BIOGRAPHICAL SKETCH

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NAME: Devreotes, Peter N.

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POSITION TITLE: Professor, Cell Biology

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
University of Wisconsin, Madison, WI	BS	1971	Physics
Johns Hopkins University, Baltimore, MD	PhD	1977	Biophysics
University of Chicago, Chicago, IL	Postdoctoral Fellow	1980	Biochemistry

A. 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 40 years including a Merit Award, I have been invited to present many named seminars, I have been elected to the National Academy of Science, and I received the **2019 E.B. Wilson Medal**, the highest award for science of the American Society of Cell Biology. I have served as Director the BCMB Graduate Program and Director of the Department of Cell Biology at Johns Hopkins School of Medicine since 1990 and 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, all of which has given me perspective across many disciplines.
I have recently stepped down as Director of Cell Biology is in progress in order to devote increased effort on the new research we are doing. In the last several years our views have been transformed by the discovery that the chemotactic signal transduction network displays biochemical excitability with nearly all its activities propagating coordinately in waves across the cell membrane. This differs completely from textbook views of signal transduction and suggests that an underlying property of the membrane controls these events. Our efforts to unravel the feedback loops that mediate excitability are suggesting that membrane surface charge may be an organizing property. We have found that these novel features are largely conserved in human cells and that cancer cells display increased excitability of these signal transduction networks. For these reasons, I am more optimistic than ever that our field will continue to make important contributions to the understanding and treatment of disease.

B. Positions, Scientific Appointments, and Honors

Positions and Employment

2009- Isaac Morris and Lucille Elizabeth Hay Professor, Department of Cell Biology, The Johns Hopkins University School of Medicine, Baltimore, MD
2000 - 2020 Director and Professor, Cell Biology, The Johns Hopkins University, Baltimore, MD

1987 - 2000 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
1980 - 1985 Assistant Professor, Biological Chemistry, The Johns Hopkins University School of Medicine, Baltimore, MD

Other Experience and Professional Memberships

2023 - Visiting Scientist, Max Planck Florida Institute for Neuroscience, Jupiter, FL
2014 - 2022 Member, Allen Institute for Cell Science Advisory Board, Seattle, WA
2007 - Reviewer, NIH Cell Structure Function Study Section
2007 - Reviewer, NRSA Cell Biology and Developmental Fellowship Study Section
2007 - 2011 Member, Searle Scholars Advisory Board
2006 - 2011 Member, Alliance for Cell Signaling
2007 - 2011 Member, Advisory Committee of the Cell Migration Consortium
2005 - Founder and Chair, Gordon Conference on Gradient Sensing and Directed Cell Migration
2004 - 2007 Elected Council Member, American Society for Cell Biology
1997 - 2004 Associate Editor, Molecular Biology of the Cell
1997 - 1999 Reviewer, NIH Biochemistry Study Section
1996 - 1997 Reviewer, NIH Cell Biology Study Section
1990 - Chair, Gordon Conference on Sensory Transduction in Microorganisms
1990 - 1993 Member, American Cancer Society Scientific Review Committee
1990 - 2000 Director, BCMB Graduate Program, Johns Hopkins University School of Medicine

Honors

2021 Distinguished Service Professor, Johns Hopkins University
2019 **Recipient of the E.B. Wilson Medal of the American Society for Cell Biology**
2016 Elected as Inaugural ASCB Fellow
2016 Endowed Chairs Speaker Series, University of Calgary, Calgary, AB, Canada
2013 Keynote Speaker, Gordon Conference on Directed Cell Migration, Galveston, TX
2010 Keynote Speaker, Axon Guidance, CSH Meeting on Synaptic Plasticity and Regeneration, Cold Spring Harbor, NY
2007 Keynote Speaker, Gordon Conference on Phosphorylation and G-Protein Mediated Signaling Networks, University of New England, Biddeford, ME
2007 Keynote Speaker, Gordon Conference on Fibronectins, Integrins & Related Molecules, Lucca (Barga), Italy
2005 Plenary Lecturer, Keystone Symposium on Cell Migration, Snowbird, UT
2005 Merit Award, National Institutes of Health, Bethesda, MD
2005 **Elected Member, National Academy of Sciences**
2004 Plenary Lecturer, Second Messengers & Phosphoproteins, Montreal, QC, Canada
2003 Plenary Lecturer, 62nd Annual Meeting, Society for Developmental Biology, Boston, MA
2003 Keynote Speaker, Keystone Symposia on Cell Migration, Breckenridge, CO
2001 Kenneth Sparks/Julia Fisher Lectureship, University of Connecticut, Storrs, CT
2001 The Myron Levine Lectureship, University of Michigan, Ann Arbor, MI
1998 Plenary Lecturer, XIII ECRO Congress, Siena (Tuscany), Italy
1994 Givaudan-Roure Lecture, American Chemosensory Society, Sarasota, FL
1984 Established Investigator, American Heart Association
1980 Faculty Research Award, American Cancer Society
1977 Fellowship, Damon Runyon Cancer Research Foundation

