BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Show-Ling Shyng

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

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
National Taiwan University, Taiwan	BS	1980-84	Zoology
Cornell University, Ithaca, NY	Ph.D.	1984-90	Neurobiology
California Institute of Technology, Pasadena, CA	Postdoc	1990-91	Neurobiology
Washington University, St. Louis, MO	Postdoc	1992-97	Cell biology & Physiology

Please refer to the Biographical Sketch sample in order to complete sections A, B, C, and D of the Biographical Sketch.

A. Personal Statement

Research in my laboratory focuses on regulation of ATP-sensitive potassium (K_{ATP}) channels in health and disease. K_{ATP} channels are complexes of an ABC transporter and an inwardly rectifying potassium channel and their activities are governed by intracellular ATP and ADP. As such, K_{ATP} channels couple cell metabolism to cell membrane excitability and regulate a wide range of physiological processes including hormone secretion, neuronal activity, and protection of cardiac and neural tissues against ischemic injuries. We are interested in understanding how K_{ATP} channels are regulated physiologically and how their function is disrupted in disease, with the ultimate goal of developing mechanism-based therapies for disease caused by channel dysfunction. My laboratory offers a multidisciplinary training environment that exposes students to modern approaches in biochemistry, cell biology, molecular biology, genetics, electrophysiology, and structural biology. Current projects are supported by two NIH R01s. One focuses on understanding the structural basis of K_{ATP} channel assembly and gating. The other focuses on understanding how leptin regulates K_{ATP} channel trafficking in normal and type 2 diabetic β-cells.

I have trained many PhD students, postdoctoral fellows, as well as undergraduate and high school students in my lab over the past twenty years. My trainees have included individual from different gender, ethnic and racial groups, reflecting my strong commitment to increasing the diversity of the scientific workforce. In addition to providing scientific training through discussions of experimental design, data interpretation, and scientific rigor during regular lab meetings and one-on-one meetings, I also provide hands-on training at the bench. I have co-authored more than 50 publications with my trainees. My students and postdocs have been successful in obtaining fellowships and awards while in my lab, and past trainees currently hold faculty positions in academic institutions, research leadership positions in industry, or health professional positions. Aside from mentoring in my own lab, I have been actively involved in teaching and mentoring throughout OHSU. I have provided training to over forty graduate students by serving as a lab rotation mentor, dissertation advisory committee member, or research collaborator. I believe my research interest and expertise as well as training record make me a well-qualified participating faculty of any research and training program.

B. Positions and Honors

Positions and Employment

1986-1988 Teaching Assistant, Cornell University

1990-1991	Post-doctoral fellow, California Institute of Technology
1992-1997	Post-doctoral fellow, Washington University School of Medicine
1997-1999	Research Assistant Professor, Washington University School of Medicine
1999-2004	Assistant Scientist, Center for Research on Occupational and Environmental Toxicology, Oregon Health & Science University
1999-2004	Assistant Professor, School of Medicine, Oregon Health & Science University
2005-2008	Scientist, Center for Research on Occupational and Environmental Toxicology, Oregon Health & Science University
2008-2010	Senior Scientist (equivalent to Full Professor), Center for Research on Occupational and Environmental Toxicology, Oregon Health & Science University
2010-present	Adjunct Professor, Department of Physiology & Pharmacology, School of Medicine, Oregon Health & Science University
2010-2011	Associate Professor, Department of Biochemistry and Molecular Biology, School of Medicine, Oregon Health & Science University.
2011-2019	Professor with tenure, Department of Biochemistry and Molecular Biology, School of Medicine, Oregon Health & Science University.
2019-present	Professor, Department of Chemical Physiology and Biochemistry, School of Medicine, Oregon Health & Science University (Note the department name change)

