in model organisms (Grillo-Hill et al., 2015 eLife. 4:e03270; Ulmschneider et al., 2016 J Cell Biol. 215:345-355).

B. Positions and Honors

Academic Positions

1977-1980 Lecturer, Department of Biology, University of California, Los Angeles
1980-1985 Predoctoral Fellow, Department of Anatomy, University of California, Los Angeles
1985-1987 NIH Postdoctoral Fellow (NRSA), Department of Physiology, University of Massachusetts Medical Center, Worcester, MA
1987-1991 Assistant Professor, Department of Surgery/Section of Anatomy, Yale University
1991-1995 Assistant Professor, Departments of Stomatology and Surgery, UCSF

1995-2001	Associate Professor, Departments of Stomatology and Surgery, UCSF
2001-2004	Professor, Department of Stomatology, UCSF
2005-2010	Professor and Vice-Chair, Department of Cell and Tissue Biology, UCSF
2010-2013	Endowed Professor and Interim Chair, Department of Cell and Tissue Biology, UCSF
2013-2022	Endowed Professor and Chair, Department of Cell and Tissue Biology, UCSF
2022-present	Recall Professor, Department of Cell and Tissue Biology, UCSF

Awards and Recognition

1985-1987	NIH Individual NRSA Postdoctoral Fellowship
1986	Joseph P. Healy Research Award, University of Massachusetts Medical Center
1995-2000	Established Investigator, American Heart Association
2001-2003	Vice-chair/Chair, Gordon Research Conference on Molecular Pharmacology
2010-2022	Leland A. and Gladys K. Barber Endowed Chair in Dentistry
2012	Elected AAAS Fellow
2012	Outstanding Faculty Mentor Award, UCSF Postdoctoral Scholars Association
2013	Faculty Research Lecture Award, UCSF School of Dentistry
2016-2019	Chair, Women in Cell Biology (WICB) for American Society of Cell Biology (ASCB)
2016-2021	Scientific Advisory Board Max Planck Institute for Experimental Medicine
2018-2022	Scientific Advisory Board European Consortium on pH and Ion Transport in Pancreatic Cancer
2019	Keynote Speaker, International Society for Cancer Metabolism (ISCaM) meeting, Portugal
2020,2021	Annual Student Invited Speaker. 2020 Department of Biochemistry and Molecular Biology, Johns Hopkins University; 2021 Program in Molecular Cell Biology, Brown University
2020	Excellence in Research and Mentoring Award, John Greene Society of School of Dentistry Students
2022	UCSF Annual Academic Senate Faculty Research Lecture Translational Science Award
2024	Elected Executive Board, Armenian Society of Fellows (ASOF)
2024	Elected Fellow, American Society for Cell Biology (ASCB)
2025	Chair, ARCS.ai: Advanced Research in Computational Sciences and Artificial Intelligence, Armenian Society of Fellows (ASOF)
2025	Annual Endowed Lectureship, University of Colorado Anschutz Medical Campus

C. Contributions to Science

1. Design principles of pH sensors

We pioneered a molecular understanding of how intracellular pH (pHi) dynamics regulates diverse cell processes. Our approaches bridge protein structure and electrostatics with cell biology. In collaboration with Matthew Jacobson at UCSF, nearly 20 years ago we began using the term “pH sensor” for proteins with activities and ligand binding affinities that are regulated within the narrow pHi range (Srivastava et al., 2006 Physiology 22:30) and this term has been widely adopted in the field. We had a major impact on the view of posttranslational modification by protons as a regulatory mechanism for protein structure and function, analogous to post-translational modification by phosphorylation and acetylation (Schönichen et al., 2013 Ann Rev Biophys. 42:289). Determining protein regulation by pHi dynamics has a number of challenges because protonation/deprotonation cannot be detected by mass spectrometry or antibodies and is not catalyzed by enzymes. However, our work has established that protein regulation by physiological pH changes includes classically defined modes such as specificity, allostery, coincidence detection and cooperativity. Moreover, because pHi dynamics can regulate multiple proteins in unison it can coordinate complex cell behaviors, including directed cell migration (2.1), dysplasia (2.3), stem cell differentiation (3.1-3.4), and how the higher pHi of cancer cells enables tumorigenic functions with charge-changing somatic mutations (2.4). Our most recent work on pH sensors identifies the molecular mechanism for pH-dependent β-catenin stability by an electrostatic interaction with the E3 ligase TrCP1 (1.4) and for transcription factor-DNA binding selectivity (Kisor et al., 2025 Nucleic Acids Res 53:gkaf474). Through our work on cell behaviors regulated by pHi dynamics we developed innovative approaches to modulate pHi, including optogenetic tools, and rigorously quantifying pHi dynamics with biosensors for single cell and *in vivo* analysis.

