BIOGRAPHICAL SKETCH

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NAME: LOREN W RUNNELS

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

POSITION TITLE: PROFESSOR

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
Colorado School of Mines	B.S.	05/1991	Engineering Physics
Stony Brook University	Ph.D.	12/1997	Physiology & Biophysics
Harvard Medical School (postdoctoral training)		06/2002	Cell Biology & Biophysics

A. Personal Statement

I began my independent research career in 2002 at Rutgers-Robert Wood Johnson Medical School. My research activities have principally focused on elucidating the function and regulation of TRPM7 and the related TRPM6 channel, which can form heteroligomers with TRPM7. TRPM7 and TRPM6 play profoundly important roles in human physiology and disease, from control of system Mg homeostasis to the pathogenesis of cancer and stroke. Our group has also uncovered unique roles for the channels during embryonic development, demonstrating that TRPM7 and TRPM6 regulate cell intercalation during gastrulation. We are currently investigating the function and regulation of TRPM7 by CNNMs, a new class of proteins we recently identified. CNNMs and their binding partners PTP4A phosphatases are implicated in the cancer. An additional focus of our lab is to investigate the contribution of CNNMs and PTP4A to TRPM7-dependent oncogenesis.

Ongoing project and publications that I would like to highlight include:

5R01HL147350
(PI: Runnels, MPI: Yue)
04/01/2019-2/28/2023
NIH/NHLBI
Regulation of TRPM7 Channels

T32GM139804
(PI: Runnels, MPI: Haimovich)
02/01/2021-01/31/2026
NIH/NIGMS
IMSD at Rutgers-New Brunswick

Citations:

1) Bai, Z. Feng, J., Franken, G.A.C., Al'Saadi, N., Cai, N., Yu, A.S., Lou, L., Komiya, Y. Hoenderop, J.G., de Baaij, J.H.F. Yue, L., and **L.W. Runnels**. (2021). CNNM proteins selectively bind to the TRPM7 channel to stimulate divalent cation entry into cells. PLoS Biol. 19(12):e3001496. PMCID: PMC8726484.

2) Cai, N., Lou, L, Al-Saadi, N., Tetteh, S. and **L.W. Runnels**. (2018). The kinase activity of the channel-kinase protein TRPM7 regulates stability and localization of the TRPM7 channel in polarized epithelial cells. *J. Biol. Chem.* 293(29):11491-11504. PMCID: PMC6065181.

3) Komiya, Y., Bai, Z., Cai, N. Lou, L., Al-Saadi, N. Mezzacappa, C., Habas, R. **and L.W. Runnels.** (2017) A Nonredundant Role for the TRPM6 Channel in Neural Tube Closure. *Scientific Reports.* 7(1):15623. PMCID: PMC5688082.

4) Cai, N., Bai, Z., Nanda, V., **and L.W. Runnels.** (2017). Mass Spectrometric Analysis of TRPM6 and TRPM7 Phosphorylation Reveals Regulatory Mechanisms of the Channel-Kinases. *Scientific Reports*.7:42739. PMCID: PMC5318989.

B. Positions, Scientific Appointments, and Honors

Positions and Employment:

2021-present	Professor, Department of Pharmacology Rutgers-Robert Wood Johnson Medical School
2002-present	Member of Cancer Institute of New Jersey
2011-2021	Associate Professor, Department of Pharmacology, Rutgers-Robert Wood Johnson Medical School
2002-2011	Assistant Professor, Department of Pharmacology, UMDNJ-Robert Wood Johnson Medical School
2000	Instructor in Pediatrics, Harvard Medical School
2002	Assistant in Cardiology, Children's Hospital, Boston, MA
1998-2001	Research Fellow, Department of Pediatrics, Harvard Medical School, in the laboratory of Dr. David Clapham.
1998-2001	Research Fellow, Department of Cardiology, Children's Hospital, Boston, MA, in the laboratory of Dr. David Clapham
1992-1998	Graduate Research Assistant, Department of Physiology and Biophysics, Stony Brook University, in the laboratory of Dr. Suzanne Scarlata.

Other Experience and Professional Memberships:

2019	Ad Hoc Member, NIH, MIST Study Section
2017	Ad Hoc Member, NIH, NTRC Study Section
2016-present	Editorial Member, Scientific Reports
2014	Ad Hoc Member, NIH, NTRC Study Section
2010	Ad Hoc Member, NCI-F Training Review Committee
2008	Ad Hoc Member, NIH, NTRC Study Section
2006	Ad Hoc Member, NIH, NTRC Study Section
2004-2005	American Heart Association Northeast 5A Peer Review Study Group
2004-present	American Society for Cell Biology
2001-present	Ad Hoc Reviewer, Cell Calcium, Journal of Biological Chemistry, Journal of Molecular Biology, Journal of General Physiology, Journal of Neurochemistry, Neuroscience Letters, Scientific Reports
1993-2005	Biophysical Society
1991	National Physics Honor Society