Other Experience and Professional Memberships

1987-1996	Society for Neuroscience
1996-present	Biophysical Society
1997-present	American Diabetes Association
2003	Society of General Physiology
2000-2006	Welcome Trust Grant reviewer
2004-2006	NIH CADO study section (Cellular Aspects of Diabetes and Obesity) ad hoc reviewer
2006-2010	NSF ad hoc grant reviewer
2006-2010	NIH Cellular Aspects of Diabetes and Obesity (CADO) study section, regular member
2011-2012	NIH Molecular and Cellular Endocrinology (MCE) study section, ad hoc reviewer
2013-2019	NIH Molecular and Cellular Endocrinology (MCE) study section, regular member
2011, 2013	American Heart Association, Basic Cell peer review study group
2013	NIH Intellectual and Developmental Disabilities Research Center Grants (U54) study section, Ad hoc reviewer and application leader
2017	Ad hoc study section member for NINDS Institutional Center Core Grants to Support Neuroscience Research (P30) and High Impact Neuroscience Research Resource Program (R24)
2017	Reviewer for NIH Director's New Innovator Award
2009-2014	Journal of Biological Chemistry Editorial Board Member
2017-2019	Diabetes, Editorial Board Member
2019-2025	Journal of General Physiology, Editorial Board Member
2020-	Function, Editorial Board Member

Honors

1986	Cornell University Biotechnology Program Fellowship
1990-1991	Drown Postdoctoral fellowship, Department of Biology, California Institute of Technology
1992-1994	McDonnell Center for Cellular and Molecular Neurobiology Postdoctoral fellowship, Washington University
1994-1996	NIH postdoctoral training fellowship
1997-2001	Career Development Award, the American Diabetes Association

C. Contributions to Science (Total of 80 peer-reviewed publications)

1. My early training in graduate school and as a postdoctoral fellow is in molecular and cellular neuroscience. My graduate school work with Dr. Miriam Salpeter focused on understanding the regulation of acetylcholine receptor turnover at the neuromuscular junction and I demonstrated dynamic changes in receptor turnover rate depending on the innervation state of the muscle. I then did a postdoc with Dr. David Harris studying

the cell biology of prion protein which when misfolded and aggregated causes prion disease. I showed that this GPI-anchored protein undergoes endocytosis and recycling via the clathrin-mediated pathway, which challenged the dogma at the time that GPI-anchored proteins are internalized via caveolae. Moreover, my work identified structural features in the prion protein that are important for its trafficking regulation. These studies helped delineate the cellular itinerary of the protein, which is important for understanding where and how the protein becomes pathogenic. Representative publications from these studies are listed below.

a. Shyng, S.-L. and M. M. Salpeter. (1989). Degradation rate of acetylcholine receptors inserted into denervated vertebrate neuromuscular junctions. *J. Cell Biol.* 108: 647-651.
b. Shyng, S.-L., R. Xu, and M. M. Salpeter. (1991). Cyclic AMP stabilizes the degradation of original junctional acetylcholine receptors in denervated muscle. *Neuron* 6: 469-475.
c. Shyng, S.-L., M. T. Huber, and D. A. Harris. (1993). A prion protein cycles between the cell surface and an endocytic compartment in cultured neuroblastoma cells. *J. Biol. Chem.* 268: 15922-15928.
d. Shyng, S.-L., J. E. Heuser, and D. A. Harris. (1994). A glycolipid-anchored prion protein is endocytosed via clathrin-coated pits. *J. Cell Biol.* 125: 1239-1250.

2. My research experience in graduate school and as a postdoctoral fellow shaped my interest to study how dynamic regulation of ion channel trafficking and gating affects cell function. In 1995, the ATP-sensitive potassium (K_{ATP}) channel was cloned and provided an excellent opportunity for ion channel research. I entered the K_{ATP} channel field as a research associate in Dr. Colin Nichols' lab and conducted a series of structure-function studies using a combination of site-directed mutagenesis and patch-clamp recording methods. These studies significantly advanced our understanding of how the channel functions in health and disease and generated some of the most cited papers in the K_{ATP} channel field. Important findings from these studies include (1) the channel is formed by four Kir6.2 and four SUR1 subunits; (2) MgADP is a key physiological regulator that opens K_{ATP} channels in response to hypoglycemia; (3) many channel mutations impair channel response to MgADP to cause congenital hyperinsulinism; (4) membrane phosphoinositides, in particular PIP_2, is an important regulator of K_{ATP} channel gating.

a. Nichols, C. G., S.-L. Shyng, A. Nestorowicz, B. Glaser, J. Clement IV, G. Gonzalez, L. Aguilar-Bryan, A. M. Permutt, and J. P. Bryan. (1996). Adenosine diphosphate as an intracellular regulator of insulin secretion. *Science* 272: 1785-1787.
b. Shyng, S.-L. and C. G. Nichols. (1997). Octameric stoichiometry of the K_{ATP} channel complex. *J. Gen. Physiol.* 110: 5-664.
c. Shyng, S.-L.*, T. Ferrigni, J. Shepard, A. Nestorowicz, B. Glaser, M. A. Permutt, and C. G. Nichols. (1998). Functional analyses of novel mutations in the sulfonylurea receptor 1 associated with familial hyperinsulinism. *Diabetes* 47: 1145-1151. *Corresponding author
d. Shyng, S.-L. and C. G. Nichols. (1998). Membrane phospholipids control nucleotide-sensitivity of K_{ATP} channels. *Science* 282: 1138-1141.

3. As an independent investigator, I have continued to work on K_{ATP} channels with a focus on how mutations in the SUR1/Kir6.2 channel genes *ABCC8* and *KCNJ11* disrupt channel biogenesis to cause disease. We documented the first congenital hyperinsulinism mutation that impairs channel biogenesis and surface expression. We are also among the first to explore the concept of pharmacological chaperones in the K_{ATP} channel field. We showed that sulfonylureas, drugs commonly used to treat type 2 diabetes, are effective chaperones for rescuing K_{ATP} channel biogenesis defects caused by a subset of mutations. Subsequently, we found that carbamazepine, an anticonvulsant, is also an effective pharmacological chaperone for trafficking-impaired K_{ATP} channels as well as a potent channel inhibitor. An important ongoing effort is to apply our knowledge of the mechanisms by which mutations affect K_{ATP} channel biology to aid in the diagnosis and treatment of K_{ATP} channelopathies. We have collaborated with clinical endocrinologists around the world to build a knowledge base of genotype-phenotype correlations in patients with K_{ATP} channel mutations. Our studies to date have uncovered many detailed mechanisms by which mutations alter channel gating and expression and how channel defects caused by some mutations can be corrected pharmacologically. The information we have accumulated has had a significant impact on disease diagnosis and treatment.

a. Cartier, E. A., L.R. Conti, C.A. Vandenberg and S.-L. Shyng. (2001). Defective trafficking and function of K_{ATP} channels caused by a sulfonylurea receptor 1 mutation associated with persistent hyperinsulinemic hypoglycemia of infancy. (2001). *Proc. Natl. Acad. Sci. USA*, 98: 2882-7. PMC30234
b. Yan, F., C.-W. Lin, E. Weisiger, E. A. Cartier, G. Taschenberger, and S.-L. Shyng. (2004). Sulfonylureas correct trafficking defects of ATP-sensitive potassium channels caused by mutations in the sulfonylurea receptor. *, J. Biol. Chem.* 279:11096-105. PMID:14707124
c. Chen, P.-C., E.M. Olson, Q. Zhou, Y. Kryukova, H. M. Sampson, D.Y. Thomas and S.-L. Shyng. (2013). Carbamazepine as a novel small molecule corrector of trafficking-impaired ATP-sensitive potassium channels identified in congenital hyperinsulinism. *J. Biol. Chem*., 288: 20942-54. PMC3774364.
d. Balamurugan, K., B. Kavitha, Z. Yang, Y. V. Mohan, V. Radha, and S.-L. Shyng. (2019). Functional characterization of activating mutations in the SUR1 (ABCC8) causing neonatal diabetes mellitus in Asian Indian Children. *Pediatr. Diabetes*, 20(4):397-407. PMID:30861254.

