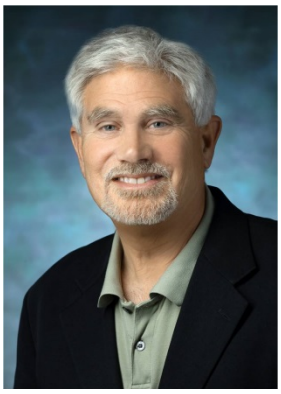
Peter N. Devreotes, Ph.D.



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Education

1971	**B.S. (Physics)** - University of Wisconsin, Madison, WI
1977	**Ph.D. (Biophysics)** - Johns Hopkins University, Baltimore, MD
1977-1980	**Postdoctoral Fellow (Biochemistry)** - University of Chicago, IL

Positions and Employment

1980 - 1985	Assistant Professor, Biological Chemistry, The Johns Hopkins University School of Medicine, Baltimore, MD
1985 - 1987	Associate Professor, Biological Chemistry, The Johns Hopkins University School of Medicine, Baltimore, MD
1987-2000	Professor, Biological Chemistry, The Johns Hopkins University School of Medicine, Baltimore, MD
2000 -	Director and Professor, Cell Biology, The Johns Hopkins University, Baltimore, MD
2009 -	Isaac Morris and Lucille Elizabeth Hay Professorship, Department of Cell Biology, The Johns Hopkins University School of Medicine, Baltimore, MD

Experience and Professional Memberships

1986 -	Member, American Society for Biochemistry and Molecular Biology
1988 -	Member, American Society for Cell Biology
1990 -	Chair, Gordon Conference on Sensory Transduction in Microorganisms
1990 - 2000	Director BCMB Graduate Program, JHU School of Medicine
1990 - 1993	Member, American Cancer Society Scientific Review Committee
1996 - 1997	Reviewer, NIH Cell Biology Study Section
1997 - 1999	Reviewer, NIH Biochemistry Study Section
1997 - 2004	Associate Editor, Molecular Biology of the Cell
2004 - 2007	Elected Council Member, American Society for Cell Biology
2005 -	Founder and Chair Gordon Conference on Gradient Sensing and Directed Cell Migration
2005 - 2010	Member, Institute for NanoBioTechnology Steering Committee
2007 -	Reviewer, NRSA Cell Biology and Development Fellowship Study Section
2007 -	Reviewer, NIH Cell Structure Function Study Section
2007 -	External Reviewer, Department of Cell Biology, University of Virginia
2007 - 2011	Member, Advisory Committee of the Cell Migration Consortium
2006 - 2011	Member, Alliance for Cell Signaling
2007 - 2011	Member, Searle Scholars Advisory Board
2014 -	Member, Allen Institute for Cell Biology Advisory Board

Honors and Named Seminars

1977	Fellowship, Damon Runyon Cancer Research Foundation
1980	Faculty Research Award, American Cancer Society
1984	Established Investigator Award, American Heart Association
1994	Givaudan-Roure Lecture, American Chemosensory Society
1995	Plenary Lecturer, Second Messengers and Protein Phosphorylation
1996	Staples Seminar, University of Maine
1998	Plenary Lecturer, XIII ECRO Congress Siena, Italy
2001	The Myron Levine Lectureship, University of Michigan, Ann Arbor, MI
2001	Kenneth Sparks/Julia Fisher Lectureship, University of Connecticut
2003	Keynote Speaker, Keystone Symposia on Cell Migration, Breckenridge
2003	Plenary Lecturer, 62nd Annual Meeting, Society for Developmental Biology, Boston, MA
2004	Keynote Speaker, 3rd TLL Life Sciences Symposium, Singapore
2004	Plenary Lecturer, Second Messengers & Phosphoproteins, Montreal, Canada
2005	Elected Member, National Academy of Sciences
2005	Merit Award, National Institutes of Health
2005	Plenary Lecturer, Keystone Symposium on Cell Migration, Snowbird, UT
2006	Keynote Speaker, 7th Annual Great Lakes GPCR Symposium
2007	Keynote Speaker, Gordon Conference on Fibronectins, Integrins & Related Molecules
2007	Keynote Speaker, Gordon Conference on Phosphorylation and G-Protein Signaling
2010	Keynote Speaker, Axon Guidance, CSH Meeting on Synaptic Plasticity and Regeneration
2012	Plenary Lecturer, Cell Signaling and Cytoskeleton in Directed Cell Migration, Vanderbilt U
2013	Keynote Speaker, Gordon Conference on Directed Cell Migration
2015	Plenary Lecturer German Society of Cell Biology
2016	Endowed Chairs Speaker University of Calgary
2016	Elected as Inaugural ASCB Fellow
2017	Inaugural Goode Lecture, University of California, Santa Barbara
2017	Bei Shizhang Lecture, Institute of Biophysics, Chinese Academy of Sciences, Beijing, China
2019	Recipient of the E.B. Wilson Medal of the American Society for Cell Biology

