BIOGRAPHICAL SKETCH

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NAME: Park, Hay-Oak

POSITION TITLE: Professor

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
Seoul National University, Seoul, Korea	BS & MS	06/1983	Biochemistry
University of Wisconsin, Madison, WI	PhD	05/1991	Biochemistry & Molecular Biology
University of California, San Francisco, CA	Postdoctoral	08/1996	Biochemistry & Cell Biology

A. Personal Statement

The long-term goal of my research is to understand how cell polarity and asymmetry are regulated and how cell polarity is linked to cellular lifespan. Since my PhD training with Elizabeth A. Craig, a pioneer in the field of heat-shock response and molecular chaperones, I have been fascinated with the intricate mechanisms underlying cellular homeostasis. As a graduate student, I studied how expression of a HSP70 gene is controlled by both positive and negative regulators in response to external stress.

During my postdoctoral training with Ira Herskowitz, a renowned geneticist and leader in cell differentiation, I learned the 'awesome power of yeast genetics' and how to convert complex biological questions into simpler questions that we can tackle experimentally. I started to address fundamental questions of cell morphogenesis using biochemical tools in combination with genetic tools. I discovered that the GTPase activating protein Bud2 plays a key role in yeast morphogenesis. Importantly, we provided the first evidence of a functional 'GTPase module' involved in yeast morphogenesis (*Park et al., 1993, Nature*). Being surrounded by highly collaborative cell biology groups at UCSF and frequent interactions with other yeast groups in the San Francisco Bay Area helped me develop from a biochemist into a biologist focused on cellular processes as well as further develop my interest in cell polarity and asymmetry.

Since establishing my lab at the Ohio State University, my research has focused on understanding how cells establish the proper axis of cell polarity. Although cell polarity has been intensively investigated, many studies have focused on mechanisms of spontaneous cell polarization (referred to as 'symmetry breaking'), leaving the role of internal spatial cues understudied. We are one of the few groups in the field that have focused on spatial-cue-directed cell polarization and have also extensively used biochemistry to dissect and reconstitute key steps of polarity establishment and characterize enzymes regulating the process, in combination with genetic *in vivo* studies. My sabbatical research with Fred Chang at Columbia University (currently at UCSF) in 2010 helped me bring state-of-the-art skills in quantitative microscopy into my research group. This new approach, combined with biochemistry, yeast genetics, and mathematical modeling, has facilitated our recent findings in polarity establishment. In particular, our discovery of biphasic Cdc42 polarization has brought new mechanistic insight into polarity establishment (*Kang et al., 2014, J Cell Biol*).

This new line of investigation is expected to fill a critical gap in our current understanding of cell proliferation and cell death and will thus allow us to make important contributions towards a better understanding of these universal questions of every living organism. The current application builds on my prior research and training experience and effectively combines interdisciplinary approaches through collaborations that involve mathematical modeling (Ching-Shan Chou, The Ohio State University), microfluidics (Derek Hansford, The Ohio State University), and functional genomics (Won-Ki Huh, Seoul

National University). With promising preliminary studies as well as proper personnel and established collaborations in place, we are perfectly poised to make rapid progress. We expect that this proposed study will allow us to extend the active research in cell polarity towards a new understanding of cell survival and cellular aging.

B. Positions

1996–2014	Assistant, AssociateProfessor, Department of Molecular Genetics, Ohio State University
2010–2011	Visiting Associate Professor, Columbia University College of Physicians and Surgeons, New York, NY
2014– present	Professor, Department of Molecular Genetics, Ohio State University, Columbus, OH Molecular Cellular Developmental Biology Program Ohio State Biochemistry Program The Interdisciplinary Biophysics Graduate Program

