

## CURRICULUM VITAE

**NAME:** WILLIAM P. SCHILLING

**DATE:** January, 2002

### **PRESENT POSITION AND ADDRESS:**

Associate Professor  
Department of Physiology and Biophysics  
Case Western Reserve University  
School of Medicine  
Cleveland OH

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### **BIOGRAPHICAL:**

Born: November 10, 1952, Montebello, California  
Marital Status: Married, three children  
Home Address: 3281 Ingleside Rd., Shaker Heights, OH 44122  
Home Phone: (216) 752-9592

### **EDUCATION:**

1970 - 1974	Chemistry	B.S.	Chapman College, Orange, California
1974 - 1976	Biochemistry		California State University at Fullerton, California and Orange County Medical Center
1976 - 1981	Pharmacology	Ph.D.	Medical University of South Carolina, Charleston, South Carolina

## PROFESSIONAL AND TEACHING EXPERIENCE:

### A. POSITIONS:

- 1995 - Present      **Associate Professor**, Department of Physiology & Biophysics, Case Western Reserve University School of Medicine, Cleveland Ohio
- 1996 - Present      **Bioscientific Staff**, Department of Medicine, Rammelkamp Center for Education and Research, MetroHealth Medical Center, Cleveland, Ohio
- 1996 - Present      **Adjunct Staff**, Department of Cell Biology, Cleveland Clinic Foundation, Cleveland, Ohio
- 1992 - 1995        **Director, Graduate Studies**, Department of Molecular Physiology & Biophysics, Baylor College of Medicine, Houston, Texas
- 1991 - 1995        **Associate Professor**, Department of Molecular Physiology & Biophysics, Baylor College of Medicine, Houston, Texas
- 1985 - 1990        **Assistant Professor**, Department of Molecular Physiology & Biophysics, Baylor College of Medicine, Houston, Texas
- 1984 - 1985        **Assistant Professor**, Department of Physiology & Biophysics, University of Texas Medical Branch, Galveston, Texas
- 1983 - 1984        **Research Instructor**, Department of Physiology & Biophysics, University of Texas Medical Branch, Galveston, Texas
- 1981 - 1983        **Research Associate**, Department of Pharmacology, Medical University of South Carolina, Charleston, South Carolina

### B. TEACHING:

- 2002                **Phol 468**, Membrane Physiology, Course Director, 3 lectures: *Introduction to Membrane Physiology, Na/Ca Exchanger, Ion channels in non-excitabile cells* (~6 contact hrs), Case Western Reserve University School of Medicine
- 2001-present      **Phol 514**, Introduction to Cardiopulmonary Physiology, Lecture: *Excitation/Contraction Coupling*, Lab: *Ca<sup>2+</sup> signaling* (1.5 contact hr.), Case Western Reserve University School of Medicine
- 1997 - present     **Phol 466**, Cell Signaling, Lecture: *Calcium signaling in non-excitabile cells* (4.5 contact hr.), Case Western Reserve University School of Medicine

- 1997 - present      **Phol 518**, Integrative approaches to cardiovascular research, Lectures: *Endothelium and vascular function, Pathophysiology and Endothelial Function* (3 contact hr.), Case Western Reserve University School of Medicine.
- 1999 - present      **Core Medical Physiology**; Combined Basic Science/Clinical Small Group Conferences on *Calcium Homeostasis*; 20 students; (2 contact hr) Organized the basic science component.
- 2001 - present      **Core Medical Physiology**; Small Group Conference on *Cardiac Electrophysiology*; 20 students; (1 contact hr), Case Western Reserve University School of Medicine
- 1996 - 1997      **Horizons in Biomedical Science**, Undergraduate Minority Summer Program, Lecture: *Receptor-operated Ca<sup>2+</sup> Channels* (1 contact hr), Case Western Reserve University School of Medicine
- 1989 - 1991      **Core Medical Physiology**, Lectures: *Membrane Physiology I thru V; The Vascular Endothelium*. Pathophysiological Correlation: *Heart Failure*, (6 contact hr.), Baylor College of Medicine
- 1987 - 1992      **Cell Regulation, Signal transduction, and Ion Channels** (Graduate Elective), Lectures: *Intracellular Signaling Mechanisms, Carrier Kinetics, Na,K-ATPase pump, Na,Ca-Exchanger*, (7.5 contact hr.), Baylor College of Medicine
- 1986 - 1989      **Core Medical Physiology**, Lectures: *Regulation of Food Intake; Salivation, Chewing and Swallowing; The Stomach; The Pancreas*, (4 contact hr.), Baylor College of Medicine
- 1980 - 1983      **Core Medical Pharmacology 601**, Laboratory exercise on isolated rabbit heart preparation, (3 contact hr.), Medical University of South Carolina, Charleston, South Carolina
- 1982 - 1983      **Core Medical Pharmacology 601**, Small Group Conference on Cardiac Drugs, (1 contact hr) Medical University of South Carolina, Charleston, South Carolina
- 1983      **Core Dental Pharmacology 621**, Lecture: *Drugs of Abuse*, (1 contact hr), Medical University of South Carolina, Charleston, South Carolina
- 1979 - 1982      **Core Dental Pharmacology 621**, Lecture: *Antiarrhythmic Agents*, (1 contact hr) Medical University of South Carolina, Charleston, South Carolina
- 1980      **Core Dental Pharmacology 621**, Lecture: *Local Anesthetics*, (1 contact hr) Medical University of South Carolina, Charleston, South Carolina

1983                            **Cardiovascular Pharmacology** (Graduate Elective; ~40 contact hr), Medical University of South Carolina, Charleston, South Carolina

1979 - 1983                    **Introduction of Principles and Practices of Pharmacology** (Undergraduate) Lecture: *Physiology and Pharmacology of the Heart*, (2 contact hr) Medical University of South Carolina, Charleston, South Carolina

**C.      TRAINEES:**

**John Drewe, Ph.D.** Graduate Student, lab rotation, 1984.

**Gretchen Hanson, Ph.D.** Graduate Student, **Dissertation research**, 1987-1989.

**Eva Strobl-Jager, M.D.** Postdoctoral Associate, 1988.

**Stephen J. Elliott, M.D.** Research Fellow, 1987-1992

**Rita Alevriadou, MS, Ph.D.** Graduate Student, **Thesis research**, 1988

**Ching-Fong Liao, Ph.D.** Graduate Student, **Dissertation research**, 1989

**Bill Ho:** Graduate Student, lab rotation, 1988

**David Rickman:** Graduate Student, lab rotation, 1990

**Olga A. Cabello, Ph.D.** Graduate Student, **Dissertation research**, 1990-1993

**Makoto Mo, M.D.** Research Fellow, 1990

**Kerry Stewart, M.D.** Research Fellow, 1991

**Yanfeng Hu, Ph.D.** Graduate Student, **Dissertation research**, 1992-1994

**Xilin Chen, Ph.D.** Postdoctoral Associate, 1992-1994

**Ying Wu, Ph.D.** Postdoctoral Associate, 1993-1994

**Yanjie Dong, Ph.D.** Postdoctoral Associate, 1994-1995.

**Reynaldo Garcia, Ph.D.** Postdoctoral Associate, 1996-1997

**William Sinkin, Ph.D.** Postdoctoral Associate, 1993-1997

**Sun-Ah You, Ph.D.,** Postdoctoral Associate, 2000-2001

**Brian Wisnosky** Graduate Student. **Dissertation Research**, 1999-present

**Monu Goel, Ph.D.** Postdoctoral Associate, 1999-present

**RESEARCH ACTIVITIES:**

**A.      AREAS OF RESEARCH:**

1. Molecular Mechanism of Signal Transduction in Vascular Endothelial Cells.
2. Role of Ca<sup>2+</sup> Channels in Cell Death

## **B. CURRENT RESEARCH SUPPORT:**

### ***Principal Investigator:***

NIH R01-GM52019-06; "*Ca<sup>2+</sup> Channels in Non-Excitable Cells*"; Annual Direct: \$228,147; Dates: 08/01/99-07/30/03.

NIH R01 HL65323; "*Role of Ion Channels in Cell death*"; Annual Direct: \$200,000; Dates: 01/01/02-12/31/06.

AHA-Postdoctoral Fellowship to Monu Goel, "*Role of immunophilins and InaD in regulation of Trp channel activity*"; Sponsor, W. P. Schilling; Annual Direct: \$35,000, Date:07/01/00-06/30/02.

### ***Co-Investigator:***

NIH GM36387; "Protease-based signaling by the P2X7 nucleotide receptor"; P.I. George R. Dubyak; Dates: 04/01/02-03/31/06.

## **C. PAST RESEARCH SUPPORT (as Principal Investigator):**

Guion Pool Keating Endowment for Research in Cardiology (BSRG); *Dihydropyridine binding in isolated cardiac sarcolemma*; Total Direct: \$10,000, Date: 1984.

AHA-Texas Affiliate Grant 85G-657; *Dihydropyridine binding in isolated cardiac sarcolemma*; Total Direct: \$50,000, Date: 1985-1987.

NIH P01 HL37044; Project 4, *Dihydropyridine binding in isolated cardiac sarcolemma preparations*; Total Direct: \$244,204, Date: 1985-1989.

NIH R29 HL44119; *Calcium signaling in vascular endothelial cells*; Total Direct: \$358,748, Date: 1989-1995.

AHA-Established Investigatorship; *Signal transduction in vascular endothelial cells*; Total Direct: \$210,000, Date: 1989-1994.

NIH R01 HL47876; *Transduction of hemodynamic signals into vascular cells*; Total Direct: \$440,920, Date: 1991-1995.

AHA-Postdoctoral Fellowship to William Sinkins, "*Structure and function of store-operated channels*" W.P. Schilling, Sponsor; Total Direct: \$53,200, Date: 1996-1998.

CWRU/HHMI-Pilot Project Grant, "*Ion Channels and Necrotic Cell Death*"; Total Direct: \$80,000, Date: 1998-2000.

AHA-Grant-in-Aid 9950014N, "Ion channels and Necrotic Cell Death", Total Direct: \$100,000; Date: 07/01/99-12/31/01.

**HONORS AND AWARDS:**

1974	B.S., <i>Magna cum Laude</i> with Honors in Chemistry
1976 - 1981	NIH Pre-Doctoral Fellowships
1983 - 1984	Drug Science Foundation Scholar
1989 - 1994	American Heart Association Established Investigatorship
1994	Excellence in Graduate Education Award, Baylor College of Medicine

**SOCIETY MEMBERSHIPS:**

1984 - Present	Biophysical Society
1991 - Present	American Association for the Advancement of Science
1993 - Present	American Physiological Society
1994 - 2001	Society of General Physiologists

**INVITED SEMINARS:**

**A. NATIONAL**

**Universities/Medical Schools**

Duke University, Department of Physiology, 1983  
University of Texas Medical Branch, Galveston, Department of Physiology, 1983  
University of California at Los Angeles, Department of Biology, 1983  
University of California at San Diego, Division of Pharmacology, 1983  
University of Colorado, Denver, Department of Physiology, 1983  
Case Western Reserve, Department of Physiology, 1988  
Rice University, Department of Chemical Engineering, 1989  
Baylor College of Medicine, Department of Medicine, Cardiovascular Sciences, 1989  
Rice University, Department of Chemical Engineering, 1990  
Medical University of South Carolina, Department of Pharmacology, 1990  
University of Houston School of Pharmacy, Department of Pharmacology, 1990  
University of Texas Medical Branch, Department of Physiology, 1990  
Cleveland Clinic, Department of Vascular Cell Biology, 1991  
Texas A&M University, Department of Medical Physiology, 1992  
Texas A&M University, Department of Pharmacology, 1993  
Zeneca Pharmaceuticals, Wilmington, DE, 1993  
Univ. of Texas Health Science Center, Houston, TX, Department of Physiology, 1994  
Univ. of Texas Health Science Center, San Antonio, TX, Department of Physiology, 1994  
Indiana University, Department of Physiology, 1994

University of Vermont, Department of Pharmacology, 1994  
Medical College of Pennsylvania, Department of Physiology, 1994  
Rice University, Department of Chemical Engineering, 1994  
Baylor College of Medicine, Department of Pathology, 1994  
Case Western Reserve University, Department of Physiology & Biophysics, 1994  
Cleveland Clinic, Department of Molecular Cardiology, 1995  
Loyola University of Chicago, Department of Physiology, 1995  
University of California at Irvine, