

BIOGRAPHICAL SKETCH

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NAME: Michael Daniel Cahalan

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

POSITION TITLE: Professor and 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
Oberlin College, Oberlin, OH	B.A.	06/70	Biology
University of Washington, Seattle, WA	Ph.D.	06/74	Physiology & Biophysics
University of Pennsylvania, Philadelphia, PA	(postdoc)	06/74-77	Membrane Biophysics

A. Personal Statement

Discoveries from my laboratory lead convergently to my current interests in ion channels, calcium signaling, in vivo imaging, and development of therapeutic approaches to modulate inflammation. Starting in 1983, we discovered that ion channels regulate cell homeostasis and activation in T lymphocytes, and identified therapeutic targets. Starting in 2001, we pioneered methods to use two-photon microscopy for real-time imaging of cellular dynamics in the lymph node. Within the past five years, we extended our immuno-imaging approach to the skin, the lung, and the spinal cord. Most recently, we are investigating mechanisms of immunoregulation that keep the immune system in check through regulatory T cells (Tregs), and are now investigating cellular and molecular mechanisms of Tregs in EAE, as a model for multiple sclerosis (MS). In parallel with this line of research on cellular choreography, we discovered the molecular basis of store-operated Ca^{2+} signaling, a process that requires molecular choreography of STIM and Orai proteins. RNAi screening allowed us to identify the STIM and Orai proteins that together comprise store-operated Ca^{2+} channels. We showed that STIM1 initiates T-cell Ca^{2+} signaling by sensing ER Ca^{2+} -store depletion and migrating to junctions with the plasma membrane. Direct interaction with STIM1 causes Orai1 channels to open and Ca^{2+} to enter the cell. We further developed a unique set of reagents based on genetically encoded calcium indicators and Orai1-based probes (the Ca^{2+} toolkit). Together, these lines of research give us confidence in pursuing research directed toward understanding and treating autoimmune and inflammatory disease processes.

1. Germain, R.N., E.A. Robey, and M.D. **Cahalan**. 2012. A decade of imaging cellular motility and interaction dynamics in the immune system. *Science* 33: 1676-81. PMID: PMC3405774.
2. Greenberg, M.L., J.G. Weinger, M.P. Matheu, K.S. Carbajal, I. Parker, W.B. Macklin, T.E. Lane, and M.D. **Cahalan**. 2014. Two-photon imaging of remyelination of spinal cord axons by engrafted neural precursor cells in a viral model of multiple sclerosis. *PNAS Jun 3;111(22):E2349-55*. PMID: PMC3608704.
3. Matheu, M.P., S. Othy, M.L. Greenberg, T.X. Dong, M. Schuijs, K. Deswarte, H. Hammad, B.N. Lambrecht, I. Parker, and M.D. **Cahalan**. 2015. Imaging regulatory T cell dynamics and CTLA4-mediated suppression of T cell priming. *Nature Communications* in press.
4. Amcheslavsky, A., M.L. Wood, A.V. Yeromin, I. Parker, J.A. Freites, D.J. Tobias, and M.D. **Cahalan**. 2015. Molecular biophysics of Orai store-operated Ca^{2+} channels. *Biophysical Journal* 108: 237-246. PMID: PMC4302196.

B. Positions and Honors**Positions and Employment**

1977-83 Assistant Professor, Department of Physiology & Biophysics, University of California, Irvine
 1983-85 Associate Professor, Department of Physiology & Biophysics, UCI
 1985-2010 Professor, Department of Physiology & Biophysics, UCI
 2007-present Chair, Department of Physiology & Biophysics, UCI

2010-present Distinguished Professor, Department of Physiology & Biophysics, UCI

Other Experience and Professional Memberships

Scientific Organizations: Biophysical Society member since 1973, Council Member 2008-2011; Society for General Physiologists since 1977, Councilor 1992-94, President 1998-99; American Association of Immunologists member

Grant review: Ad hoc member NIH study sections CMI-A, MBPP, TME, MCDN; reviewed grants for Pasteur Institute; French, Swiss, Israeli, and Austrian Science agencies

Editorial service: Journal of General Physiology Editorial Board 1988-98; Advisory Editor 2002-present; Physiological Reviews Editorial Board 2002-07

Manuscript review: *Nature*, *Science*, *Cell*, *PNAS*, others (>150 reviews completed in the past five years).

Teaching: I have had the privilege of teaching more than 3000 medical students, most of whom are now physicians in the state of California. Medical Physiology (100 medical students, 35 years), lectures and discussion in cardiovascular physiology; Physiology of Ion Channels (5-15 graduate students, 23 years). Lecture and discussion of molecular and cellular aspects of ion channel function; Integrative Immunology (15-20 graduate students, 5 years). Lecture and discussion of lymphocyte signaling and in vivo trafficking.