4. In addition to studying disease mutations, we are interested in understanding the fundamental mechanisms governing channel protein folding, assembly, and trafficking in β-cells and how these processes impact β-cell excitability and insulin secretion. Earlier work used proteomic approaches to identify molecular chaperone proteins involved in channel folding, assembly, and degradation in the ER. Recent efforts are focused on regulation of K_{ATP} channel density at the β-cell membrane by physiological signals, in particular the adipocyte-derived hormone leptin. In our initial study we showed that leptin causes a transient increase in K_{ATP} channel density and that this regulation is dependent on the activity of AMPK and PKA, and on actin depolymerization. In a second study, we made a fortuitous discovery that leptin also upregulates the surface density of Kv2.1 channels without affecting several other ion channels or membrane proteins we tested. These findings reveal a novel mechanism by which physiological signals such as leptin regulates insulin secretion, namely, by regulating surface density of key ion channels involved in determining β-cell membrane excitability. The concerted regulation of K_{ATP} and Kv2.1 channels by leptin via the same signaling pathway presents a synergistic mechanism to effectively reduce β-cell excitability and insulin secretion. Significance of our new findings is reflected by selection of both papers by *J. Biol. Chem.* as "Paper of the Week." Most recently, we showed that the effect of leptin is mediated by the ionotropic glutamate NMDA receptors, revealing a novel role of NMDA receptors in β-cells.
    a. Yan, F.-F., E.B. Pratt, P.-C. Chen, F. Wang, W.R. Skach, L.L. David, and S.-L. Shyng. (2010). Role of Hsp90 in biogenesis of the β-cell ATP-sensitive potassium channel complex*. Mol. Biol. Cell* 21(12):1945-54. PMC2883939.
    b. Chen, P.-C., Y.N. Kryukova and S.-L. Shyng. (2013). Leptin regulates K_{ATP} channel trafficking in pancreatic β-cells by a signaling mechanism involving AMPK and PKA*. J. Biol. Chem.* 288(47):34098-109. PMC3837151. ***Journal cover**, **JBC Paper of the Week.***
    c. Wu, Y., S.-L. Shyng*, and P.-C. Chen*. (2015). Concerted trafficking regulation of Kv2.1 and K_{ATP} channels by leptin in pancreatic β-cells. *J. Biol. Chem.* 290: 29676-90. *Co-corresponding authors, PMC3837151. ***JBC Paper of the Week, featured in JBC paper of the week podcast.***
    d. Wu, Y., D.A. Fortin, V.A. Cochrane, P.-C. Chen, and S.-L. Shyng. (2017). NMDA receptors mediate leptin signaling and regulate potassium channel trafficking in pancreatic β-cells. *J. Biol. Chem.* 292: 15512-24. PMC5602408.

5. In the last few years, we have incorporated chemical biology and single-particle cryo-EM approaches to studying K_{ATP} channel structure and function. Using site-directed unnatural amino acid-mediated crosslinking, we demonstrated that both sulfonylureas and carbamazepine correct K_{ATP} channel biogenesis defects by promoting physical interactions between Kir6.2 and SUR1. In 2016, we reported the first subnanometer K_{ATP} channel structure by single-particle cryoEM. A subsequent higher resolution structure at 3.7Å allowed us to identify the detailed binding sites of the anti-diabetic drug glibenclamide and the physiological inhibitory ligand ATP. Most recently, we resolved channel structures bound to two other inhibitor chaperones, repaglinide and carbamazepine and showed that they share the same binding pocket in SUR1 as glibenclamide. Importantly, we found that drug binding stabilizes the distal N-terminus of Kir6.2 in the central cavity formed by two halves of the ABC core domain of SUR1. The finding reveals a mechanism whereby drug binding enhances interactions between Kir6.2 and SUR1 to promote channel assembly. It also shows that these drugs inhibit channel activity by trapping the Kir6.2 N-terminus in SUR1's ABC core central cavity, a conformation that prevents the NBDs of SUR1 from dimerization and

also reduces nucleotide-independent channel open probability. These studies are major breakthroughs in the K_{ATP} channel field and pave the way for structural studies proposed in this application to understand the regulatory mechanisms of cardiovascular K_{ATP} channels and develop channel subtype specific modifiers to treat human disease.

