BIOGRAPHICAL SKETCH

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NAME: Kim Orth

eRA COMMONS USER NAME (credential, e.g., agency login): kimorth

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
Texas A&M University, College Station, TX	B.S.	1984	Biochemistry
UCLA School of Medicine, Los Angeles, CA	M.S.	1986	Biological Chemistry
UT Southwestern Medical Center, Dallas, TX	Ph.D.	1993	Biochemistry and Molecular Biology

A. Personal Statement

My laboratory is very active in elucidating mechanisms used by virulence factors expressed by bacterial pathogens. Studies using microbial genetics, biochemistry, cell biology, biophysics and bioinformatics on effectors from *Yersinia* and *Vibrio* have uncovered many mechanisms that bacteria use to subvert host signaling pathways, including the discovery of two novel post translational modifications: YopJ Ser/Thr Acetylation and VopS AMPylation. For the latter, we expanded our programs to fly and mouse models and now human disease. With the pathogen *Vibrio parahaemolyticus*, we have expanded our studies on host pathogen interactions and bacterial signal transduction complexes.

My program is ideal for training scientists to foster new and creative ideas using rigorous methodology and analysis to test hypothesis driven basic science research.

Over the years, I have contributed to varies programs including panel discussions at American Society for Biochemistry and Molecular Biology (2017,2018), group discussion at Gordon Research Conference on Microbial Toxins and Pathogenesis (2018) and group sessions at FASEB meetings (2015, 2017, 2019, 2021). For my ASBMB Merck Award (2018), I wrote a solicited, personal reflection on my path in science for the *Journal of Biological Chemistry* to provide tools for younger scientists. In light of COVID-19, I helped co-host two virtual international meetings: VibriOnline, 2020 and AMPylationPlus, 2020 and a FASEB Pathogenesis Meeting 2021.

B. Positions, Scientific Appointments, and Honors

2015 - present Investigator, Howard Hughes Medical Institute
2011 - present Professor, Dept. of Molecular Biology, UT Southwestern Med. Center
2010 - present Secondary Appointment, Department of Biochemistry, UTSWMC
2007 - 2011 Associate Professor, Dept. Molecular Biology, UT Southwestern Med. Center
2001 - 2007 Assistant Professor, Dept. Molecular Biology, UT Southwestern Med. Center
1995 - 2001 Postdoc Fellow and Research Inv., Dept. Bio. Chem., Univ. of Mich.
1991 - 1995 Ph.D. Student/Postdoctoral Fellow, UT Southwestern Med. Center
1987 - 1990 Research Associate, HHMI & UT Southwestern Medical Center
1985 - 1986 Master Student, Dept. Bio. Chem., UCLA School of Medicine

Other Experiences and Professional Memberships

Rev. Board Editor: PNAS 2020-present; eLife '18-'22;

2000-present	Referee for Journals including but not limited to Science Journals, Nature Journals, Cell Journals, PNAS, JBC, PLoS Journals, mBio, I&I, Molecular Microbiology, Cellular Microbiology, Journal of Bacteriology 2000-present
2001-present	AAAS
2002-present	ASBMB
2004	NIH Special Emphasis
2006-present	ASCB
2006-present	ASM
2008, 2012-2018	NIH Molecular & Integrative Signal Transduction (permanent member)
2008, 2013-15	Beckman Research Foundation Young Investigator Award Review Panel
2009	Panel NIH Special Emphasis Panel
2009-11, 2020	NIH Challenge Grants in Health and Science Research
2009	NIH IDM-A (R21, R15, R03, R35)
2011	NIH IDM-F13-C
2020-present	Beckman Foundation, Scientific Advisory Council
2020-2025	ASBMB Awards committee
2021	Chan/Zuckerberg
2021, 2022	Ben Barres Spotlight Awards
2021-present	HHMI Review boards
2022- present	ASBMB Meeting Organizing Committee
2022-present	TAMEST Board of Directors
2023-2025	National Academy of Science, Awards Committee
2022-2025	National Academy of Science, CMC
2025-2028	National Academy of Science, Council