Research Presentations. In the past five years, I have made over 30 research presentations, at symposia and invited lectures including: Nobel Symposium on High-resolution in vivo imaging of cell biology (Stockholm); the American Society for Histocompatibility and Immunogenetics (keynote); AAI Immunoimaging symposium (organizer/speaker); the Biophysical Society Store-operated calcium channels symposium (organizer/speaker); World Pharma Channelopathies symposium in Copenhagen; Frontiers in Intravital Microscopy at NIH, Cell traffic and the 4-D immune response at AAAAI; the Bristol-Myers Squibb lecture at UCI; the Curran lecture at Yale; the Allergan lecture at the Beckman Center of the NAS; the Krebs lecture at the University of Washington; the SGP Traveling Lectureship at Northwestern and the University of Chicago; as well as invited lectures at Cedars-Sinai, the Institute for Research in Biomedicine (Bellinzona, Switzerland); NIEHS, the Scripps Research Institute, and the Pasteur Institute in Paris.

Honors and Awards

1969	Elected Phi Beta Kappa
1970	Graduated Magna Cum Laude
1976-77	Muscular Dystrophy Postdoctoral Fellowship
1982-87	NIH Research Career Development Award
1989-90	Alexander von Humboldt Senior Scientist Award, Max Planck Institute, Göttingen, Germany
1997	Athalie Clark Research Achievement Award, UCI
2000	Kenneth S. Cole Award in Membrane Biophysics, Biophysical Society
2006-13	Javits Investigator Award, National Institute of Neurological Disorders and Stroke
2008	Elected to the Henry Kunkel Society
2009,11,13	Excellence in Teaching Award from medical students
2010	Elected to the US National Academy of Sciences
2011	UCI Distinguished Faculty Award for Research

C. Contribution to Science

My work evolved from postdoctoral research experience as an electrophysiologist working on neuronal ion channels. As an Assistant Professor, I decided to work on cells of the immune system, originally from my own blood, using a home-built patch clamp rig to record from small single cells. My research subsequently unfolded in the five main directions outlined below. Sixty-four of my papers have been cited more than 100 times, and six more than 500 times (h-index, 80). Since 2002, 14 of my publications have been highlighted by the Faculty of 1000. Cahalan lab alumni include 12 faculty members in academia and 10 scientists in biotech companies.

1. Functional network of ion channels in cells of the immune system. Ion channels are well known for generating electrical signaling in nerve and muscle cells. We were the first to show that ion channels also contribute to immune system function. Over the past 30 years, we characterized the biophysical and molecular properties of five channel types in T lymphocytes. Using ion channel blockers and genetic approaches, we discovered previously unknown functions of ion channels to regulate gene expression, proliferation, differentiation, volume regulation, ionic homeostasis, and calcium signaling.

- a DeCoursey, T.E., K.G. Chandy, S. Gupta, and M.D. **Cahalan**. 1984. Voltage-gated K channels in human T lymphocytes: a role in mitogenesis? *Nature* 307: 465-468. PMID: 6320007.

- b Grissmer, S., R.S. Lewis, and M.D. **Cahalan**. 1992. Ca^{2+} -activated K^+ channels in human leukemic T cells. *J Gen Physiol* 99: 1-23. PMID: PMC2216598.
- c Lewis, S., P. Ross, and M.D. **Cahalan**. 1993. Chloride channels activated by osmotic stress in T lymphocytes. *J Gen Physiol* 101: 801-826. PMID: PMC2216748.
- d **Cahalan**, M.D. and K.G. Chandy. 2009. The functional network of ion channels in T lymphocytes. *Immunological Reviews* 231: 59-87. PMID: PMC3133616.

2 Kv1.3 from current to clinic for treatment of autoimmune disorders. Our work on Kv1.3 potassium channels in T cells has included the following milestones: description of the biophysical fingerprint of a voltage-gated current in T cells; identifying ever more potent and selective blockers to the picomolar range of affinity; using blockers to identify cellular functions; cloning the gene, identifying effector memory T cells as a vulnerable T cell subset; animal studies, including EAE models, leading to successful Phase 1 human clinical trials and FDA approval in 2012-2013 of ShK-186 peptide (dalazatide). Our studies have identified Kv1.3 in T cells as a potential “Achilles heel” of autoimmunity, for selective targeting of chronically activated T cells without disrupting acute immune responses to viral or bacterial infection. Four papers highlight an equal collaboration on Kv1.3 with George Chandy in my Department:

