BIOGRAPHICAL SKETCH

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NAME: John S. Parkinson

eRA COMMONS USER NAME: JSParkinson

POSITION TITLE: Distinguished Professor of 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	Completion Date	FIELD OF STUDY
Haverford College, Haverford, PA	A.B.	06/1965	Biology
California Institute of Technology, Pasadena, CA	Ph.D.	10/1969	Genetics & Biophysics
University of Wisconsin, Madison, WI	postdoctoral	08/1972	Biochemistry & Genetics

A. Personal Statement

I've been an independent principal investigator in the field of microbial signal transduction for over 40 years, during which time my research has been continuously funded by NIGMS. My scientific expertise is mainly in the use of genetic and molecular approaches to elucidate the signaling mechanisms that underlie chemotactic behaviors in *E. coli*. My lab collaborates closely with researchers who have expertise in complementary areas, including biochemistry, biophysics, structural biology, molecular dynamics and mathematical modeling. Together, we have made sustained and substantive contributions to current molecular understanding of chemoreceptor function, motility mechanisms, and two-component signaling systems in microorganisms.

(a) Parkinson, J.S. & E.C. Kofoid (1992) Communication modules in bacterial signaling proteins. *Annu. Rev. Genet.* **26:** 71-112.

(b) Parkinson, J.S. (1993) Signal transduction schemes of bacteria. *Cell* **73:** 857-871.

(c) Parkinson, J.S. (2010) Signaling mechanisms of HAMP domains in chemoreceptors and sensor kinases. *Annu. Rev. Microbiol*. **6**4:101-122.

(d) Parkinson, J.S., G.L. Hazelbauer & J.J. Falke (2015) Signaling and sensory adaptation in *Escherichia coli* chemoreceptors: 2015 update. *Trends Microbiol* **23:** 257-266.

B. Positions and Honors

Positions and Employment

1969 Visiting Assistant Professor, Dept. Microbiology, Oregon State University, Corvallis, Oregon

1970 Postdoctoral Fellow, Department of Biochemistry, U. Wisconsin, Madison, Wisconsin

1972 Assistant Professor, Department of Biology, University of Utah

1976 Associate Professor, Department of Biology, University of Utah

1981 Professor, Department of Biology, University of Utah

1982-1995 Adjunct Professor, Dept. Cellular, Viral and Molecular Biology, U. Utah School of Medicine

Other Experience and Professional Memberships

1976-1979 Microbial Chemistry Study Section, NIH

1979-1980 Microbial Genetics Study Section, NIH

1982-1988 Editorial Board, *Journal of Neurogenetics*

1989-1991	Microbial Physiology and Genetics Study Section, NIH
1988-2005	Editorial Board, *Journal of Bacteriology*
1990-1992	Director, Molecular Biology Program, University of Utah
1996-2001	Chairman, Department of Biology, University of Utah
2002-2013	Director, Microbial Biology Program, University of Utah
2005-2015	Editor, *Journal of Bacteriology*
2012-2017	Editorial Advisory Board, *Molecular Microbiology*
memberships:	American Society for Microbiology; American Association for the Advancement of Science

Honors

1966-1969	NDEA Title IV Graduate Fellowship, California Institute of Technology
1970-1971	NSF Postdoctoral Fellowship
1971-1972	NIH Postdoctoral Fellowship
1980-1981	Alexander von Humboldt Research Fellow, EMBL, Heidelberg, West Germany
1992-2001	NIH MERIT award
1996	elected fellow, American Academy of Microbiology
1999	Distinguished Research Award, University of Utah
2009	Distinguished Professor, University of Utah

C. Contributions to science

1. Bacteria extensively use two types of stimulus-response systems to cope with selective challenges: two-component signaling pathways that mediate changes in gene expression and chemotaxis signaling pathways that control locomotor behaviors. My lab's early genetic work on *E. coli* chemotaxis identified the protein components of the chemotaxis signaling pathway, defined their functions, and established their communication connections. Those studies produced a comprehensive picture of the "wiring diagram" of the chemotaxis circuitry and described the signaling properties of communication modules with which bacteria assemble a vast array of two-component signaling pathways. These insights paved the way for subsequent molecular analyses of the underlying signaling mechanisms.

   During the course of our research, my group has developed and disseminated thousands of bacterial strains and plasmids to labs around the world for studies of chemotaxis and motility in various microbes.

   (a) Parkinson, J.S. (1977) Behavioral genetics in bacteria. *Annu. Rev. Genetics* **11:**397-414.

   (b) Parkinson, J.S. & P.T. Revello (1978) Sensory adaptation mutants of *Escherichia coli*. *Cell* **15**:1221-1230.