Honors and Awards

2022	*Elected*, American Association for the Advancement of Science
2022	*Elected*, Fellow, ASBMB
2022	Celebrating Women Wall, UT Southwestern Medical Center
2021-2023	American Society of Microbiology Distinguish Lecturer
2020	Member, The Academy of Medicine, Engineering and Science of Texas
2020	*Elected*, National Academy of Sciences
2019	Nirit and Michael Shaoul Visiting Scholar, Tel Aviv University
2018	ASBMB Merck Award
2016	*Elected*, American Academy of Microbiology
2013	Earl A. Forsythe Chair in Biomedical Science
2012	ASBMB Young Investigator Award
2011	TAMEST; 2011 Edith & Peter O'Donnell Award in Science
2010	Welch Foundation Norman Hackerman Award in Chemical Science
2006-2013	Burroughs Wellcome Investigator in Pathogenesis of Infectious Disease
2003-2006	Arnold and Mabel Beckman Young Investigator Award
2001-present	W.W. Caruth Jr. Scholar in Biomedical Research
1998-2001	Walther Cancer Institute, Dawson Research Fellowship
1993-1998	NCI Postdoctoral Fellowship, Molecular Genetics, Univ. of Mich.

C. Contributions to Science

1. AMPylation/deAMPylation as posttranslational mechanism to regulate eukaryotic signaling. A variety of cellular processes are commonly subverted in disease, one of which is the unfolded protein response (UPR) that occurs in the endoplasmic reticulum (ER). In normal cells, improperly folded or glycosylated proteins will occasionally accumulate in the ER due to a variety of causes, including altered glucose levels, redox state, calcium levels, and chemical stressors. The cell activates the UPR to prevent accumulation of unfolded proteins, which eventually leads to proteotoxicity and cell death. Importantly, heightened expression of BiP, an essential chaperone protein in the ER, is a critical factor

for this survival mechanism in a variety of cancers. In 2014, we discovered a new form of BiP regulation, AMPylation/deAMPylation mediated by eukaryotic Fic. We observe that Fic adds an adenosine monophosphate (AMP) molecule to a threonine near the ATP binding site of BiP during normal growth conditions. This modification is rapidly removed by the same enzyme Fic under cellular ER stress-inducing conditions. *Most recently we have demonstrated that this "AMPylation rheostat" for BiP by FicD is essential for maintaining homeostasis using both fly and mouse animal models. Currently we are using mice to model a rare genetic disorder in humans where FicD weakly AMPylate but is unable to deAMPylate, resulting in infant onset diabetes and neuro-muscular disorders.*

a. Casey, A.K., Stewart, N., Zaidi, N., Gray, H., Fields, H.A., Sakurai,M., Pinzon-Arteaga, C.A., Evers, B.M., Wu, J. & **Orth, K** (2024) Dysregulation of FicD AMPylation causes diabetes by disrupting pancreatic endocrine homeostasis. ***Molecular Metabolism***, *95 (2025) 102120) https://doi.org/10.1016/j.molmet.2025.102120*.

b. Gulen, B., Casey, A.K., Blevins, A., Stewart, N.M., Gray, H., **& Orth, K.** (2024) FicD Sensitizes Cellular Response to Glucose Fluctuations in Mouse Embryonic Fibroblasts ***PNAS USA*** *2024 Sep 17;121(38):e2400781121. doi:*

c. Casey, Chimalapati, S., A.K., Gray, H., Fields, H.A. Gulen, B., Henandez, G., Stewart, N., & **Orth, K.** (2022) Fic-mediated AMPylation tempers the unfolded protein response during physiological stress. ***PNAS USA*** Aug 9;119(32):e2208317119. doi: 10.1073/pnas.2208317119. Epub 2022 Aug

d. Casey, A.K., Moelman, A., Zhang, J., Servage, K., Kramer, H. & **Orth, K.** *(*2017) Fic-mediated deAMPylation of BiP is not dependent on homo-dimerization and rescues toxic AMPylation in flies. ***J Biol Chem.*** 292 (51) pg 21193-21204