Honors and Awards:

2012-2013	Excellence in Teaching Award – Foundation of UMDNJ
2004-2007	American Heart Association, Heritage Scientist Developmental Grant.
1998-2001	National Research Service Award
1997	Sigma Xi Travel Award
1997	Sigma Xi Excellence in Research Award

C. Contributions to Science

1. **Regulation of Phospholipase C-beta enzymes:** I received a B.S. in Engineering Physics at the Colorado School of Mines. Upon graduation, I joined the Biophysics program in the Department of Physiology at Stony Brook University, where I worked with Dr. Suzanne Scarlata, an expert in optical biophysics. Dr. Scarlata instructed me in optical spectroscopy and gave me the opportunity to apply my theoretical skills towards the development of a new theory to describe homotransfer, a special case of fluorescence energy resonance transfer (FRET) between molecules of the same type. This work led to my first, first author paper, which was published in the *Biophysical Journal*. The article was well received, and I was honored to have one figure from the paper incorporated as an example of fluorescence homotransfer in Joseph R. Lakowicz's influential book *Principles of Fluorescence Spectroscopy*. I continued my studies in Dr. Scarlata's lab, acquiring skills in protein purification, fluorescence spectroscopy, and signal transduction, which culminated in another three first author publications detailing the mechanisms by which phospholipase C beta (PLC-β) isozymes are regulated by biological membranes and heterotrimeric G proteins.

    a. **Runnels, L.W.** and Scarlata, S.F. (1995) Theory and Application of Fluorescence Homotransfer to Melittin Oligomerization. Biophysical Journal. 69: 1569-1583.

    b. **Runnels, L.W**., Jenco, J., Morris, A. and Scarlata, S. (1996) Membrane Binding of Phospholipases C-β_1 and C-β_2 Is Independent of Phosphatidylinositol 4,5-Bisphosphate and the α and $\beta\gamma$ Subunits of G Proteins. Biochemistry. 35(51): 16824-16832.

    c. **Runnels, L.W.** and Scarlata, S.F. (1998) Regulation of the Rate and Extent of Phospholipase C β_2 Effector Activation by the Subunits of Heterotrimeric G Proteins. Biochemistry. 37(44):15563-15574.

    d. **Runnels, L.W.** and Scarlata, S.F. (1999) Determination Of The Affinities Between Heterotrimeric G Protein Subunits And Their Phospholipase C-Beta Effectors. Biochemistry. 38(5): 1488-96.

2. **Discovery of TRPM7.** For my postdoctoral studies I joined Dr. David Clapham's lab at Harvard Medical School. Dr. Clapham is a world leader in ion channel biology with a reputation for applying recent advances in applied physics towards biological questions. I joined his research group to learn confocal and two-photon microscopy as well electrophysiology techniques. While in his lab I continued my research on PLC by performing a yeast two-hybrid (Y2H) screen using the COOH-terminal of PLC-β1 as bait. The screen uncovered TRPM7 as the first ion channel to contain its own kinase domain. The initial characterization of the bifunctional protein describing its ion channel and kinase properties was published in the journal *Science*. While completing my postdoctoral studies, together with Dr. LIxia Yue, we determined that stimulation of receptors coupled to PLC inactivates the channel through hydrolysis of PLC's substrate phosphatidylinositol 4,5-bisphosphate (PIP_2), which gates the channel. This work, which was published in *Nature Cell Biology*, was the first to demonstrate gating of a TRP ion channel by PIP_2.

    a. **Runnels, L.W.**, Yue, L., and D.E. Clapham. (2001) TRP-PLIK, a bifunctional protein with Kinase and Ion Channel Activities. Science. 291(5506): 1043-1047.

    b. **Runnels, L.W.**, Yue, L., and D.E. Clapham. (2002) The TRPM7 channel is inactivated by PIP_2 hydrolysis. Nature Cell Biology. 4(5):329-36.

3. **Fundamental Roles for TRPM7 and TRPM6 Channels and Mg^{2+} in Neural Tube Closure.**

