Stanford



Richard Lewis

Professor of Molecular and Cellular Physiology, Emeritus

CONTACT INFORMATION

- **Administrative Contact**

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Bio

ACADEMIC APPOINTMENTS

- Emeritus Faculty, Acad Council, Molecular and Cellular Physiology
- Member, Bio-X
- Member, Wu Tsai Neurosciences Institute

ADMINISTRATIVE APPOINTMENTS

- Chair, Stanford University School of Medicine - Molecular & Cellular Physiology, (2004-2009)
- Director of Graduate Studies, Stanford University School of Medicine - Molecular & Cellular Physiology, (2021-2026)

HONORS AND AWARDS

- Junior Faculty Scholar, HHMI (1996-1998)
- MERIT Award, National Institute of General Medical Sciences (2012 - 2022)
- Elected Member, National Academy of Sciences (2020)
- Kenneth S. Cole Award, Biophysical Society (2021)

PROFESSIONAL EDUCATION

- B.S., Yale University , Molecular Biophysics and Biochemistry (1978)
- Ph.D., California Inst. of Technology , Neurobiology (1985)

LINKS

- Lewis Lab site: http://med.stanford.edu/lewislab

Research & Scholarship

CURRENT RESEARCH AND SCHOLARLY INTERESTS

Research in our laboratory is focused on the molecular mechanisms of calcium signaling through store-operated Ca2+ channels (SOCs). This class of ion channels is regulated in a unique way, by the depletion of Ca2+ from the lumen of the endoplasmic reticulum (ER) which normally occurs following

stimulation of cell surface receptors that generate IP3. They are expressed in practically all cells, where they contribute to diverse functions including secretion, gene expression, and cell differentiation. A SOC called the Ca2+ release-activated Ca2+ channel, or CRAC channel, is particularly important in T cells, where it generates sustained Ca2+ signals that are essential for triggering T cells to proliferate and carry out immune functions. Loss of function of the CRAC channel by a single mutation in its structural gene leads to a devastating severe combined immunodeficiency (SCID) syndrome in humans.

A major effort in the lab is to understand how the depletion of Ca2+ from the ER triggers the opening of CRAC channels in the plasma membrane. Since the recent discovery of genes encoding the ER Ca2+ sensor (STIM1) and the CRAC channel (Orai1), we have made rapid progress in revealing the choreographic nature of this process. Following store depletion, STIM1 moves from locations throughout the ER to accumulate in ER subregions positioned within 10-25 nm of the plasma membrane (PM). Simultaneously, the CRAC channel gathers at corresponding sites in the PM directly opposite STIM1, where it is opened through an interaction with STIM1. This is an unprecedented mechanism for channel activation, in which a stimulus acts to bring a channel and its activator/sensor together for interaction across apposed membrane compartments. We are currently studying how changes in ER Ca2+ drive the redistribution of STIM1 and the mechanism by which STIM1 and Orai1 interact across the ER-PM gap. For these studies we combine protein engineering with patch-clamp electrophysiology and live-cell imaging using total internal reflection fluorescence (TIRF), confocal, and single-molecule microscopy.

A second major area of interest is how specific information is encoded in Ca2+ signals. Specificity is an acute problem for pluripotent messengers like Ca2+ that are involved in multiple signaling pathways. We have shown that transcriptional specificity in T cells can be achieved through the amplitude and dynamics of Ca2+ signals generated by CRAC channels. We are now studying how these features contribute to cell fate decisions during T cell development. In the thymus, self-reactive thymocytes are deleted through negative selection, while cells with the appropriate avidity for “self” are allowed to mature into T cells and populate the periphery (positive selection). To study the role of Ca2+ in this choice, we have developed a novel thymic slice preparation in which we use two-photon microscopy to track and record Ca2+ signals in single thymocytes as they migrate through tissue engineered to provide defined selection signals. We have found that positive selection is associated with Ca2+ oscillations, which immobilize the cells at locations of self-antigen recognition to promote gene activation. We are currently comparing signaling during positive and negative selection to determine how the Ca2+ signal “signature” helps a T cell decide whether to live and prosper or die.