C. Contributions to Science & Selected Publications

1. **Defining the key role of GTPase modules in polarity establishment:** My early contributions include establishing the key role of the Ras and Rho GTPase modules in polarity establishment. I discovered that Bud2 is a GTPase activating protein (GAP) for Rsr1 (also known as Bud1), a Ras family GTPase, and provided the first biochemical evidence for the involvement of the small GTPase in polarity development. Importantly, we provided the concept of functional 'GTPase modules' involved in yeast morphogenesis. In subsequent studies, we demonstrated that the homotypic interaction of Rsr1 and the heterotypic interaction between Rsr1 and Cdc42, a Rho family GTPase, couple the selection of a growth site to the development of cell polarity. While Cdc42 was first discovered and characterized by John Pringle and colleagues, this evolutionally conserved protein has been subsequently identified in almost all organisms. Alan Hall and colleagues' discovery of Rho GTPases (including Cdc42) and their key roles in mammalian cell polarization further support the idea that yeast indeed serves as a universal model for this important question of cell polarization.

   a. **Park, H.-O.**, J. Chant, and I. Herskowitz (1993) *BUD2* encodes a GTPase activating protein for Bud1/Rsr1 necessary for proper bud-site selection in yeast. *Nature* 365: 269–274. PMID: 8371782

   b. Kang, P. J., A. Sanson, B. Lee, and **H.-O. Park** (2001) A GDP/GTP exchange factor involved in linking a spatial landmark to cell polarity. *Science* 292:1376–1378. PMCID: PMC4386611
   Highlighted in Science Express (2001 Apr 19); featured in the review, Curr. Biol. (2001) 11:R610

   c. Kozminski, K. G., L. Béven, E. Angerman, A. H. Y. Tong, C. Boone, and **H.-O. Park** (2003) Interaction between a Ras-like and a Rho-like GTPase couples the selection of a growth site to the development of cell polarity. *Mol. Biol. Cell* 14: 4958–4970. PMCID: PMC284798
   MBoC Paper of the Year Award (2004)

   d. Kang, P. J., L. Béven, S. Hariharan and **H.-O. Park** (2010) The Rsr1/Bud1 GTPase interacts with itself and the Cdc42 GTPase during bud-site selection and polarity establishment in budding yeast. *Mol. Biol. Cell* 21:3007–3016. PMCID: PMC2929994

2. **Establishing the roles of regulators of GTPases in cell polarization:** My major contributions include uncovering spatial and temporal regulation of Cdc42. My group first demonstrated the coupling between spatial cues and the Rsr1 GTPase module, providing a mechanistic insight into spatial cue-directed cell polarization. Another key contribution is our discovery of biphasic activation of Cdc42 by sequential actions of two GDP-GTP exchange factors in the G1 phase of the cell cycle. This spatial and temporal regulation of Cdc42 is likely to be fundamental to appropriate recognition and readout of cell polarity cues during yeast budding. We also combined quantitative microscopy and computational modeling in collaboration with Wing Cheong Lo and C.-S. Chou to show fine-tuning of Cdc42 polarization dynamics and negative regulation of Cdc42 polarization by Rga1, a Cdc42 GAP. Importantly, our recent studies suggest that biphasic Cdc42 polarization in the G1 phase is coupled to stepwise assembly of the septin ring for bud emergence (*Kang et al., submitted*). Given the evolutionally conserved role of Cdc42 in cell polarization, the stepwise activation of Cdc42 may turn out to be another conserved mechanism underlying cell polarization in general.

a. Kang, P.J., M.E. Lee, and **H.-O. Park** (2014) Bud3 activates Cdc42 to establish a proper growth site in budding yeast. *J. Cell Biol.* 206: 19–28. PMCID:PMC4085707
Highlighted in "In This Issue" of the J Cell Biol (July 07, 2014)

b. Lee, M. E., W.-C Lo, K. E. Miller, C.-S. Chou, and **H.-O. Park** (2015) Regulation of Cdc42 polarization by the Rsr1 GTPase and Rga1, a Cdc42 GTPase activating protein, in budding yeast. *J. Cell Sci.* 128: 2106–2117. PMCID:PMC4457026
Highlighted in "In This Issue" of the J Cell Sci 128:e1103 (June 1, 2015)