Personal Statement

I began pursuing mechanisms of chemotaxis during my post-doctoral fellowship at that time when directed migration in eukaryotic cells was poorly recognized. As outlined in Contributions to Science, my research has advanced the understanding and appreciation of this fascinating process. Many of the concepts we discovered by developing *Dictyostelium* as a model system extend to human leukocytes and metastasizing cancer cells, demonstrating the importance of this fundamental cell biological process in physiology and medicine. I have published extensively including many invited reviews on chemotaxis, presented our studies at over 400 national and international venues, and founded a popular Gordon Research Conference on Directed Cell Migration. I have trained over 65 students and fellows, many of whom hold advanced academic or industry positions related to cell signaling and migration. In recognition of our work, I have received continuous NIH support for 35 years including a Merit Award, I have been invited to present named seminars, and I have been elected to the National Academy of Science. I served as Director the BCMB Graduate Program for 10 years and as Director of the Department of Cell Biology at Johns Hopkins School of Medicine since 2000. I have served on numerous NIH study sections, the ASCB Council, the Searle Scholars Advisory Board, and the Advisory Board of the Allen Institute for Cell Science. These experiences and my training in Physics and Biophysics have given me perspective across many disciplines.

Contributions to Science

1. My research has been instrumental in making Dictyostelium a powerful discovery model for directed migration of eukaryotic cells. My studies in the late 1970s elucidated the cell-cell signaling responses that generated self-organized waves of the chemoattractant cAMP that guide *Dictyostelium* cells to aggregate. I discovered the process of **adaptation** whereby cells respond transiently to changes in receptor occupancy and then adjust their sensitivity to the current level of stimulus. Our group identified the family of surface **cAMP receptors** that mediate chemotaxis and cell-cell signaling. Together with rhodopsin, the α-factor receptor in yeast, and the β-adrenergic receptors, our sequences of the cARs helped define the GPCRs class of receptors. With gene deletions, we validated the cARs and their associated G-proteins as the chemoattractant detection system. Five years later a similar system was identified in leukocytes. We showed that agonist-mediated phosphorylation of the C-terminal of the receptor mediated its internalization as described for other GPCRs but that adaptation was independent of phosphorylation. We also showed that GPCRs could function independently of G-proteins, which was later verified in mammalian cells. In summary, our work provided the first molecular insights to chemotaxis and showed it to be a highly-conserved, fundamental cell biological process.

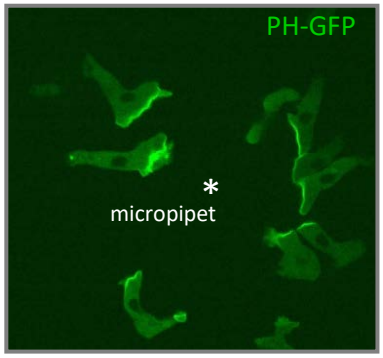
a. **Devreotes PN**, Steck TL. Cyclic 3',5' AMP relay in *Dictyostelium discoideum*. II. Requirements for the initiation and termination of the response. **J Cell Biol.** 1979 Feb;80(2):300-9. PMC2110342.
b. Tomchik KJ, **Devreotes PN**. Adenosine 3',5'-monophosphate waves in *Dictyostelium discoideum*: a demonstration by isotope dilution--fluorography. **Science**. 1981 Apr 24;212(4493):443-6. **(Cover Article).** PMID: 6259734.
c. Klein PS, Sun TJ, Saxe CL 3rd, Kimmel AR, Johnson RL, **Devreotes PN**. A chemoattractant receptor controls development in *Dictyostelium discoideum*. **Science**. 1988 Sep 16;241(4872):1467-72. PMID: 3047871.
d. Lilly P, Wu L, Welker DL, **Devreotes PN**. A G-protein beta-subunit is essential for *Dictyostelium development*. **Genes Dev.** 1993 Jun;7(6):986-95. PMID: 8099335.