- a **Cahalan**, M.D., K.G. Chandy, T.E. DeCoursey, and S. Gupta. 1985. A voltage-gated K^+ channel in human T lymphocytes. *J Physiol* 358: 197-237. PMID: PMC1193339.
- b Beeton, C., H. Wulff, J. Barbaria, O. Clot-Faybesse, M. Pennington, D. Bernard, M.D. **Cahalan**, K.G. Chandy, and E. Beraud. 2001. Selective blockade of T lymphocyte K^+ channels ameliorates experimental autoimmune encephalitis, a model for multiple sclerosis. *PNAS* 98: 13942-13947. (corresponding author) PMID: PMC61146.
- c Chandy, K.G., H. Wulff, C. Beeton, M. Pennington, G.A. Gutman, M.D. **Cahalan**. 2004. K^+ channels as targets for specific immunosuppression. *Trends in Pharmacological Sciences* 25: 280-289. PMID: PMC2749963.
- d Matheu, M.P., C. Beeton, A. Garcia, V. Chi, K. Monaghan, M.I. Uemura, D. Li, S. Pal, L.M. de la Maza, E. Monuki, A. Flugel, M.W. Pennington, I. Parker, K.G. Chandy, and M.D. **Cahalan**. 2008. Imaging of effector memory T cells during DTH and suppression by Kv1.3 channel block. *Immunity* 29: 602-614. PMID: PMC2953540.

3 Ca^{2+} signaling in T lymphocytes. Our contributions to the field of calcium signaling include the first biophysical characterization (in 1989) of the Ca^{2+} release-activated Ca^{2+} (CRAC) channel. By single-cell Ca^{2+} imaging, we showed that cytosolic Ca^{2+} concentration oscillates within individual T cells following T cell receptor stimulation. We quantitatively determined the time course and Ca^{2+} dependence of NFAT-driven gene expression, and showed an all-or-none gene expression response in single cells. We also determined the Ca^{2+} dependence of cellular motility, and showed how T cells remain anchored to the sites of antigen presentation during formation of the immunological synapse. More recently, we demonstrated that Ca^{2+} entry takes place locally in T cells at the site of antigen presentation.

- a Lewis, R.S. and M.D. **Cahalan**. 1989. Mitogen-induced oscillations of cytosolic Ca^{2+} and transmembrane Ca^{2+} current in human leukemic T cells. *Cell Regulation* 1: 99-112. PMID: PMC361429.
- b Negulescu, P., N. Shastri, and M.D. **Cahalan**. 1994. Intracellular calcium dependence of IL-2 gene expression in single T lymphocytes. *PNAS* 91: 2873-2877. PMID: PMC43473.
- c Negulescu, P.A., A. Khan, T.B. Krasieva, H.H. Kerschbaum, and M.D. **Cahalan**. 1996. Polarity of T cell shape, motility, and sensitivity to antigen. *Immunity* 4: 421-430. PMID: 8630728.
- d Liudyno, M.I., J.A. Kozak, A. Penna, O. Safrina, S.L. Zhang, D. Sen, J. Roos, K.A. Stauderman, and M.D. **Cahalan**. 2008. Orai1 and STIM1 move to the immunological synapse and are up-regulated during T cell activation. *PNAS* 105:2011-2016. PMID: PMC2538873.

4 Molecular identification of STIM and Orai. The molecular identity of CRAC channels, and store-operated Ca^{2+} channels more generally, remained enigmatic from the late 1980s until 2005. Our Ca^{2+} indicator-based candidate and genome-wide RNAi screens provided key breakthroughs. We showed that knocking down either STIM or Orai inhibits CRAC channel activity, and that overexpression of both together greatly amplifies CRAC channel activity. By mutagenesis and functional analysis, we identified the molecular mechanism for CRAC channel activation: ER-resident STIM proteins sense the depletion of Ca^{2+} within the lumen of the ER, translocate to junctions adjacent to the plasma membrane, and promote clustering and opening of Orai1 channels that conduct Ca^{2+} ions into the cell. These discoveries were highlighted by *Science* magazine as “Cell Signaling Breakthroughs of the Year” in 2005 and 2006.