C. 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. doi: 10.1083/jcb.80.2.300. PMID: 222770. 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).** doi: 10.1126/science.6259734. 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. doi: 10.1126/science.3047871. 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. doi: 10.1101/gad.7.6.986. 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. doi: 10.1016/0092-8674(92)90411-5. 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. 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 of signal transduction events, 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 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. doi: 10.1016/s0092-8674(00)81784-5. 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. doi: 10.1126/science.1055835. 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)**. doi: 10.1016/s0092-8674(02)00745-6. 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 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 activator (or excitor) and an inhibitor, which balance to regulate the response. Increases in receptor occupancy initiate fast and slow increases in the activator and inhibitor, respectively, and a transient response 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 activator, the response is persistently elevated at the front and depressed at the rear.

While it is clear that G-protein activation represents the activator, the molecular identity of the inhibitor remains one of our important aims going forward. Intuition suggests that our discovery of a **master regulator of the acquisition of chemotactic competence,** GATA transcription factor, GtaC, and its remarkable mode of regulation, provides an important clue. The developmental program of *Dictyostelium* is mediated by self-organized oscillatory signals of extracellular cAMP which provide both chemotactic gradients and induce the chemotaxis genes. The inhibitor in the LEGI scheme controls the activity of the adenylyl cyclase in these oscillations. Each oscillation activates GtaC and then, counterintuitively, promotes its reversible exit from 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. The exit from the nucleus is mediated by ERK and GSK3 phosphorylation of GtaC. The tight coordination of this exit ed with the period of the oscillation, suggest that the LEGI inhibitor may also be a target of ERK and GSK3.

a. Parent CA, **Devreotes PN**. A cell's sense of direction. **Science**. 1999 Apr 30;284(5415):765-70. doi: 10.1126/science.284.5415.765. 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. 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.

d. 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.

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 cell migration and signal transduction in general. We discovered that cell motility is driven by the stochastic activation of an **excitable signal transduction network** that organizes an independent **excitable cytoskeletal network**. Using biosensors for Ras activity and other activities, we found that signal transduction events display characteristics of excitable systems including propagating as coordinated waves along the cell cortex, all-or-none responses, and refractory period. Coupling of the broad signal transduction waves to rapid puncta of cytoskeletal networks 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).

Excitable networks minimally require positive and delayed negative feedback loops. We have defined positive feedback loops consisting of mutual inhibition between Rap/Ras activity and negatively charged PI(4,5)P2 and PI(3,4)P2. As Rap/Ras activity increases, each of these PIP2s decrease. In turn, acute lowering of either PIP2 activates Rap/Ras. The activation appears in part to be regulated by several Rap and Ras GAPs which bind to these PIP2s and dissociate from the membrane as PIP2 levels fall. The observation of reversible, local assembly/disassembly of signal transduction components and events suggests organization by a common underlying property of the membrane. That is, the process more akin to the regulation action potential in a neuron than the wiring diagrams typically presented textbook view.

a. 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. (Inaugural Article)
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. Miao Y, Bhattacharya S, Edwards M, Cai H, Inoue T, Iglesias P, **Devreotes PN**. 2017. Altering the threshold of an excitable signal transduction network changes cell migratory mode. **Nat Cell Biol.** Apr;19(4):329-340. PMC5394931.
b. Banerjee T, Biswas D, Pal DS, Miao Y, Iglesias PA, **Devreotes PN**. 2022. Spatiotemporal dynamics of membrane surface charge regulates cell polarity and migration. **Nat Cell Biol.** 2022 Oct 6. Online ahead of print. doi: 10.1038/s41556-022-00997-7.

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