1.1 Frantz, C, Barreiro, G, Dominguez, L, Chen, X, Eddy, R, Condeelis, J, Kelly, M, Jacobson, MP and Barber, DL. 2008 Cofilin is a pH sensor for actin free barbed end formation. J Cell Biol. 183:865-879 (Highlighted in Journal) PMID:19029335; PMCID: PMC2592832

1.2 Srivastava, J, Barreiro, G, Groscurth, S, Gingras, AR, Goult BT, Critchley DR, Kelly MJ, Jacobson MP, Barber DL. 2008 Structural model and functional significance of pH-dependent talin-actin binding for focal adhesion remodeling. Proc Natl Acad Sci U S A. 105(38):14436-41. PMID: 18780792

1.3 Choi, CC, Webb, BA, Chimenti, MS, Jacobson, MP and Barber, DL. 2013 pH sensing by FAK-His58 regulates focal adhesion remodeling. J Cell Biol. 202:849-59. [Commentary: C. Lawson and D. D. Schlaepfer, "pHocal adhesion kinase regulation is on a FERM foundation", J Cell Biol. 202:833-836.] [Commentary: K. Legg, "Factoring pH into FAK phosphorylation", Cell Migration Gateway]. PMID:24043700; PMCID: PMC3776353

1.4 White, KA, Grillo-Hill, BK, Esquivel, M, et al. and Barber, DL. 2018 β-catenin is a pH sensor with decreased stability at higher intracellular pH. J Cell Biol. 217:3965-3976. (Republished in a special JCB edition on noteworthy work for 2018) PMID: 30315137; PMCID: PMC6219716

2. pHi dynamics and cancer cell behaviors

We made seminal findings on a molecular understanding of how dysregulated pHi dynamics contributes to cancer cell behaviors, including highly cited reviews (Webb et al., 2011 Nature Cancer Rev. 11:671; White et al., 2017 J Cell Sci. 130:663). Our work revealed how the higher pHi of cancer cells promotes directed cell migration (2.1), proliferation (2.2), dysplasia (2.3), and metabolic reprogramming (Manoli et al., 2021 Am J Physiol Cell Physiol. 321:C147) as well as enables the tumorigenic functions of charge changing mutations (2.4).

2.1 Denker, SP and Barber, DL. 2002 Cell migration requires both ion translocation and cytoskeletal anchoring by the Na-H exchanger NHE1. J Cell Biol. 159:1087-1096. (Highlighted in Journal [Using acid to find direction. J Cell Biol. 2002 159:911]) PMID: 12486114; PMCID: PMC2173980

2.2 Putney, L.K., and Barber, D.L. 2003 Na-H exchange-dependent increase in intracellular pH times G2/M entry and transition. J. Biol. Chem. 278:44645-44649. PMID: 12947095

2.3 Grillo-Hill, BK, Choi, CC, Jimenez-Vidal, M and Barber, DL. 2015 Increased H+ efflux is sufficient to induce dysplasia and necessary for viability with oncogene expression. eLife. 4:e03270. PMID: 25793441; PMCID: PMC4392478

2.4 White, KA, Garrido Ruiz, G, Szpiech, ZA, Strauli, NB, Hernandez, RD, Jacobson, JP and Barber, DL. 2017 Cancer-associated arginine to histidine mutations confer a gain in pH sensing to mutant proteins. Sci. Signaling 10(495). pii: eaam9931. PMID: 28874603; PMCID: PMC6022362

3. pHi and actin filament dynamics for stem cell differentiation

We are one of the first groups to identify a role for pHi dynamics in stem cell differentiation. Using three different models; mouse embryonic stem cells (3.1), adult Drosophila follicle stem cells (3.1, 3.2), and mouse intestinal stem cells (3.3) we showed that stem cells have a lower pHi than differentiated daughter cells and that blocking increased pHi inhibits stem cell differentiation as well as lineage specification. Additional work reported for the first time how the Arp2/3 complex and actin filament remodeling regulate mouse (Aloisio et al., 2002 Stem Cell Reports 17:1-16) and human (Meyer et al., 2024 eLife 13:e89725) embryonic stem cell differentiation.

