BIOGRAPHICAL SKETCH

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NAME: Campbell, Kevin P.

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

POSITION TITLE: Investigator, Howard Hughes Medical Institute, Director, Wellstone Muscular Dystrophy Specialized Research Center, Chair, Department of Molecular Physiology and Biophysics

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
Manhattan College, Bronx, NY	B.S.	05/1973	Physics
University of Rochester, Rochester, NY	M.S.	01/1976	Biophysics
University of Rochester, Rochester, NY	Ph.D.	09/1979	Biophysics
University of Toronto, Toronto, Canada	Postdoc	08/1981	Membrane Biochemistry

A. Personal Statement

My laboratory is focused on understanding the molecular, cellular and physiological basis of various forms of muscular dystrophy, and on developing therapeutic strategies to treat these diseases. My early studies at the University of Iowa focused on elucidating the structure and function of calcium channels and calcium release channels (ryanodine receptors) in skeletal muscle. For the past thirty years, however, my laboratory has actively investigated the molecular pathogenesis of muscular dystrophy. We have used biochemical, cell biological, genetic and physiological techniques to identify and define disease mechanisms that cause various forms of muscular dystrophy. We cloned and characterized dystroglycan, and demonstrated that it links the cytoskeleton to the extracellular matrix in skeletal muscle. My studies on dystroglycan have since led to significant insights into its basic function as an extracellular matrix receptor in skeletal muscle, its role in the maintenance of muscle-cell membrane integrity and its role in the molecular pathogenesis of glycosylation-deficient muscular dystrophy.

As Director of the University of Iowa's Wellstone Muscular Dystrophy Specialized Research Center for the past fifteen years, I have successfully led a collaborative team of investigators performing pre-clinical and clinical translational research on the various muscular dystrophies that arise from abnormal processing of the dystroglycan protein (dystroglycanopathies). Our research team has increased the understanding of the functional glycosylation of dystroglycan, identified and characterized novel dystroglycanopathy genes, revealed new clinical insights related to genotype-phenotype relationships, and provided critical diagnostic services to the broader neuromuscular research community.

As Center Director and head of my laboratory, I have been dedicated to maintaining the highest standards in research and providing outstanding research training and mentorship for many undergraduates, graduate students, and postdoctoral and clinical fellows at the University of Iowa. Many of my former trainees have embarked on promising research and clinical careers and are now leaders in the fields of physiology, neurology, molecular genetics, and cellular biology. Examples of publications from my graduate student trainees are listed below, with postdoctoral fellows' publications included among those listed in the Contributions to Science section. Undergraduate trainees are also often among the contributing authors.

- Lim, LE., Duclos, F., Broux, O., Bourg, N., Sunada, Y., Allamand, V., Meyer, J., Richard, I., Moomaw, C., Slaughter, C., Tome, FMS., Fardeau, M., Jackson, CE., Beckman, JS., and **Campbell, KP**. (1995) β-Sarcoglycan: Characterization and Role in Limb-Girdle Muscular Dystrophy Linked to 4q12. *Nat. Genet*. 11:257-65. PMID: 7581448.
- Gurnett, CA., De Waard, M., and **Campbell, KP**. (1996) Dual Function of the Voltage-Dependent Ca^{2+} Channel α2δ Subunit in Current Stimulation and Subunit Interaction. *Neuron* 16:431-440. PMID: 8789958.
- Bansal, D., Miyake, K., Vogel, SS., Groh, S., Chen, CC., Williamson, R., McNeil, PL., and **Campbell, KP**. (2003) Defective Membrane Repair in Dysferlin-Deficient Muscular Dystrophy. *Nature* 423:168-72. PMID: 12736685.
- Walimbe AS, Okuma H, Joseph S, Yang T, Yonekawa T, Hord JM, Venzke D, Anderson ME, Torelli S, Manzur A, Devereaux M, Cuellar M, Prouty S, Ocampo Landa S, Yu L, Xiao J, Dixon JE, Muntoni F, **Campbell KP**. (2020) POMK regulates dystroglycan function via LARGE1-mediated elongation of matriglycan. *eLife* 2020 Sep 25;9:e61388. PMID: 32975514, PMC7556876.