2. Discovering a strategy to decipher biochemical mechanism used by bacterial effectors

After starting my independent research laboratory, we discovered that *Yersinia* YopJ uses acetylation to inhibit signaling pathways. Using an *in vitro* system, we found that YopJ inhibited MKKs and IKKβ by acetylating serine and threonine residues within the kinase activation loops. Acetylation of these residues by YopJ prevented their subsequent phosphorylation and inactivated them. This work is one of the first examples of a competitive post-translational modification where one modification (acetylation), directly competes for another (phosphorylation). This discovery is important because our work on YopJ is proof of principle that effectors aid in discovery of new regulatory mechanisms that can involve novel chemistries. Their diversity obscures bioinformatic predictions; biochemistry is crucial to determine enzymatic activity. *Importantly, we discovered a successful strategy for elucidating the molecular mechanisms used by bacterial effectors to manipulate and disrupt host signaling pathways: identify the target of the effector, assess how the target has changed, and then decipher the molecular mechanism used by the effector to cause this change.*

a. Peng, W., Garcia, N., Servage, K.A., Kohler, J.J., Ready, J.M., Tomchick, D.R., Fernandez, J.**& Orth, K.** (2024) *Pseudomonas* effector AvrB is a glycosyltransferase that rhamnosylates plant guardee protein RIN4. ***Science Advs*** 10(7):eadd5108. doi: 10.1126/sciadv.add5108

b. Salomon D., Guo, Y., Kinch, L.N., Grishin, N.V., Mirzaei, H. & **Orth, K.** (2013) Effectors of animal and plant pathogens use a common domain to bind host phosphoinositides. ***Nature Communications*** 4:2973. PMID: 24346350

c. Broberg, C. A., Zhang, L.L., Gonzalez, H., Laskowski-Arce, M.A. & **Orth, K.** (2010) A *Vibrio* Effector Protein is an Inositol Phosphatase and Disrupts Host Cell Membrane Integrity. ***Science*** 329:1660-2.

d. Yarbrough, M., Li, Y., Kinch, L.N., Grishin, N.V., Hall B.E., & **Orth, K.** (2009) AMPylation of Rho GTPases by *Vibrio* VopS disrupts effector binding and downstream signaling. ***Science*** 323: 269-272*. (Epub, Nov. 2008).*

2. Orchestrated killing of one host cell in 3 hours by 3 bacteria

Sequencing of *V. parahaemolyticus* revealed the existence two pathogenicity islands that encode two Type III Secretion Systems (T3SS). The first system, T3SS1, is associated with all strains of the bacterium and is proposed to be essential for providing a selective advantage in the environment. We have demonstrated that the T3SS1 effectors work in concert to orchestrate a multifaceted and temporally regulated host cell infection by inducing autophagy, cell rounding, and then cell lysis. *By establishing this profile of orchestrated killing, we were able to move forward and decipher the molecular mechanisms of the effectors secreted by the T3SS1 (next section).*

a. De Nisco, N.J., Casey, A.K., Kanchwala,M., LaFrance, A.E., Coskun, F., Kinch, L.N., Grishin, N., Xing, C. & **Orth, K.** (2021) Manipulation of noncanonical IRE1-dependent MAPK signaling by a Vibrio agonist-antagonist effector pair. ***mSystems****,* Feb 9;6(1):e00872-20. doi: 10.1128/mSystems.00872-20.

b. Peng, W., Fernandez, J., Casey, A. K., Servage, K. A., Chen, Z., Li, Y., Tomchick, D.R. & **Orth, K.** (2020) Unique virulence mechanism for Vibrio effector revealed by cryo-EM structures of VopQ in complex with V-ATPase. ***Nat Struct Mol Biol*** May 18. doi: 10.1038/s41594-020-0429-1. PMID: 32424347

c. De Nisco, N.J., Kanchwala, M., Li, P., Fernandez, J., Xing, C. & **Orth, K.** (2017) Cytotoxic Vibrio T3SS1 Rewires Host Gene Expression to Subvert Cell Death Signaling and Activate Cell Survival Networks. ***Sci Signal*** May 16;10(479). pii: eaal4501. doi: 10.1126/scisignal.aal4501

d. Salomon D., Guo, Y., Kinch, L.N., Grishin, N.V., Mirzaei, H. & **Orth, K.** (2013) Effectors of animal and plant pathogens use a common domain to bind host phosphoinositides. ***Nature Communications*** 4:2973. PMID: 24346350

3. *Vibrio parahaemolyticus* is a facultative intracellular pathogen: survival, proliferation and escape from host cell