- a Roos, J. DiGregorio, P.J., A.V. Yeromin, K. Ohlsen, M. Liudyno, S. Zhang, O. Safrina, J.A. Kozak, S. Wagner, M.D. **Cahalan**, G. Velicelebi, and K.A. Stauderman. 2005. STIM1, an essential and conserved component of store-operated calcium channel function. *J Cell Biol* 169: 435-445. PMID: PMC2171946.
- b Zhang S.L. Y. Yu, J. Roos, J.A. Kozak, T.J. Deerinck, M.H. Ellisman, K.A. Stauderman, and M.D. **Cahalan**. 2005. STIM1 is a Ca²⁺ sensor that activates CRAC channels and migrates from the Ca²⁺ store to the plasma membrane. *Nature* 437: 902-905. PMID: PMC1618826.
- c Zhang S.L., A.V. Yeromin, X.H-F. Zhang, Y. Yu, O. Safrina, A. Penna, J. Roos, K.A. Stauderman, and M.D. **Cahalan**. 2006. Genome-wide RNAi screen of Ca²⁺ influx identifies genes that regulate CRAC channel activity. *PNAS* 103: 9357-9362. PMID: PMC1482614.
- d Yeromin, A.V., S.L. Zhang (co-first author), W. Jiang, Y. Yu, O. Safrina, and M.D. **Cahalan**. 2006. Molecular identification of the CRAC channel by altered ion selectivity in a mutant of Orai. *Nature* 443:226-229. PMID: PMC2756048.

5 Immuno-imaging of cellular dynamics in the immune system. Introduced by our group to the field of immunology, two-photon (2P) microscopy permits real-time visualization of living cells within lymphoid organs, revealing an elegant cellular choreography. I have collaborated since 2001 with Ian Parker in these studies, which continue to illuminate the cellular dynamics of antigen recognition, lymphocyte priming, differentiation, cellular migration, the action of adjuvants, and effects of immunosuppressive drugs.

- a Miller, M.M., S.H. Wei, I. Parker, and M.D. **Cahalan**. 2002. Two-photon imaging of lymphocyte motility and dynamic antigen responses in intact lymph node. *Science* 296: 1869-1873. PMID: 12016203.
- b Miller, M.J., A.S. Hejazi, S.H. Wei, I. Parker, and M.D. **Cahalan**. 2004. T cell repertoire scanning is promoted by dynamic dendritic cell behavior and random T cell motility in the lymph node. *PNAS* 101: 998-1003. PMID: PMC327133.
- c Okada, T., M.J. Miller, I. Parker, M.F. Krummel, M. Neighbors, S.B. Hartley, A. O'Garra, M.D. **Cahalan**, and J.G. Cyster. 2005. Antigen-engaged B cells undergo chemotaxis toward the T zone and form motile conjugates with helper T cells. *PLoS, Biology* 3: 1047-061. PMID: PMC1088276.
- d Matheu, M.P., J.R. Teijaro, K.B. Walsh, M.L. Greenberg, D. Marsolais, I. Parker, H. Rosen, M.B.A. Oldstone, and M.D. **Cahalan**. 2013. Three phases of CD8 T cell response in the lung following H1N1 influenza infection and sphingosine 1 phosphate agonist therapy. *PLoS-ONE* 10.1371/journal.pone.0058033. PMID: PMC3606384.

Complete list of publications on PubMed: <http://www.ncbi.nlm.nih.gov/pubmed/?term=Cahalan+MD>

D. Research Support

Ongoing Research Support

R01 NS-014609 (Cahalan) 04/01/13-03/31/18

NIH/NINDS Funded since 1979

Molecular Mechanisms of Ion Channels in T Lymphocytes

The major goal of this project is to determine how the molecular components (STIM and Orai) of the Ca²⁺ release-activated Ca²⁺ (CRAC) channel function to regulate influx in T lymphocytes. Role: PI.

R21 AI-117555 (Cahalan) Funded 2/1/15-1/31/17

NIH/NIAID Impact Score 17

A Transgenic Mouse Line to Map Cell-Type Specific Calcium Signals In Vivo

We are developing a mouse model that will enable us to see calcium signals that report the inner activation state of living cells in the body. This advance will open new avenues of investigation into therapies for autoimmune diseases and neurological disorders. Role: PI

Pending

RO1 AI121945 (Cahalan)

NIH/NIAID

Cellular and Molecular Mechanisms of Regulatory T cells in EAE

We are using two-photon microscopy to image cells within the lymph node and spinal cord of a mouse model of MS, in order to investigate how regulatory T cells limit damage caused by pathogenic Th17 cells. Our experimental approach includes evaluation of therapies that limit the access of Th17 cells into the nervous

system, promote remyelination through transplantation of stem cells, and block cellular calcium signaling pathways that cause Th17 cell activation.

Completed Research Support:

R01 GM41514 (Cahalan) 04/1/10-03/31/14

NIH/NIGMS Funded since 1985

Functional immuno-imaging of lymphocyte motility and cell interactions in lymph node

Utilizing optical and molecular approaches, we investigated how the default antigen-search strategy of T cells is optimized in lymph nodes, how tolerogenic B cells and regulatory T cells (Tregs) interfere with naïve T cell activation, and how Kv1.3 K⁺ channels in T cells can be targeted for immunosuppression in vivo. Role: PI