Teaching

COURSES

2024-25

- Imaging: Biological Light Microscopy: BIO 152, MCP 222 (Win)

2023-24

- How Cells Work: Energetics, Compartments, and Coupling in Cell Biology: MCP 256 (Spr)
- Imaging: Biological Light Microscopy: BIO 152, MCP 222 (Aut)

STANFORD ADVISEES

Doctoral Dissertation Reader (AC)

Wagner Nors, Jim Zhang

GRADUATE AND FELLOWSHIP PROGRAM AFFILIATIONS

- Biophysics (PhD Program)
- Molecular and Cellular Physiology (PhD Program)

- Neurosciences (PhD Program)

Publications

PUBLICATIONS

- **Structural rearrangements underlying the activation of STIM1 by ER calcium depletion.** *Proceedings of the National Academy of Sciences of the United States of America*
  Qiu, R., Lewis, R. S.
  2026; 123 (34): e2602410123
- **Structural rearrangements underlying the activation of STIM1 by ER calcium depletion.** *bioRxiv : the preprint server for biology*
  Qiu, R., Lewis, R. S.
  2026
- **Multiple weak brakes act in concert to control STIM1 and store-operated calcium entry.** *Proceedings of the National Academy of Sciences of the United States of America*
  Qiu, R., Lewis, R. S.
  2025; 122 (50): e2518622122
- **Conformational dynamics of auto-inhibition in the ER calcium sensor STIM1.** *eLife*
  van Dorp, S., Qiu, R., Choi, U. B., Wu, M. M., Yen, M., Kirmiz, M., Brunger, A. T., Lewis, R. S.
  2021; 10
- **Store-Operated Calcium Channels: From Function to Structure and Back Again.** *Cold Spring Harbor perspectives in biology*
  Lewis, R. S.
  2019
- **Structural features of STIM and Orai underlying store-operated calcium entry.** *Current opinion in cell biology*
  Qiu, R., Lewis, R. S.
  2019; 57: 90–98
- **Physiological CRAC channel activation and pore properties require STIM1 binding to all six Orai1 subunits.** *The Journal of general physiology*
  Yen, M., Lewis, R. S.
  2018
- **Functional Analysis of Orai1 Concatemers Supports a Hexameric Stoichiometry for the CRAC Channel.** *Biophysical journal*
  Yen, M., Lokteva, L. A., Lewis, R. S.
  2016; 111 (9): 1897-1907
- **Orai1 pore residues control CRAC channel inactivation independently of calmodulin.** *journal of general physiology*
  Mullins, F. M., Yen, M., Lewis, R. S.
  2016; 147 (2): 137-152
- **The inactivation domain of STIM1 is functionally coupled with the Orai1 pore to enable Ca2+-dependent inactivation.** *journal of general physiology*
  Mullins, F. M., Lewis, R. S.
  2016; 147 (2): 153-164
- **Calcium influx through CRAC channels controls actin organization and dynamics at the immune synapse.** *eLife*
  Hartzell, C. A., Jankowska, K. I., Burkhardt, J. K., Lewis, R. S.
  2016; 5
- **STORE-OPERATED CALCIUM CHANNELS** *PHYSIOLOGICAL REVIEWS*
  Prakriya, M., Lewis, R. S.
  2015; 95 (4): 1383-1436
- **Alternative splicing converts STIM2 from an activator to an inhibitor of store-operated calcium channels.** *journal of cell biology*
  Rana, A., Yen, M., Sadaghiani, A. M., Malmersjö, S., Park, C. Y., Dolmetsch, R. E., Lewis, R. S.

2015; 209 (5): 653-670

- **Single-molecule analysis of diffusion and trapping of STIM1 and Orai1 at endoplasmic reticulum-plasma membrane junctions** *MOLECULAR BIOLOGY OF THE CELL*
  Wu, M. M., Covington, E. D., Lewis, R. S.
  2014; 25 (22): 3672-3685
- **Stoichiometric requirements for trapping and gating of Ca2+ release-activated Ca2+ (CRAC) channels by stromal interaction molecule 1 (STIM1)** *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA*
  Hoover, P. J., Lewis, R. S.
  2011; 108 (32): 13299-13304
- **Essential Role for the CRAC Activation Domain in Store-dependent Oligomerization of STIM1** *MOLECULAR BIOLOGY OF THE CELL*
  Covington, E. D., Wu, M. M., Lewis, R. S.
  2010; 21 (11): 1897-1907
- **STIM1 Clusters and Activates CRAC Channels via Direct Binding of a Cytosolic Domain to Orai1** *CELL*
  Park, C. Y., Hoover, P. J., Mullins, F. M., Bachhawat, P., Covington, E. D., Raunser, S., Walz, T., Garcia, K. C., Dolmetsch, R. E., Lewis, R. S.
  2009; 136 (5): 876-890
- **Oligomerization of STIM1 couples ER calcium depletion to CRAC channel activation** *NATURE*
  Luik, R. M., Wang, B., Prakriya, M., Wu, M. M., Lewis, R. S.
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- **The molecular choreography of a store-operated calcium channel** *NATURE*
  Lewis, R. S.
  2007; 446 (7133): 284-287
- **Ca2+ store depletion causes STIM1 to accumulate in ER regions closely associated with the plasma membrane** *JOURNAL OF CELL BIOLOGY*
  Wu, M. M., Buchanan, J., Luik, R. M., Lewis, R. S.
  2006; 174 (6): 803-813
- **The elementary unit of store-operated Ca2+ entry: local activation of CRAC channels by STIM1 at ER-plasma membrane junctions** *JOURNAL OF CELL BIOLOGY*
  Luik, R. M., Wu, M. M., Buchanan, J., Lewis, R. S.
  2006; 174 (6): 815-825
- **Regulation of CRAC channel activity by recruitment of silent channels to a high open-probability gating mode** *JOURNAL OF GENERAL PHYSIOLOGY*
  Prakriya, M., Lewis, R. S.
  2006; 128 (3): 373-386
- **Calcium oscillations regulate thymocyte motility during positive selection in the three-dimensional thymic environment** *NATURE IMMUNOLOGY*
  Bhakta, N. R., Oh, D. Y., Lewis, R. S.
  2005; 6 (2): 143-151
- **Calcium oscillations increase the efficiency and specificity of gene expression** *NATURE*
  Dolmetsch, R. E., XU, K. L., Lewis, R. S.
  1998; 392 (6679): 933-936
- **Optical single-channel recording of CRAC channels with HaloTag and a Ca2+-sensitive ligand.** *bioRxiv : the preprint server for biology*
  Dhillon, H., Lewis, R. S.
  2026
- **Cavbeta1 regulates T cell expansion and apoptosis independently of voltage-gated Ca2+ channel function.** *Nature communications*
  Erdogmus, S., Concepcion, A. R., Yamashita, M., Sidhu, I., Tao, A. Y., Li, W., Rocha, P. P., Huang, B., Garippa, R., Lee, B., Lee, A., Hell, J. W., Lewis, et al
  2022; 13 (1): 2033

- **Numbers count: How STIM and Orai stoichiometry affect store-operated calcium entry** *CELL CALCIUM*
  Yen, M., Lewis, R. S.
  2019; 79: 35–43

- **Universal intracellular biomolecule delivery with precise dosage control** *SCIENCE ADVANCES*
  Cao, Y., Chen, H., Qiu, R., Hanna, M., Me, E., Hjort, M., Zhang, A., Lewis, R. S., Wu, J. C., Melosh, N. A.
  2018; 4 (10): eaat8131

- **Abnormal Calcium Handling Properties Underlie Familial Hypertrophic Cardiomyopathy Pathology in Patient-Specific Induced Pluripotent Stem Cells** *CELL STEM CELL*
  Lan, F., Lee, A. S., Liang, P., Sanchez-Freire, V., Nguyen, P. K., Wang, L., Han, L., Yen, M., Wang, Y., Sun, N., Abilez, O. J., Hu, S., Ebert, et al
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  Lewis, R. S.
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- **Molecular Basis of Calcium Signaling in Lymphocytes: STIM and ORAI** *ANNUAL REVIEW OF IMMUNOLOGY, VOL 28*
  Hogan, P. G., Lewis, R. S., Rao, A.
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- **Differential Contribution of Chemotaxis and Substrate Restriction to Segregation of Immature and Mature Thymocytes** *IMMUNITY*
  Ehrlich, L. I., Oh, D. Y., Weissman, I. L., Lewis, R. S.
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- **STIM1 and calmodulin interact with Orai1 to induce Ca2+-dependent inactivation of CRAC channels** *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA*
  Mullins, F. M., Park, C. Y., Dolmetsch, R. E., Lewis, R. S.
  2009; 106 (36): 15495-15500

- **Some assembly required: Constructing the elementary units of store-operated Ca2+ entry** *CELL CALCIUM*
  Wu, M. M., Luik, R. M., Lewis, R. S.
  2007; 42 (2): 163-172