3.1 Ulmschneider, B, Grillo-Hill, BK, Benitez, M, Azimova, D, Barber. DL and Nystul, T.G. 2016 Increased intracellular pH is necessary for adult epithelial and embryonic stem cell differentiation. J Cell Biol. 215:345-355 (featured focus article in journal). PMID: 27821494; PMCID: PMC5100294

3.2 Benitez, M, Tatapudy S, Barber, DL, Nystul, T. 2019 Drosophila anion exchanger 2 is required for proper ovary development and oogenesis. Dev Biol. 452:127-133. PMID: 31071312

3.3 Liu Y, Reyes E, Castillo-Azofeifa D, Klein OD, Nystul T, Barber DL. 2023 Intracellular pH dynamics regulates mouse small Intestinal stem cell lineage specification. Nat Commun 14(1):3745. Highlighted in Bakar Ageing Research Institute Newsletter. PMID: 37353491; PMCID: PMC10290085

3.4 Tatapudy, S, Aloisio, F, Barber, DL, Nystul, T. 2017 Cell fate decisions: emerging roles for metabolic signals and cell morphology. EMBO Reports 18:2105-2118. PMID: 29158350; PMCID: PMC5709733

4. Molecular regulation of ion transport proteins

We made major contributions to understanding how signaling mechanisms directly regulate the activity of plasma membrane ion transporters and how ion transport proteins function as signaling platforms, the later reviewed in Denker et al., 2002 Curr. Opin. Cell Biol. 14:214; Meima et al., 2007 Curr. Opin. Nephrol. Hypertens. 16:365). We first showed that the ubiquitously expressed Na-H exchanger NHE1 anchors actin filaments by directly binding the ERM proteins ezrin, radixin and moesin (4.1) and subsequent work from other groups confirmed a similar anchoring mechanism for other NHE isoforms as well as other plasma membrane ion transport proteins.

This landmark study also showed that ERM binding/actin anchoring is necessary to localize NHE1 to the distal margin of membrane protrusions, which in turn is necessary for pHi dynamics to enable membrane protrusions and cell migration. We first identified that NHE1 is a substrate for the kinases Rho kinase ROCK (4.2), Akt (4.3), and NIK/MAP4K4 (Yan et al., 2001 J. Biol. Chem. 276:31349), including identifying distinct phosphorylated serine residues in NHE1 for these kinases as well as functional significance for growth factor and GPCR signaling and actin filament dynamics. We also first identified and cloned cDNA encoding a previously unknown calcium-binding protein we named CHP (calcineurin B homologous protein) through a genetic screen for NHE1-interacting proteins (4.4). This finding generated new directions that resulted in recognition of a CHP family of three distinct members belonging to a superfamily of calcium-binding proteins that includes calmodulin, calcineurin B, recoverin, Kv channel interacting proteins, frequinins, neruocalcins and integrin binding proteins. Moreover, work by our group and others has shown diverse regulatory functions for CHP family members in the activity of several ion transport proteins, intracellular vesicle trafficking and gene transcription.