c. Miller, K. E., W.-C. Lo, M.E. Lee, P. J. Kang, and **H.-O. Park** (2017) Fine-tuning the orientation of the polarity axis by Rga1, a Cdc42 GTPase activating protein. *Mol Biol Cell* 28(26):3773-3788. PMCID: PMC5739294

d. Kang, P. J., K. E. Miller, J. Guéguéniat, Laure Béven and **H.-O. Park** (2018) The shared role of the Rsr1 GTPase and Gic1/Gic2 in Cdc42 polarization. *Mol Biol Cell* 29(20):2359-2369. PMID: 30091649

3. **Charactering assembly of macromolecular complexes that define a site for polarized growth:** A specific site of polarized growth in budding yeast is determined by a cell-type-specific cortical marker, which is linked to the common GTPase signaling pathway. We have investigated the macromolecular structures of the cortical marker that sets up cellular asymmetry and dictate the orientation of polarity axis. Our studies have provided a deeper understanding of the assembly of the axial landmark in haploid cell types and its interaction with the septin cytoskeleton as well as the bipolar landmark, which provides spatial information for diploid cell polarization.

   a. Kang, P. J., E. Angerman, K. Nakashima, J. R. Pringle, and **H.-O. Park** (2004) Interactions among Rax1p, Rax2p, Bud8p, and Bud9p in Marking Cortical Sites for Bipolar Bud-site Selection in Yeast. *Mol. Biol. Cell* 15: 5145–5158. PMCID: PMC524791

   b. Kang, P. J., E. Angerman, C.-H. Jung, and **H.-O. Park** (2012) Bud4 mediates the cell-type-specific assembly of the axial landmark in budding yeast. *J. Cell Sci*. 125:3840–9. PMCID: PMC3462081

   c. Kang, P. J., J. K. Hood-DeGrenier, and **H.-O. Park** (2013) Coupling of septins to the axial landmark by Bud4 in budding yeast. *J. Cell Sci.* 126:1218–26. PMCID: PMC3635463

4. **Investigation of stress response and stress-induced cell death:** My earlier investigation of stress response had focused on transcriptional regulation of the heat shock genes. We serendipitously found that Rho5 is necessary for cell death upon exposure to oxidants or heat stress. Since other members of the Rho family GTPase including Cdc42 and Rho1 are critical for cell proliferation and cell integrity, this surprising role of Rho5 suggest the complex regulation of cellular homeostasis by Rho GTPases.

   a. **Park, H.-O.** and E. A. Craig (1989) Positive and Negative Regulation of Basal Expression of a Yeast HSP70 Gene. *Mol Cell Biol* 9: 2025–2033. PMCID: PMC362995

   b. **Park, H.-O.** and E. A. Craig (1991) Transcriptional regulation of a yeast HSP70 gene by heat shock factor and an upstream repression site-binding factor. *Genes & Dev* 5: 1299–1308. PMID: 2065978

   c. Singh, K., P. J. Kang, and **H.-O. Park** (2008) The Rho5 GTPase is necessary for oxidant-induced cell death in budding yeast. *Proc Natl Acad Sci USA* 105: 1522–1527. PMCID: PMC2234177

   d. Lee, M. E., K. Singh, J. Snider, A. Shenoy, C. M. Paumi, I. Stagljar and **H.-O. Park** (2011) The Rho1 GTPase acts together with a vacuolar glutathione S-conjugate transporter to protect yeast cells from oxidative stress. *Genetics* 188:859–870. PMCID: PMC3176091

5. **Contributing technical development in fluorescent-based assays:** We have extensively applied bimolecular fluorescent complementation (BiFC) assays to monitor protein-protein interactions in budding yeast and also collaborated with Igor Stagljar in large-scale interaction studies on yeast membrane proteins. In addition, we contributed to the application and quantification of a fluorescence-based GTPase biosensor *in vivo*.