I began my career as an independent investigator at Rutgers-Robert Wood Johnson Medical School with a focus on understanding the biological functions of TRPM7. Knockout of TRPM7 from mice causes early embryonic lethality, underscoring a critical role for this bifunctional protein in vertebrate physiology. To investigate TRPM7 *in vivo*, I collaborated with Dr. Raymond Habas, and expert in Wnt signaling, and utilized *Xenopus laevis* as a model system and discovered a requirement of the channel for gastrulation and neural fold closure. Our studies demonstrated a role for TRPM7 in control of cell adhesion. Later work revealed that depletion of TRPM7 from cells and developing *Xenopus laevis* embryos produces a loss in cell polarity and directional cell migration that can be suppressed by Mg^{2+} supplementation or by expression of the

magnesium transporter SLC41A2. While it is well known that Ca^{2+} is vital to the control of cell migration, targeting numerous Ca^{2+}-dependent proteins to influence actin and focal adhesion remodeling among others processes, our work is the first to demonstrate a fundamental role for Mg^{2+} in early development and in polarized cell movements. Our research revealed that TRPM7's channel activity, but not its kinase domain, is essential for the protein's control of polarized cell movements in fibroblasts as well as for convergent extension cell movement (medical intercalation) in developing *Xenopus* embryos. Deletion of TRPM6 in mice was reported to cause neural tube closure defects. Our studies in *Xenopus* revealed that unlike TRPM7, whose loss interferes with mediolateral intercalation cell movements during gastrulation, depletion of TRPM6 disrupted radial intercalation cell movements. Our lab continues to investigate the molecular mechanisms by which the TRPM7 and TRPM6 channels as well as Mg^{2+} regulate embryogenesis. Below are representative articles.

a. Su, L.T., Agapito, M.A., Li, M., Simonson, W.T., Huttenlocher, A., Habas, R., Yue, L. and L.W. Runnels. (2006) TRPM7 regulates cell adhesion by controlling the calcium-dependent protease calpain. *J. Biol. Chem.* 281(16): 11260-70. PMCID: PMC3225339.
b. Liu, W., Su, L-T, Khadka, D.K., Mezzacappa, C., Sato, A., Habas, R., and L.W. Runnels. (2011) TRPM7 Regulates Gastrulation During Vertebrate Embyrogenesis. *Dev. Biol.* 350(2):348-57. PMCID: PMC3292586.
c. Su, L.T., Liu, W, Chen, H.C., González-Pagán O, Habas R, and L.W. Runnels. (2011) TRPM7 regulates polarized cell movements. *Biochem J.* 434(3):513-21. PMCID: PMC3507444.
d. Komiya, Y., Bai, Z., Cai, N. Lou, L., Al-Saadi, N. Mezzacappa, C., Habas, R. and L.W. Runnels. (2017) A Nonredundant Role for the TRPM6 Channel in Neural Tube Closure. *Scientific Reports.* 7(1):15623. PMCID: PMC5688082.

4.**Regulatory Mechanisms Controling TRPM7.** Given TRPM7's significant association with pathological conditions such as stroke, cancer, and heart disease and the vital importance of discovering novel approaches for blocking TRPM7's cellular activities, our lab has also been extremely active in conducting studies to elucidate the regulation of TRPM7. We've shown that TRPM7 is regulated post-translationally by the protein Hepatocystin and discovered a novel mechanism by which TRPM7 kinase activity can be regulated by phosphorylation. Our discovery that TRPM7's kinase plays a critical role in controlling the protein levels and cellular localization offers a new paradigm for how TRPM7 channel is controlled *in vivo*. More recently, we made a breakthrough for the field by our discovery of CNNM proteins (CNNM1-4) as binding partners and regulators of TRPM7. CNNM proteins bind to members of the PTP4A family, which are highly expressed many forms of cancers, ARL15, and Mg-ATP. Our laboratory is highly focused now elucidation the function and regulation of CNNM-TRPM7 complexes *in vivo.*

a. Overton, J.D., Komiya, H., Mezzacappa C., Nama, K., Cai, N., Lou, L., Fedeles, S.V. Habas, R. and L.W. Runnels. (2015) Hepatocystin is Essential for TRPM7 Function During Early Embryogenesis. *Scientific Reports.* 5:18395. PMCID: PMC4680866.
b. Cai, N., Bai, Z., Nanda, V., and L.W. Runnels. (2017). Mass Spectrometric Analysis of TRPM6 and TRPM7 Phosphorylation Reveals Regulatory Mechanisms of the Channel-Kinases. *Scientific Reports*.7:42739. PMCID: PMC5318989.
c. Cai, N., Lou, L, Al-Saadi, N., Tetteh, S. and L.W. Runnels. (2018). The kinase activity of the channel-kinase protein TRPM7 regulates stability and localization of the TRPM7 channel in polarized epithelial cells. *J. Biol. Chem.* 293(29):11491-11504. PMCID: PMC6065181.
d. Bai, Z. Feng, J., Franken, G.A.C., Al'Saadi, N., Cai, N., Yu, A.S., Lou, L., Komiya, Y. Hoenderop, J.G., de Baaij, J.H.F. Yue, L., and L.W. Runnels. (2021). CNNM proteins selectively bind to the TRPM7 channel to stimulate divalent cation entry into cells. PLoS Biol. (19(12):e3001496. PMCID: PMC8726484.

Complete List of Published Work in My Bibliography:

https://www.ncbi.nlm.nih.gov/myncbi/loren.runnels.1/bibliography/public/