4.1 Denker, SP. Huang, DC, Orlowski, J, Furthmayr, H and Barber, DL. 2000 Direct binding the Na-H exchanger NHE1 to ERM proteins regulates the cortical cytoskeleton and cell shape independently of H^+ translocation. Mol Cell 6:1425-1436. PMID: 11163215; no PMCID

4.2 Tominaga, T., Ishizaki, T., Narumiya, D., and Barber, D.L. 1998 p160ROCK mediates RhoA activation of Na-H exchange. EMBO J. 17:4712-4722. PMID: 9707430; no PMCID

4.3 Meima, ME, Webb, BE, Witkowska, HE, and Barber, DL. 2009 The Na-H exchanger NHE1 is an Akt substrate necessary for actin filament reorganization by growth factors. J Biol Chem. 284(39):26666-75. PMID:19622752; PMCID: PMC2785354

4.4 Lin, X and Barber, DL. 1996 A calcineurin homologous protein inhibits GTPase activation of Na-H exchange. Proc Natl Acad Sci. 93:12631-12636. PMID: 8901634; PMCID: PMC38044

5. Regulation of metabolic and cytoskeleton proteins

We made major contributions on a molecular understanding of the regulation and function of the metabolic enzyme phosphofuctokinase-1 (PFK-1), including the first reports on a crystal structure of human PFK-1 (5.1) and assembly into filaments (5.2). We also were the first to report that phosphorylation of the actin regulatory Arp2/3 complex increases nucleating activity and actin remodeling (5.3), including how phosphorylation is regulated by the kinase NIK/MAPK4K (LeClaire et al., 2002 J Cell Biol. 208:161). Our work on actin filament dynamics and regulatory proteins, including publications cited above, also includes showing critical roles in epithelial-mesenchymal transition (5.4).

5.1 Webb BA, Forouhar F, Szu FE, Seetharaman J, Tong L, Barber DL. 2015 Structures of human phosphofructokinase-1 and atomic basis of cancer-associated mutations. Nature 523:111-114. PMID: 25985179; PMCID: PMC4510984

5.2 Webb BA, Dosey AM, Wittmann T, Kollman J, Barber DL 2017 Filament assembly by the glycolytic enzyme phosphofructokinase 1. J Cell Biol 216:2305-2313. (Spotlight article in Journal "Strength in numbers: Phosphofructokinase polymerization prevails in the liver" J Cell Biol. 216:2239-2241). (Republished in a special J Cell Biol. edition on noteworthy work on cell biophysics) PMID: 28646105; PMCID: PMC5551713

5.3 LeClaire, LL III, Baumgartner, M, Iwasa, JH, Mullins, RD and Barber, DL. 2008 Phosphorylation of the Arp2/3 complex is necessary to nucleate actin filaments. J Cell Biol. 182:647-654. (Highlighted commentary in Journal 182:617) PMID: 18725535; PMCID: PMC2518704

5.4 Haynes, J., Srivastava, J., Madson, N., Wittmann, T and Barber, DL. 2011. Dynamic actin remodeling during epithelial-mesenchymal transition depends on increased moesin expression. Mol. Biol. Cell 22 4750-4764. PMID: 22031288; PMCID: PMC3237619

Complete List of Published Work in MyBibliography:

http://www.ncbi.nlm.nih.gov/sites/myncbi/1zyn8uk9wTQQB/bibliography/40099561/public/?sort=date&direction=ascending

D. Additional information: Research Support

Current support

NIH R01 CA197855-01 (Barber) 04/01/2016-03/31/2028

Roles for intracellular pH dynamics in cancer

Cancer League (Barber) 07/01/26-06/30/27
Therapeutics restoring tumor suppressor activity of mutant p53

Completed support (past 5 years)
Cancer League (Barber) 06/01/2024-05/31/2025
Targeting mutant p53 as a cancer therapeutic

UCSF Alliance for Therapeutics in Neuroscience 07/01/2022-06/30/2024
Targeting lysosome pH to limit neurodegeneration

NIH R21DE032164 (Barber) 07/14/2022-07/13/2025
Regulation of transcription factor activity in neural crest development by pH dynamics

UCSF Catalyst (Barber) 07/01/2020-11/01/2021
New technology and therapeutic discovery targeting dysregulated lysosomes in cancer and neurodegenerative disorders

UCSF Program in Breakthrough Biomedical Research (Barber and M. Jacobson) 07/01/2020-06/31/2021
Intracellular pH-regulated transcription factor-DNA binding specificity

NSF P0538109 (Barber and T. Nystul) 08/01/2020-07/31/2022
The role of intracellular pH in the specification of cell fate

NSF 2203629 (Barber) 08/01/2022-07/31/2024
Protein biophysics for pH-regulated transcription factor-DNA binding selectivity