   (c) Parkinson, J.S. & S.R. Parker (1979) Interaction of the *cheC* and *cheZ* gene products is required for chemotactic behavior in *Escherichia coli*. *Proc. Natl. Acad. Sci. USA* **76**:2390-2394.

   (d) Kofoid, E. & J.S. Parkinson (1988) Transmitter and receiver modules in bacterial signaling proteins. *Proc. Natl. Acad. Sci. USA* **85**:4981-4985.

2. In motile bacteria and archaea, chemoreceptors known as methyl-accepting chemotaxis proteins (MCPs) convert information about external attractant and repellent levels into signals that control locomotor behavior. The extensively studied MCPs of *Escherichia coli* serve as important models for understanding transmembrane and intracellular signal transduction. Our molecular studies of *E. coli* MCPs showed that the cytoplasmic hairpin tip of a receptor molecule forms stable complexes with a signaling autokinase (CheA) and with a scaffolding protein (CheW) that couples CheA activity to receptor control. We showed that the receptor core complex, the minimal signaling unit, is assembled

from trimers of receptor dimers interacting at their cytoplasmic tips. We found that receptors of different detection specificities signal collaboratively within a mixed trimer, leading to integration of stimulus inputs. More recently, in a collaboration with Ady Vaknin's group (Hebrew University, Jerusalem), we identified a protein-protein interaction between the CheA and CheW proteins that networks receptor core complexes into a signaling array that operates like a highly cooperative, multi-subunit, allosteric enzyme. Amino acid replacements in CheA or CheW that disrupt that key interface dissipate receptor arrays into individual core signaling complexes, which detect and respond to chemoeffectors, but with little or no cooperativity. We found that such mutants could not track shallow chemoeffector gradients, demonstrating that the structural features that link chemoreceptors into a cooperative ensemble confer a valuable behavioral advantage in the microbial world.

(a) Liu, J.D. & J.S. Parkinson (1989) Role of CheW protein in coupling membrane receptors to the intracellular signaling system of bacterial chemotaxis. *Proc. Natl. Acad. Sci. USA* **86:**8703-8707.

(b) Ames, P., C.A. Studdert, R.H. Reiser & J.S. Parkinson (2002). Collaborative signaling by mixed chemoreceptor teams in *Escherichia coli*. *Proc. Natl. Acad. Sci. USA* **99:**7060-7065.

(c) Studdert, C.A. & J.S. Parkinson (2004) Crosslinking snapshots of bacterial chemoreceptor squads. *Proc. Natl. Acad. Sci. USA* **101:**2117-2122.

(d) Pinas G.E., V. Frank, A. Vaknin & J.S. Parkinson (2016) The source of high signal cooperativity in bacterial chemosensory arrays. *Proc. Natl. Acad. Sci. USA* **113:**3335-3340.

3. Transmembrane chemoreceptors and sensor kinases typically contain a HAMP domain located in the membrane-proximal portion of their cytoplasmic signaling domain. HAMP domains comprise four-helix bundle signaling elements that mediate input-output transactions in many microbial signaling proteins. Over the past ten years, my group carried out extensive mutational analyses of the HAMP domain in Tsr, the *E. coli* serine chemoreceptor, that led to a new signaling paradigm with likely widespread relevance to biological signal transduction mechanisms. We found that HAMP domains are not discrete two-state signaling devices, but rather operate over a range of essentially isoenergetic conformations ("dynamic-bundle" model). Input signals shift the HAMP conformational landscape, which in turn governs the dynamic behavior of the chemoreceptor tip to elicit output responses. These studies provided the conceptual framework for the emerging view that highly sensitive chemoreceptor molecules, like those of bacteria, contain serially connected signaling elements whose structural interactions are dynamically poised to respond to low-energy ligand-binding events. Dynamics-based signaling may prove to be a general mechanistic strategy of sensory transduction systems in all organisms.

   (a) Zhou, Q., P. Ames & J.S. Parkinson (2009) Mutational analyses of HAMP helices suggest a dynamic bundle model of input-output signalling in chemoreceptors. *Mol. Microbiol.* **73:**801-814.

   (b) Zhou, Q., P. Ames & J.S. Parkinson (2011) Biphasic control logic of HAMP domain signalling in the *Escherichia coli* serine chemoreceptor. *Mol. Microbiol.* **80:**596-611.

   (c) Ames, P., Q. Zhou & J.S. Parkinson (2014) HAMP domain structural determinants for signalling and sensory adaptation in Tsr, the *Escherichia coli* serine chemoreceptor. *Mol. Microbiol.* **91**:875-886.

   (d) Lai, R.Z. & J.S. Parkinson (2014) Functional suppression of HAMP domain signaling defects in the *E. coli* serine chemoreceptor. *J. Mol. Biol*. **426**:3642-3655.