   a. Snider J., A. Hanif, M. E. Lee, K. Jin, A. R Yu, M. Chuk, D. Damjanovic, C. Graham, M. Wierzbicka, P. Tang, D. Balderes, V. Wong, B.-J. San Luis, I. Shevelev, S. L. Sturley, C. Boone, M. Babu, Z. Zhang, C. Paumi, **H.-O. Park**, S. Michaelis and I. Stagljar (2013) Mapping the functional yeast ABC transporter interactome. *Nature Chem Biol* 9:565–72. PMCID:PMC3835492

b. Miller, K. E., Y. Kim, W.-K. Huh, and **H.-O. Park** (2015) Bimolecular Fluorescence Complementation (BiFC) Analysis: Advances and Recent Applications for Genome-wide Interaction Studies *J. Mol. Biol.* 427(11):2039-55. PMCID:PMC4417415

c. Lam, M. H. Y., J. Snider, M. Rehal, V. Wong, F. Aboualizadeh, L. Drecun, O. Wong, B. Jubran, M. Li, M. Ali, M. Jessulat; V. Dieneko, R. Miller, M. E. Lee, **H.-O. Park**, A. Davidson, M. Babu, and I. Stagljar (2015) A comprehensive membrane interactome mapping of Sho1p reveals Fps1p as a novel key player in the regulation of the HOG Pathway in *S. cerevisiae*. *J Mol Biol* 427(11):2088-103. PMCID:PMC5331858

d. Okada, S., M.E. Lee, E. Bi, and **H.-O. Park** (2017) Probing Cdc42 polarization dynamics in budding yeast using a biosensor, Methods Enz Vol. 589, pp. 171-190. Epub 2017 Feb 20. PMCID:PMC5367485

D. Research Support

Ongoing Research Support

NIH/NIGMS, R01 GM114582 H.-O. Park (PI) 05/07/2015–03/31/2019
Spatial and Temporal Regulation of Polarity Establishment in Budding Yeast
The goal of this project is to elucidate the mechanism by which cell polarity is established during the cell cycle.
Role: PI

NIH/NIA, R21 AG060028 H.-O. Park (PI) 95%; C.-S. Chou (PI) 5% 08/15/2018–4/30/2020
Cell polarity signaling in lifespan control
The goal of this project is to develop techniques for microfluidic-based long-term imaging and computational methods for image analysis.
Role: contact PI

Seilhamer Fellowship, The Jeffrey J. Seilhamer Cancer Foundation 01/01/2018–12/31/2018
Regulation of Rga1, a Cdc42 GTPase-activating-protein required for proper orientation of the polarity axis
Kristi E. Miller, Graduate Trainee
Role: Mentor

Completed Research Support (past 3 year)

NIH/NIGMS, 3R01GM114582-03S1 H.-O. Park (PI) 04/01/2017–03/31/2018
Adm Supplemental grant
The goal of this project is the same as the parental grant by allowing the purchase of accessories for the microfluidics system and a spectrofluorometer.
Role: PI

NIH/NIGMS, 3R01 GM114582-02S1 H.-O. Park (PI) 04/01/2016–03/31/2017
Supplemental Equipment Grant
The goal of this project is the same as the parental grant by allowing the purchase of an automated imaging system with a highly sensitive camera.
Role: PI

Postdoctoral fellowship, Mathematical Bioscience Institute, Ohio State University
Computational modeling of cell polarity 06/01/2012–05/31/2015
Wing Cheong Lo, Postdoctoral fellow
Role: Co-Mentor

Pelotonia Undergraduate Fellowship, Ohio State University 06/01/2014–05/31/2015
Mapping of Yeast Interactome by Bimolecular Fluorescence Complementation
Rachel Miller, Undergraduate Trainee
Role: Mentor