- **New insights into the molecular mechanisms of store-operated Ca2+ signaling in T cells** *TRENDS IN MOLECULAR MEDICINE*
  Luik, R. M., Lewis, R. S.
  2007; 13 (3): 103-107

- **A mutation in Orai1 causes immune deficiency by abrogating CRAC channel function** *NATURE*
  Feske, S., Gwack, Y., Prakriya, M., Srikanth, S., Puppel, S. H., Tanasa, B., HOGAN, P. G., Lewis, R. S., Daly, M., Rao, A.
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- **Real-time measurement of signaling and motility during T cell development in the thymus** *SEMINARS IN IMMUNOLOGY*
  Bhakta, N. R., Lewis, R. S.
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- **A severe defect in CRAC Ca2+ channel activation and altered K+ channel gating in T cells from immunodeficient patients** *JOURNAL OF EXPERIMENTAL MEDICINE*
  Feske, S., Prakriya, M., Rao, A., Lewis, R. S.
  2005; 202 (5): 651-662

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- **Enhancement of calcium signalling dynamics and stability by delayed modulation of the plasma-membrane calcium-ATPase in human T cells** *JOURNAL OF PHYSIOLOGY-LONDON*
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- **Separation and characterization of currents through store-operated CRAC channels and Mg2+-inhibited cation (MIC) channels** *JOURNAL OF GENERAL PHYSIOLOGY*
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- **Potentiation and inhibition of Ca2+ release-activated Ca2+ channels by 2-aminoethyldiphenyl borate (2-APB) occurs independently of IP3 receptors** *JOURNAL OF PHYSIOLOGY-LONDON*
  Prakriya, M., Lewis, R. S.
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- **Mitochondrial control of calcium-channel gating: A mechanism for sustained signaling and transcriptional activation in T lymphocytes** *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA*
  Hoth, M., Button, D. C., Lewis, R. S.
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  Lewis, R. S.
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- **A fluorometric method for estimating the calcium content of internal stores** *CELL CALCIUM*
  Bergling, S., Dolmetsch, R., Lewis, R. S., Keizer, J.
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- **Mitochondrial regulation of store-operated calcium signaling in T lymphocytes** *JOURNAL OF CELL BIOLOGY*
  Hoth, M., Fanger, C. M., Lewis, R. S.
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- **Differential activation of transcription factors induced by Ca2+ response amplitude and duration** *NATURE*
  Dolmetsch, R. E., Lewis, R. S., Goodnow, C. C., Healy, J. I.
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- **Function follows form: The role of store-operated calcium channels in T-cell activation** *CELLULAR PHYSIOLOGY AND BIOCHEMISTRY*
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- **Calcium-dependent potentiation of store-operated calcium channels in T lymphocytes** *JOURNAL OF GENERAL PHYSIOLOGY*
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- **CHARACTERIZATION OF T-CELL MUTANTS WITH DEFECTS IN CAPACITATIVE CALCIUM-ENTRY - GENETIC-EVIDENCE FOR THE PHYSIOLOGICAL ROLES OF CRAC CHANNELS** *JOURNAL OF CELL BIOLOGY*
  Fanger, C. M., Hoth, M., Crabtree, G. R., Lewis, R. S.
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  Zweifach, A., Lewis, R. S.

1995; 270 (24): 14445-14451

- **RAPID INACTIVATION OF DEPLETION-ACTIVATED CALCIUM CURRENT (I-CRAC) DUE TO LOCAL CALCIUM FEEDBACK** *JOURNAL OF GENERAL PHYSIOLOGY*
  Zweifach, A., Lewis, R. S.
  1995; 105 (2): 209-226
- **SIGNALING BETWEEN INTRACELLULAR CA2+ STORES AND DEPLETION-ACTIVATED CA2+ CHANNELS GENERATES [CA2+](I) OSCILLATIONS IN T-LYMPHOCYTES** *JOURNAL OF GENERAL PHYSIOLOGY*
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- **MITOGEN-REGULATED CA2+ CURRENT OF T-LYMPHOCYTES IS ACTIVATED BY DEPLETION OF INTRACELLULAR CA2+ STORES** *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA*
  Zweifach, A., Lewis, R. S.
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- **CHLORIDE CHANNELS ACTIVATED BY OSMOTIC-STRESS IN T-LYMPHOCYTES** *JOURNAL OF GENERAL PHYSIOLOGY*
  LEWIS, R. S., ROSS, P. E., CAHALAN, M. D.
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