4. A longstanding aim of our research program has been to determine the mechanism(s) by which chemoreceptors activate and deactivate CheA autophosphorylation in core signaling complexes. Our early work established the functional architecture of the CheA molecule and identified its substrate (P1), target acquisition (P2), catalytic (P4) and receptor coupling (P5) domains and, more recently, defined the determinants for productive interaction of the P1 and P4 domains. In a collaboration with Grant Jensen's cryo-EM group at Caltech, we found that the P1 and P2 domains had different dynamic behaviors in receptor arrays that were mutationally locked in kinase-OFF or kinase-ON signaling states. That study provided the first evidence that receptors might signal through dynamic motions that control

the interactions between CheA domains. Recently, we showed that chemoreceptors control kinase activity not through a direct connection to the CheA.P5 regulatory domain, as studies from several groups had claimed, but rather through a shared connection to the CheW protein.

(a) Morrison, T.B. & J.S. Parkinson (1994) Liberation of an interaction domain from the phosphotransfer region of CheA, a signaling kinase of *Escherichia coli*. *Proc. Natl. Acad. Sci. USA* **91**:5485-5489.

(b) Briegel, A., P. Ames, J.C. Gumbart, C.M. Oikonomou, J.S. Parkinson & G.T. Jensen (2013) The mobility of two kinase domains in the *Escherichia coli* chemoreceptor array varies with signalling state. *Mol. Microbiol.* **89:** 831-841.

(c) Piñas, G.E., DeSantis, M.D. & J.S. Parkinson (2018) Noncritical signaling role of a kinase-receptor interaction surface in the *Escherichia coli* chemosensory core complex. *J. Mol. Biol.* **430**:1051-1054.

5. An important focus of our current research is to elucidate the molecular mechanism(s) of transmembrane signaling in chemoreceptors. Working with the serine receptor Tsr, we identified a five-residue "control cable" segment that links a signaling transmembrane helix (TM2) to a HAMP helix (AS1). We obtained evidence for a structural change (“helix clutch”) at the TM2-control cable junction that negotiates the intensity of register clashes between the TM2 and AS1 helices to modulate the packing stability of the HAMP bundle. We found that the sidechain of one control cable residue (I214) plays a critical role in the signaling transition induced by a serine stimulus. Molecular dynamics simulations by our collaborator Keith Cassidy (U. Illinois) revealed that I214 might stabilize the kinase-OFF output state through an interaction with hydrophobic residues in nonsignaling TM1 helices that “freeze” dynamic motions of the TM2 helix normal to the plane of the membrane. This mechanism of transmembrane signaling would be distinctly different from the TM2 “piston” displacement mechanism that other groups have proposed for the aspartate/maltose (Tar) and the ribose/galactose (Trg) receptors.

   (a) Ames, P. & J.S. Parkinson (1988) Transmembrane signaling by bacterial chemoreceptors: *E. coli* transducers with locked signal output. *Cell* **55**:817-826.

   (b) Kitanovic, S., P. Ames, & J.S. Parkinson (2011) Mutational analysis of the control cable that mediates transmembrane signaling in the *E. coli* serine chemoreceptor. *J. Bacteriol.* **193**:5062-5072.

   (c) Kitanovic S., P. Ames & J.S. Parkinson (2015) A trigger residue for transmembrane signaling in the *Escherichia coli* serine chemoreceptor. *J. Bacteriol.* **197**:2568-2579.

   (d) Ames, P., S. Hunter & J.S. Parkinson (2016) Evidence for a helix-clutch mechanism of transmembrane signaling in a bacterial chemoreceptor. *J. Mol. Biol.* **428:** 3776-3788.

Complete List of Published Work in MyBibliography:

https://www.ncbi.nlm.nih.gov/sites/myncbi/john.parkinson.1/bibliography/41158607/public/?sort=date&direction=descending

D. Additional Information: Research Support and/or Scholastic Performance:

Ongoing Research Support

5R01 GM19559-45 Parkinson (PI) 05/01/2015 - 02/28/2019

NIH/NIGMS: Intracellular signaling by bacterial chemoreceptors

This project uses molecular genetic and molecular dynamics approaches to elucidate the mechanisms of intracellular signaling by *Escherichia coli* chemoreceptors. Recent studies focus on: the structure and function of receptor signaling complexes and higher-order receptor arrays; the role of the HAMP domain in mediating input-output control in chemoreceptors; receptor mechanism(s) for transmembrane signaling.

Role: PI

BSF 2017356 (A. Vaknin and JS Parkinson, co-PI's) 10/01/2018 - 09/30/2022

U.S.-Israel Binational Science Foundation: Allosteric coupling within bacterial chemossnsory arrays

The goal of this international collaboration is to define the allosteric interactions between the components of chemoreceptor core complexes, using array interface 2 mutants.

Role: co-PI