a. Martin, G.M., C. Yoshioka, E.A. Rex, J. F. Fay, Q. Xie, M.R. Whorton, J.Z. Chen, and S.-L. Shyng. (2017). Cryo-EM structure of the ATP-sensitive potassium channel illuminates mechanisms of assembly and gating. *Elife*, Jan. 16; 6. pii: e24149. doi: 10.7554/eLife.24149. PMC5344670. First posted in *bioRxiv* on Dec. 16, 2016.
***Webpage image: a close look at a closed channel, March 9, 2017; accompanying "Insight" editorial piece "From ions to insulin" by Voula Kanelis, eLife, 6: e25159. Recommended for F1000Prime.**
b. Martin, G.M., B. Kandasamy, C. Yoshioka, and S.-L. Shyng. (2017). Anti-diabetic drug binding site in a mammalian K_{ATP} channel revealed by Cryo-EM. *Elife*, Oct. 16; 6. pii: e31054. doi: 10.7554/eLife.31054. PMC5655142.
c. Martin, G.M., M.W. Sung, Z. Yang, L. M. Innes, B. Kandasamy, L.L. David, C. Yoshioka and S.-L. Shyng. (2019). Mechanism of pharmacochaperoning in a mammalian K_{ATP} channel revealed by cryo-EM. *Elife*, Jul. 25; 8. pii: e46417. doi: 10.7554/eLife.46417. PMC6699824.
d. Sung, M.W., Z.Y. Yang, C.M. Driggers, B.L. Patton, B. Mostofian, J.D. Russo, D.M. Zuckerman, and S.-L. Shyng. Vascular K_{ATP} channel structural dynamics reveal regulatory mechanism by Mgnucleotides. (2021). *PNAS*, Nov 2;118(44):e2109441118. doi: 10.1073/pnas.2109441118.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40718429/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

R01 DK066485-13 (PI: Shyng) 2/07/2020 – 1/31/2025
NIH/NIDDK
Title: Structural basis of K_{ATP} channel gating
The major goal of this project is to understand the molecular and structural mechanisms underlying the assembly and gating of the SUR1/Kir6.2 K_{ATP} channel using single particle cryo-EM, molecular dynamic simulations and functional testing. A particular focus is to capture open state conformations of the channel.

Pending

R01 GM145784 (Shyng PI) 04/01/2022-03/31/2027
NIH/NIGMS
Title: Correlating structure and function in K_{ATP} channel isoforms
Major Goals: The major goals are (1) to understand the structural mechanisms that underlie the functional diversity in K_{ATP} channel isoforms, specifically focusing on the cardiac K_{ATP} formed by SUR2A and Kir6.2 and vascular K_{ATP} formed by SUR2B and Kir6.1, (2) to understand how mutations in SUR2 and Kir6.1 cause Cantú syndrome, and (3) to develop K_{ATP} isoform specific inhibitors for normalizing Cantú mutant channel activity, using a combination of cryoEM, MD simulations, *in silico* drug screens, biochemical and electrophysiology approaches.
Role on project: PI

Recently completed

R01 DK 57699-16 (PI: Shyng) 8/01/2016 – 7/31/2021
NIH/NIDDK
Title: ATP-sensitive potassium channels and insulin secretion
The goal of the project is to elucidate the mechanism by which leptin regulates trafficking of both K_{ATP} and Kv2.1 channels in pancreatic β-cells.