Ongoing and recently completed projects that I would like to highlight include:

Investigator, Campbell (PI) 10/01/1989-11/30/2024
Howard Hughes Medical Institute
Cell Biological Studies of Muscular Dystrophy
The overall goal of this project is to understand the molecular pathogenesis of muscular dystrophy.

2 P50 NS053672-18, Campbell (PI) 06/08/2005-06/30/2025
NIH/NINDS
Senator Paul D. Wellstone Muscular Dystrophy Specialized Research Center (MDSRC)
The overall goal of The University of Iowa MDSRC is to perform research on the various muscular dystrophies that arise from abnormal processing of the dystroglycan protein (dystroglycanopathies).

51823, Campbell (PI) 03/14/2021-03/13/2023
Pacific Northwest Center for Cryo-EM (PNCC)
Cryo-EM Structure of the Bifunctional Glycosyltransferase LARGE in Complex with its Substrate, Dystroglycan, Will Reveal the Mechanism of Matriglycan Polymerization
The overall goal of this project is to understand how LARGE1 polymerizes matriglycan on dystroglycan by determining the near-atomic resolution cryo-EM structures of LARGE1.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2005-	Director, Wellstone Muscular Dystrophy Specialized Research Center
2005-	Chair, Department of Molecular Physiology and Biophysics, University of Iowa
2005-2017	Professor, Department of Internal Medicine
2002-2005	Interim Department Chair, Department of Physiology and Biophysics, Univ. of Iowa
1999-	Roy J. Carver Biomedical Research Chair in Molecular Physiology and Biophysics
1997-	Professor, Dept. of Neurology, University of Iowa
1989-	Investigator, Howard Hughes Medical Institute
1988-	Professor, Dept. of Molecular Physiology and Biophysics, University of Iowa
1989-1999	University of Iowa Foundation Distinguished Professor of Physiology and Biophysics
1985-1988	Associate Professor, Dept. of Molecular Physiology and Biophysics, University of Iowa
1981-1985	Assistant Professor, Dept. of Molecular Physiology and Biophysics, University of Iowa
1979-1981	Postdoctoral Fellow with Dr. David MacLennan, University of Toronto
1976-1978	Teaching Assistant, Undergraduate and Graduate Biochemistry, University of Rochester
1973-1977	Graduate Student, Department of Radiation Biology and Biophysics, University of Rochester

Honors

2020	Herbert Tabor Research Award, American Society for Biochemistry and Molecular Biology
2020	Tamio Yamakawa Award, Japan Consortium for Glycobiology and Glycotechnology
2017	Society for Glycobiology President's Innovator Award
2016	American Society for Cell Biology Lifetime Achievement Fellow

2009 March of Dimes Prize in Developmental Biology
2006 Elected to American Academy of Arts and Sciences
2005 Carver College of Medicine Distinguished Mentor Award
2004 Elected to the National Academy of Sciences
2001 S. Mouchly Small, MDA Scientific Achievement Award
2000 G. Conte Prize for Basic Research, Mediterranean Society of Myology
1999 Elected to the National Academy of Medicine
1999 Roy J. Carver Biomedical Research Chair in Molecular Physiology and Biophysics
1997 Duchenne-Erb-Preis Award (German Muscular Dystrophy Association)
1995 INSERM/ Prix de l'Académie des Sciences
1994 International Albrecht Fleckenstein Award
1994 ASBMB-Amgen Award
1993 Muscular Dystrophy Association Service Merchandise Leadership Award
1984-1989 Established Investigator of the American Heart Association
1978-1981 Medical Research Council Postdoctoral Fellowship, University of Toronto
1973 Phi Beta Kappa, Manhattan College

Other Experience and Professional Memberships

2010- Co-Editor-in-Chief: Skeletal Muscle
2005-2009 Council Member, National Arthritis and Musculoskeletal and Skin Disease Advisory Council
2001-2005 Skeletal Muscle Biology and Exercise Physiology Study Section, National Institutes of Health
2000-2004 Editorial Board: Journal of Cell Biology
1996-2009 Muscular Dystrophy Association Scientific Advisory Committee
1991-1995 Physiology Study Section Member, National Institutes of Health
1989-1995 Muscular Dystrophy Association Fellowship Review Committee
1988-2001 Editorial Board: Journal of Biological Chemistry

C. Contributions to Science

1. Skeletal muscle excitation-contraction coupling and calcium channels

Muscle contraction is initiated by a depolarization of the transverse tubular membrane which in turn signals the release of Ca^{2+} from the junctional sarcoplasmic reticulum. One goal of my early research was to understand the structure and function of protein components of the junctional sarcoplasmic reticulum membrane. We purified the ryanodine receptor of rabbit muscle sarcoplasmic reticulum and showed that it can mediate single channel activity identical to that of the Ca^{2+} release channels of the sarcoplasmic reticulum. The morphology of the purified ryanodine receptor has revealed that the ryanodine receptor is identical to the "SR feet" and thus indicates that it plays a dual role in excitation-contraction coupling as the Ca^{2+} release channel and as the bridging structure in the junctional gap. A second goal of my research on excitation-contraction coupling concerned the dihydropyridine-sensitive Ca^{2+} channel of skeletal muscle and its dual role as a voltage sensor for excitation-contraction coupling and a Ca^{2+} channel. The dihydropyridine receptor was purified from rabbit skeletal muscle and shown to consist of four subunits (α1, α2δ, β and γ). We have determined the structure of the α2δ subunit and γ-subunit of the dihydropyridine receptor. We demonstrated that the β-subunit binds to a conserved domain within the α1 subunit of the calcium channel. Mutations within conserved domain alter the characteristic current stimulation and kinetic changes induced by the β-subunit and hence identify the critical importance of this interaction site in calcium channel regulation.

- Jay, SD, Ellis, SB, McCue, AF, Williams, ME, Vedvick, TS, Harpold, MM and **Campbell, KP**. (1990) Primary Structure of the γ Subunit of the DHP-Sensitive Calcium Channel from Skeletal Muscle. *Science* 248:490-492. PMID: 2158672.
- Witcher, DR., De Waard, M., Sakamoto, J., Franzini-Armstrong, C., Pragnell, M., Kahl, SD., and **Campbell, KP**. (1993) Subunit Identification and Reconstitution of the N-Type Ca^{2+} Channel Complex Purified from Brain. *Science* 261:486-489. PMID: 8392754.
- De Waard, M, Pragnell, M and **Campbell, KP**. (1994) Ca^{2+} Channel Regulation by a Conserved β Subunit Domain. *Neuron* 13:495-503. PMID: 8060623.

- Pragnell, M, De Waard, M, Mori, Y, Tanabe, T, Snutch, TP and **Campbell, KP**. (1994) Calcium Channel β Subunit Binds to a Conserved Motif in the I-II Cytoplasmic Linker of the α1-Subunit. *Nature* 368:67-70. PMID: 7509046.

2. Dystrophin-glycoprotein complex

In 1989 I began a series of experiments aimed at identifying membrane proteins that associate with dystrophin—the protein encoded by the Duchenne muscular dystrophy (*DMD*) gene—in order to understand its function in normal skeletal muscle. Using both biochemistry and molecular biology, I discovered the dystrophin-glycoprotein complex and established that it is essential for linking dystrophin (and thereby the cytoskeleton) to the extracellular matrix in skeletal muscle, and thereby protects the muscle-cell membrane from contraction-induced injury. Subsequent studies by my laboratory and others showed that mutations in genes encoding various components of the dystrophin-glycoprotein complex cause distinct forms of limb-girdle muscular dystrophy, as well as other congenital forms of muscular dystrophy.

- **Campbell, KP** and Kahl, SD. (1989) Association of Dystrophin and an Integral Membrane Glycoprotein. *Nature* 338:259-262. PMID: 2493582.
- Ervasti, JM, Ohlendieck, K, Kahl, SD, Gaver, M and **Campbell, KP.** (1990) Deficiency of a Glycoprotein Component of the Dystrophin Complex in Dystrophic Muscle. *Nature* 345:315-319. PMID: 2188135.
- Ervasti, JM and **Campbell, KP.** (1991) Membrane Organization of the Dystrophin-Glycoprotein Complex. *Cell* 66:1121-1131. PMID: 1913804.
- Matsumura, K, Tomé, FMS, Collin, H, Azibi, K, Chaouch, M, Kaplan, J-C, Fardeau, M, and **Campbell, KP.** (1992) Deficiency of the 50K Dystrophin-Associated Glycoprotein in Severe Childhood Autosomal Recessive Muscular Dystrophy. *Nature* 359:320-2. PMID: 1406935.

