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, Dept 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 twenty 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 recent Center trainees are listed below.

- de Greef JC, Slütter B, Anderson ME, Hamlyn R, O'Campo Landa R, McNutt EJ, Hara Y, Pewe LL, Venzke D, Matsumura K, Saito F, Harty JT, **Campbell KP**. Protective role for the N-terminal domain of α-dystroglycan in Influenza A virus proliferation. *Proc Natl Acad Sci U S A.* 2019 Jun 4;116(23):11396-11401. doi: 10.1073/pnas.1904493116. Epub 2019 May 16. PubMed PMID: 31097590; PubMed Central PMCID: PMC6561248.
- Inamori K, Willer T, Hara Y, Venzke D, Anderson ME, Clarke NF, Guicheney P, Bönnemann CG, Moore SA, **Campbell KP**. Endogenous glucuronyltransferase activity of LARGE or LARGE2 required for functional modification of α-dystroglycan in cells and tissues. *J Biol Chem.* 2014 Oct 10;289(41):28138-48. doi: 10.1074/jbc.M114.597831. Epub 2014 Aug 19. PubMed PMID: 25138275; PubMed Central PMCID: PMC4192470.
- Rader EP, Turk R, Willer T, Beltrán D, Inamori K, Peterson TA, Engle J, Prouty S, Matsumura K, Saito F, Anderson ME, **Campbell KP**. Role of dystroglycan in limiting contraction-induced injury to the sarcomeric cytoskeleton of mature skeletal muscle. *Proc Natl Acad Sci U S A.* 2016 Sep 27;113(39):10992-7. doi: 10.1073/pnas.1605265113. Epub 2016 Sep 13. PubMed PMID: 27625424; PubMed Central PMCID: PMC5047148.
- Turk R, Hsiao JJ, Smits MM, Ng BH, Pospisil TC, Jones KS, **Campbell KP**, Wright ME. Molecular Signatures of Membrane Protein Complexes Underlying Muscular Dystrophy. *Mol Cell Proteomics.* 2016 Jun;15(6):2169-85. doi: 10.1074/mcp.M116.059188. Epub 2016 Apr 20. PubMed PMID: 27099343; PubMed Central PMCID: PMC5083101.

B. Positions and Honors

Positions and Employment

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

Other Experience and Professional Memberships

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

Honors

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

2004 Elected to the National Academy of Sciences
2005 Carver College of Medicine Distinguished Mentor Award
2006 American Academy of Arts and Sciences
2009 March of Dimes Prize in Developmental Biology
2016 Lifetime Achievement Fellow, American Society for Cell Biology
2017 Society for Glycobiology President's Innovator Award
2019 Herbert Tabor Research Award, American Society for Biochemistry and Molecular Biology

C. Contributions to Science

1. Identification of basis of skeletal muscle excitation-contraction coupling and roles of 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 structure that bridges 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 determined the structure of the α2δ subunit and the γ-subunit of this receptor, and demonstrated that the β-subunit binds to a conserved domain within the α1 subunit of the calcium channel. We also discovered that mutations within conserved domain alter the characteristic current stimulation and kinetic changes induced by the β-subunit; this finding highlights 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. Identification and characterization of the dystrophin-glycoprotein complex and its links to disease

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 that it 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. Discovery that dystroglycan is a novel receptor for extracellular matrix proteins

In 1992, my laboratory cloned dystroglycan and revealed that it functions 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 in modification of the phosphorylated *O*-mannosyl residues on dystroglycan by the like-acetylglucosaminyltransferase LARGE1 (i.e., the modification required for high-affinity laminin binding). Overall, my laboratory's studies revealed that the T192M substitution in mouse LARGE 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. Discovery of disrupted post-translational processing of dystroglycan in 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 in various congenital muscular dystrophies abnormal post-translational processing of α-dystroglycan results in loss of its function as an extracellular matrix receptor. We demonstrated that glycosylation defects in dystroglycan are central to the skeletal muscle pathology and 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 it 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. Identifying the moiety that LARGE adds to α-dystroglycan and explaining the high-affinity of binding to laminin

Despite extensive efforts—by several groups and over the course of nearly twenty years—to identify the laminin-binding moiety on α-dystroglycan, its identity remained a mystery. At least 18 gene products, many of which are glycosyltransferases, are involved in biosynthesis of the functional modififcation of α-dystroglycan. 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 LARGE protein synthesizes a polysaccharide that is comprised of alternating glucuronic acid (GlcA) and xylose (Xyl) residues. The LARGE-synthesized $[\text{-GlcA-}\beta\text{1,3-Xyl-}\alpha\text{1,3-}]_n$ heteropolysaccharide (termed matriglycan) was shown to bind LG domain-containing proteins *in vitro*. We also demonstrated that LARGE glycans on α-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 both 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 α-dystroglycan. Crystal structures of the LG4-5 region of laminin in complex with a LARGE-synthesized oligosaccharide revealed mechanism of carbohydrate recognition that was unprecedented 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.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/kevin.campbell.1/bibliography/40337863/public/?sort=date&direction=descending

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

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.

5 U54 NS053672-15 — Campbell (PI) — 06/08/2005-06/30/2020
NIH/NINDS
Senator Paul D. Wellstone Muscular Dystrophy Specialized Research Center
The overall goal of this proposal is to create a Muscular Dystrophy Cooperative Research Center which will use translational research and advance diagnostic services to explore therapeutic strategies for the treatment of various forms of muscular dystrophy.