2. We identified many of the genes and defined the "logic" of the circuitry linking the components in the chemotactic signal transduction network. Among the genes we identified early were the Ras GEF (AleA), showing that **Ras signaling** was important for chemotaxis, the adenylyl cyclases (ACA) that generate the self-organizing cAMP gradients that guide cells, and a cytosolic regulator of adenylyl cyclase (Crac) that provided the first **biosensor for PIP3** (see contribution 3). We discovered a novel protein, **Pianissimo (PiaA)** needed for chemotaxis in *Dictyostelium* and growth in yeast. PiaA genes were conserved through human and were later found to be the signature subunits of **Tor Complex 2 (TorC2)**. We established links among signal transduction components and revealed the parallel structure of the network by showing that inhibition of chemotaxis requires simultaneous blocks in multiple pathways. We organized the literature into major reviews and increased awareness of the remarkable similarities between chemotactic signal transduction networks in amoebae and mammalian cells.

a. Pitt GS, Milona N, Borleis J, Lin KC, Reed RR, **Devreotes PN**. Structurally distinct and stage-specific adenylyl cyclase genes play different roles in *Dictyostelium* development. **Cell**. 1992 Apr 17;69(2):305-15. PMID: 1348970.
b. Insall R, Kuspa A, Lilly PJ, Shaulsky G, Levin LR, Loomis WF, **Devreotes P**. CRAC, a cytosolic protein containing a pleckstrin homology domain, is required for receptor and G protein-mediated activation of adenylyl cyclase in *Dictyostelium*. **J Cell Biol.** 1994 Sep;126(6):1537-45. PMC2290948.
c. Chen MY, Long Y, **Devreotes PN**. A novel cytosolic regulator, Pianissimo, is required for chemoattractant receptor and G protein-mediated activation of the 12 transmembrane domain adenylyl cyclase in *Dictyostelium*. **Genes Dev.** 1997 Dec 1;11(23):3218-31. PMC316743.
d. Swaney KF, Huang CH, **Devreotes PN**. Eukaryotic chemotaxis: a network of signaling pathways controls motility, directional sensing, and polarity. **Annu Rev Biophys.** 2010;39:265-89. PMC4364543.

3. We discovered that phosphoinositides play a key role in chemotaxis and defined the basic strategy that eukaryotic cells use to sense gradients: The biosensor for PIP3 we developed enabled us to **visualize signal transduction events** at the front of cells for the first time. We had shown that chemoattractant receptors and G-proteins remain uniformly distributed on the cell surface regardless of the external cue and, with a **FRET assay for G-protein activation** we devised, that it paralleled the shallow external gradient. In contrast, PIP3 was sharply localized toward the high side of a gradient, as shown by the PH domain of Crac fused to GFP in the image below. By disrupting the gene **for tumor suppressor, PTEN**, we proved that PIP3 activated cytoskeletal activity and promoted pseudopod production. These studies showed that, early in the signal transduction cascade, cells convert the external gradient into a sharp internal gradient, which is now recognized as a basic strategy for sensing. Consistently, we discovered an asymmetric localization of PIP3 at the poles of cells undergoing cytokinesis. Others expanded on these findings, showing roles for asymmetric PIP3 in phagocytosis and epithelial cell polarity.

The excessive spreading phenotype caused by deletion of PTEN in *Dictyostelium* was reversed by expressing human PTEN and this enabled a structural-functional analysis of this important tumor suppressor. We discovered that the phosphorylated C-terminal tail of the enzyme folded back in an intramolecular inhibitory interaction. We defined a series of residues in PTEN that "open" the molecule causing its recruitment to the membrane and activating it. In a related study, we found that a fraction of tumor causing mutations in PTEN act specifically by preventing its association with the membrane.



The enzymes that control local PIP3 levels were the first examples of **dynamic "front" and "back"** signal transduction markers. PIP3 accumulates locally because PI3K is recruited to, and PTEN dissociates from, the membrane toward the high side of the gradient. We subsequently found that many other events are regulated in a similar, highly coordinated manner in response to chemotactic stimuli. These include Ras and Rac GTPases, PI3Ks, TorC2, phospholipase C (PLC), Mst1/2 kinase, myosin heavy chain kinase (MHCK), and protein kinases B (PKBs), which are activated, and PTEN, novel back protein CynA, MHC, and cortexillin, which dissociate from the membrane and are inactivated.

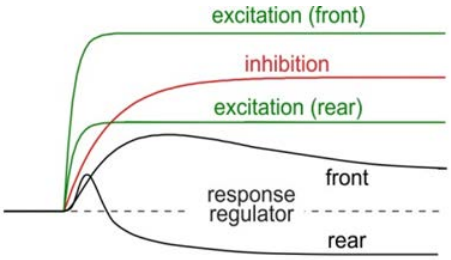
a. Xiao Z, Zhang N, Murphy DB, **Devreotes PN**. Dynamic distribution of chemoattractant receptors in living cells during chemotaxis and persistent stimulation. **J Cell Biol.** 1997 Oct 20;139(2):365-74. PMC2139806.

b. Parent CA, Blacklock BJ, Froehlich WM, Murphy DB, **Devreotes PN**. G protein signaling events are activated at the leading edge of chemotactic cells. **Cell**. 1998 Oct 2;95(1):81-91. PMID: 9778249.

c. Janetopoulos C, Jin T, **Devreotes P**. Receptor-mediated activation of heterotrimeric G-proteins in living cells. **Science**. 2001 Mar 23;291(5512):2408-11. PMID: 11264536.

d. Iijima M, **Devreotes P**. Tumor suppressor PTEN mediates sensing of chemoattractant gradients. **Cell**. 2002 May 31;109(5):599-610. **(Cover Article)**. PMID: 12062103.

4. We introduced conceptual advances to chemotaxis field, including the "LEGI" model. Through a series of genetic and pharmacological perturbations, we showed that chemotaxis comprises separable processes of **motility, directional sensing, and polarity**. For example, directional sensing occurs even in cells that are immobilized with cytoskeletal inhibitors: front or back events, such as PI3K or PTEN activation, localize toward or away, from the high side of the gradient. These observations proved that eukaryotic cells must use a **spatial mechanism for gradient sensing**, comparing concentrations across the cell. These events are localized and persistent in a stable gradient and track the gradient when it is repositioned. With uniform stimuli, front or back events transiently increase or decrease uniformly around the cell perimeter. To explain this spatial-temporal regulation, we proposed the **local excitation and global inhibition (LEGI)** model, which has had considerable influence on thinking in the chemotaxis field.



In the LEGI scheme, receptor occupancy determines the steady-state levels of an excitor and an inhibitor, which balance to control the level of a response regulator. Increases in receptor occupancy initiate fast and slow increases in the excitor and inhibitor, respectively, and a transient increase in the response regulator ensues until the balance is restored and cells **adapt** to the current level of stimulus. In a gradient, since the inhibitor is more global than the excitor, the response regulator is persistently elevated at the front and depressed at the rear, differences that depend on the steepness and not the midpoint of the gradient.

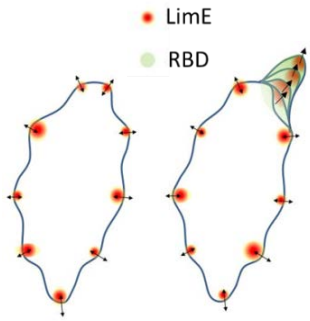
a. Parent CA, **Devreotes PN**. A cell's sense of direction. **Science**. 1999 Apr 30;284(5415):765-70. PMID: 10221901.

b. Janetopoulos C, Ma L, **Devreotes PN**, Iglesias PA. Chemoattractant-induced phosphatidylinositol 3,4,5-trisphosphate accumulation is spatially amplified and adapts, independent of the actin cytoskeleton. **Proc Natl Acad Sci U S A**. 2004 Jun 15;101(24):8951-6. PMC428453.

c. Xiong Y, Huang CH, Iglesias PA, **Devreotes PN**. Cells navigate with a local-excitation, global-inhibition-biased excitable network. **Proc Natl Acad Sci U S A**. 2010 Oct 5;107(40):17079-86. PMC2951443.

d. Shi C, Huang CH, **Devreotes PN**, Iglesias PA. Interaction of motility, directional sensing, and polarity modules recreates the behaviors of chemotaxing cells. **PLoS Comput Biol.** 2013;9(7): e1003122. PMC3701696.

5. We discovered that a coordinated series of excitable networks control gene expression, cell-cell signaling, and chemotaxis. Our most recent studies of biochemically excitable systems are transforming our understanding of the gene expression events and mechanics involved in cell migration. At one level, we discovered a GATA transcription factor, GtaC, which is a **master regulator of the acquisition of chemotactic competence** and has a remarkable mode of regulation. The developmental program *Dictyostelium* is mediated by self-organized oscillatory signals of extracellular cAMP which provide chemotactic gradients and induce the chemotaxis genes. We found that each stimulus activates GtaC and then, counterintuitively, promotes its exit from the nucleus; as the chemoattractant level falls, GtaC reenters the nucleus. Each cycle results in a transient burst of transcription of the regulated genes so that the amount of transcription depends on the number of stimuli. This biological circuit functions as a "positive edge detector" used in computers to count events. Similar regulatory mechanisms may control systems in development and learning that respond exclusively to oscillatory or repeated stimulation.



At another level, we discovered that cell motility is driven by the stochastic activation of an **excitable signal transduction network** that organizes independent **cytoskeletal oscillators,** as shown in cartoon. Using biosensors for Ras activity (RBD), we found that signal transduction events propagate as waves along the cell cortex and that brief chemotactic stimuli trigger all-or-none responses, characteristics of an excitable network. Coupling of the signal transduction and cytoskeletal networks (LimE) generates larger protrusions that mediate cell migration. Thus, excitability of the signal transduction network is the "pacemaker" and primary driver of cell motility. **Directional sensing** is mediated by the LEGI response regulator that enhances, or suppresses, excitability at front, or rear, of the cell (see contribution 4). These studies are still in the early phases but represent a completely new and elegant paradigm for directed cell migration.

a. Cai H, Das S, Kamimura Y, Long Y, Parent CA, **Devreotes PN**. Ras-mediated activation of the TORC2-PKB pathway is critical for chemotaxis. **J Cell Biol.** 2010 Jul 26;190(2):233-45. PMC2930282.

b. Huang CH, Tang M, Shi C, Iglesias PA, **Devreotes PN**. An excitable signal integrator couples to an idling cytoskeletal oscillator to drive cell migration. **Nat Cell Biol.** 2013 Nov;15(11):1307-16. PMC3838899.

c. Cai H, Katoh-Kurasawa M, Muramoto T, Santhanam B, Long Y, Li L, Ueda M, Iglesias PA, Shaulsky G, **Devreotes PN**. Nucleocytoplasmic shuttling of a GATA transcription factor functions as a development timer. **Science**. 2014 Mar 21;343(6177):1249531. PMC4061987.

d. Tang M, Wang M, Shi C, Iglesias PA, **Devreotes PN**, Huang CH. Evolutionarily conserved coupling of adaptive and excitable networks mediates eukaryotic chemotaxis. **Nat Commun.** 2014 Oct 27;5:5175. PMC4211273.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/peter%20n..devreotes.1/bibliography/43791685/public/?sort=date&direction=ascending

Research Support

Ongoing

NIH R35 GM118177 Devreotes (PI) 05/01/2016-21
Excitable Networks in Directed Cell Migration
Role: PI

DOD AFSOR MURI Losert (PI) 04/01/2016-2019
Subaward from University of Maryland
Understanding and Controlling the Coupled Electrical, Chemical, & Mechanical Excitable Networks of Living Systems
Role: Co-PI

DARPA-16-17-BC-FP-005 Iglesias (PI) 09/23/2016-03/30/2020
Design of a pathogen-specific chemotactic network
Role: Co-PI

Recently Terminated

NIH R01 GM034933-29 Devreotes (PI) 02/01/1987-03/31/2016
Temporal and Spatial Signaling in Chemotaxis
This grant focuses on feedback loops in excitable networks and adaptation mechanisms in chemotaxis.
Role: PI

NIH R37 GM028007-36 Devreotes (PI) 07/01/1980-06/30/2016
Signaling Networks in Chemotaxis and Cytokinesis
This grant aims to identify novel genes involved in motility and cytokinesis.
Role: PI