V. parahaemolyticus is a globally disseminated Gram-negative marine bacterium and the leading cause of seafood-borne acute gastroenteritis. Pathogenic bacterial isolates a second T3SS (T3SS2) which is considered to be the main virulence factor in mammalian hosts. For many decades, *V. parahaemolyticus* has been studied as an exclusively extracellular bacterium. However, we demonstrated with the recent characterization of the T3SS2 effector protein VopC this pathogen has the ability to invade, survive, and replicate within epithelial cells. The remarkable molecular aspect of this system is that it can use the same T3SS to invade and replicate inside the host cell and to cause cytotoxicity from outside the host cell. The manipulation of host signaling is quite impressive as the host cells do not appear to change despite being invaded. *We are only beginning to understand the molecular mechanisms used by effectors to manipulate signaling and metabolism in the host cell.*

a. Kinch, L.N., Schaeffer, R.D., Zhang, J., Cong, Q., *__Orth, K.__ & *Grishin, N. (2023) Insights into virulence: Structure Classification of the *Vibrio Parahaemolyticus* Mobilome. ***mSystems*** 8(6):e0079623. doi: 10.1128/msystems.00796-23.

b. Zou, A., Kinch, L., Chimalapati, S., Rodriguez, N.G., Tomchick, D. & **Orth, K.** (2023) Bile Salts as Agonist/Antogonist for Vibrio Receptor VtrA/C. ***J Biol Chem.*** 299(4):104591. doi: 10.1016/j.jbc.2023.104591.

c. **Lafrance, A.,** Chimalapati, S., Rodriguez, Kinch, L., Kaval, K. G. & **Orth, K.** (2022) Enzymatic Specificity of Conserved Rho GTPase Deamidases Promotes Invasion at the Expense of Infection in *Vibrio parahaemolyticus. **mBio*** Aug 30;13(4):e0162922. doi: 10.1128/mbio.01629-22. Epub 2022 Jul 7.

d. Chimalapati, S.*, de Souza Santos, M.*, Lafrance, A., Ray, A., Lee, W-R., Rivera-Cancel, G., Vale, G., Pawłowski, K., Mitsche, M., McDonald, J.G. , Liou, J. & **Orth, K.** (2020) Vibrio deploys a Type 2 secreted lipase to esterify cholesterol with host fatty acids and mediate T3SS2-mediated cell egress. *contributed equally ***eLife*** (2020) Aug 18;9:e58057. doi: 10.7554/eLife.58057

5. Novel bacterial signal transduction mechanisms.

Bile salts, used both for digestion and defense by animals, are also ligands for activating receptors in bacteria. In the case of *Vibrio parahaemolyticus* a bile salt receptor is known to induce the production of the Type 3 secretion system 2 (T3SS2) that mediates invasion into host cells. Recently, we discovered that VtrA/VtrC is a member of a newly described superfamily of co-component signaling systems found in enteric pathogens (Kinch et al, PNAS 2022). These receptors bind to ligands in the periplasm and transfer a signal across the membrane to a membrane bound transcription factor in the cytoplasm to induce the T3SS2. *Further studies have revealed that co-component receptors likely will use "transertion" to efficiently assemble transmembrane complexes using localized transcription, translation, and membrane insertion.*

a. Kaval, K. G., Chimalapati, S., Siegel, S., Rodriguez, N.G., Dalia, A., & **Orth, K.** (2023) Membrane-localized expression, production and assembly of *Vibrio parahaemolyticus* T3SS2 provides evidence for transertion. ***Nature Comm.*** Mar 2;14(1):1178. doi: 10.1038/s41467-023-36762-z.

b. Zou, A., Kinch, L., Chimalapati, S., Rodriguez, N.G., Tomchick, D. & **Orth, K.** (2023) Bile Salts as Agonist/Antogonist for Vibrio Receptor VtrA/C. ***J Biol Chem.*** 299(4):104591. doi: 10.1016/j.jbc.2023.104591.

c. Kinch, L., Jaishankar, J., Cong, Q., & **Orth, K.** (2022) Co-Component Receptors: Fast-evolving virulence regulating cassettes in enteric bacteria discovered with the VtrA/VtrC operon. ***PNAS USA*** (2022) Inaugural article. Jun 14;119(24):e2203176119. doi: 10.1073/pnas.2203176119. Epub 2022 Jun 1. PMID: 35648808. *PNAS Inaugural Paper*

d. Li, P., Rivera-Cancel, G., Kinch, L.N., Salomon, D., Tomchick, D. R., Grishin, N.V., & **Orth, K.** (2016) Bile salt receptor complex activates pathogenic Type III secretion system. ***eLife*** 5:e15718 PMCID: PMC4933562

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