3. Dystroglycan: Novel extracellular matrix receptor

In 1992, my laboratory cloned dystroglycan and elucidated its function as an extracellular matrix receptor in muscle. We established that dystroglycan serves as an essential structural link between the cytoskeleton and the basement membrane that surrounds the cell, and that disruption of its expression and/or ability to interact with these structures is responsible for the pathogenesis of Duchenne muscular dystrophy. Although dystroglycan has been studied extensively, as late as 2011 no patient mutation had been identified in the encoding gene (DAG1). At that point, my laboratory identified a dystroglycan missense mutation in a patient with mild muscular dystrophy accompanied by cognitive impairment. Interestingly, the missense mutation in DAG1 leads to selective impairment of LARGE-mediated functional modification of the phosphorylated *O*-mannosyl residues on dystroglycan (i.e., that required for high-affinity laminin binding). Overall, my laboratory's studies revealed that the T192M substitution in mice recapitulates both the biochemical and pathological phenotypes of patients with dystroglycanopathies, even though all of the glycosyltransferases are normally expressed.

- Ibraghimov-Beskrovnaya, O, Ervasti, JM, Leveille, CJ, Slaughter, CA, Sernett, SW, and **Campbell, KP.** (1992) Primary Structure of Dystrophin-Associated Glycoproteins Linking Dystrophin to the Extracellular Matrix. *Nature* 355:696-702. PMID: 1741056.
- Ervasti, JM and **Campbell, KP.** (1993) A Role for the Dystrophin-Glycoprotein Complex as a Transmembrane Linker Between Laminin and Actin. *J. Cell Biol. 122*:809-23. PMID: 8349731.
- Cohn, RD., Henry, MD., Michele, DE., Barresi, R., Saito, F., Moore, SA., Flanagan, JD., Skwarchuk, MW., Robbins, ME., Mendell, JR., Williamson, R., and **Campbell, KP**. (2002) Disruption of *Dag1* in Differentiated Skeletal Muscle Reveals a Role for Dystroglycan in Muscle Regeneration. *Cell* 110:639-48. PMID: 12230980
- Hara, Y, Balci, B, Kanagawa, M, Beltran-Valero de Bernabe, D, Gundesli, H, Yoshida-Moriguchi, T, Willer, T, Satz, JS, Burden, SJ, Oldstone, MBA, Accardi, A, Talim, B, Muntoni, F, Topaloglu, H, Dincer, P and **Campbell, KP.** (2011) A Dystroglycan Mutation Associated with Limb-Girdle Muscular Dystrophy. *N. Eng. J. Med.* 364: 939-46. PMID: 21388311.

4. Disruption of the post-translational processing of dystroglycan and congenital muscular dystrophies

In 2002, we found that O-linked glycosylation of α-dystroglycan is required for its binding to extracellular matrix ligands and that abnormal post-translational processing of α-dystroglycan results in loss of its function as an extracellular matrix receptor in various congenital muscular dystrophies. We demonstrated that glycosylation defects in dystroglycan are central to the skeletal muscle pathology and the developmental brain abnormalities seen in congenital muscular dystrophies including Walker-Warburg syndrome, muscle-

eye-brain disease and Fukuyama congenital muscular dystrophy. Overall, this research has revolutionized our understanding of the molecular basis of these devastating diseases and has profound clinical implications for the diagnosis and treatment of congenital muscular dystrophies with developmental brain abnormalities.

- Michele, DE, Barresi, R, Kanagawa, M, Saito, F, Cohn, RD, Satz, JS, Dollar, H, Nishino, I, Kelley, RI, Somer, H, Straub, V, Mathews, KD, Moore, SA and **Campbell, KP.** (2002) Posttranslational Disruption of Dystroglycan-Ligand Interactions in Congenital Muscular Dystrophies. *Nature 418*:417-422. PMID: 12140558.
- Barresi, R, Michele, DE, Kanagawa, M, Harper, HA, Dovico, SA, Satz, JS, Moore, SA, Zhang, W, Schachter, H, Dumanski, JP, Cohn, RD, Nishino, I and **Campbell, KP.** (2004) LARGE Can Functionally Bypass α-Dystroglycan Glycosylation Defects in Distinct Congenital Muscular Dystrophies. *Nat. Med.* 10:696-703. PMID: 15184894.
- Kanagawa, M, Saito, F, Kunz, S, Yoshida-Moriguchi, T, Barresi, R, Kobayashi, YM, Muschler, J, Dumanski, JP, Michele, DE, Oldstone, MB and **Campbell, KP.** (2004) Molecular Recognition by LARGE is Essential for Expression of Functional Dystroglycan. *Cell 117*:953-64. PMID: 15210115.
- Willer, T, Lee, H, Lommel, M, Yoshida-Moriguchi, T, Beltran Valero de Bernabe, D, Venzke, D, Cirak, S, Schachter, H, Vajsar, J, Voit, T, Muntoni, F, Loder, AS, Dobyns, WB, Winder, TL, Strahl, S, Mathews, KD, Nelson, SF, Moore, SA, and **Campbell, KP**. (2012) *ISPD* Loss-of-Function Mutations Disrupt Dystroglycan O-Mannosylation and Cause Walker-Warburg Syndrome. *Nat. Genet.* 44:575-80. PMID: 22522420.

5. <u>LARGE modification of dystroglycan</u>

Despite extensive efforts to identify the laminin-binding moiety on alpha-dystroglycan, its identity remained a mystery. At least 18 gene products, many of which are glycosyltransferases, are involved in biosynthesis of the functional alpha-dystroglycan modification. In 2010, we discovered that this modification is initiated by a unique *O*-linked trisaccharide, GalNAc-β1,3-GlcNAc-β1,4-Man-Ser/Thr, which is phosphorylated at position 6 of the mannose residue. This phosphorylated trisaccharide is required for laminin binding, via an unknown mechanism. In 2012, we showed that the bifunctional like-acetylglucosaminyltransferase (LARGE) synthesizes a polysaccharide that is comprised of alternating glucuronic acid (GlcA) and xylose (Xyl) residues. The LARGE-synthesized [-GlcA-β1,3-Xyl-α1,3-]$_n$ heteropolysaccharide (matriglycan) was shown to bind LG domain-containing proteins *in vitro*. We demonstrated that LARGE glycans on dystroglycan function as a tunable matrix scaffold to prevent dystrophy. These findings led us to propose that the ultrastructural organization of the basement membrane can be modified by extension of the LARGE-glycan. Our findings redefine the cellular significance of dystroglycan and support a new model for the underpinnings of dystroglycan-related disease. Most recently, we used a multidisciplinary approach to determine the structural basis of the high-affinity binding of laminin to dystroglycan. Crystal structures of the laminin LG4-5 region in complex with a LARGE-synthesized oligosaccharide revealed an unprecedented mechanism of carbohydrate recognition among animal lectins: one GlcA-β1,3-Xyl disaccharide unit straddles a calcium ion in the LG4 domain, with oxygen atoms from both sugars replacing calcium-bound water molecules. This chelating binding mode accounts for the unusually high affinity of this protein-carbohydrate interaction.

- Inamori, K, Yoshida-Moriguchi, T, Hara, Y, Anderson, ME, Yu, L and **Campbell, KP**. (2012) Dystroglycan Function Requires Xylosyl- and Glucuronyltransferase Activities of LARGE. *Science* 335: 93-96. PMID: 22223806.
- Yoshida-Moriguchi, T, Willer, T, Anderson, ME, Venzke, D, Whyte, T, Muntoni, F, Lee, H, Nelson, SF, Yu, L., **Campbell, KP.** (2013). SGK196 is a Glycosylation-Specific O-Mannose Kinase Required for Dystroglycan Function. *Science* 341: 896-9. PMID: 23929950.
- Goddeeris, MM, Wu, B, Venzke, D, Yoshida-Moriguchi, T, Saito, F, Matsumura, K, Moore, SA, **Campbell, KP.** (2013) Large Glycans on Dystroglycan Function as a Tunable Matrix Scaffold to Prevent Dystrophy. *Nature 503:* 136-40. PMID: 24132234.
- Briggs, D., Yoshida-Moriguchi, T., Zheng, T., Venzke, D., Anderson, M., Strazzulli, A., Moracci, M., Yu, L., Hohenester, E., **Campbell, KP**. (2016). Structural Basis of Laminin Binding to the LARGE Glycans on Dystroglycan. *Nat Chem Biol*. 12(10):810-814. PMID: 27526028.

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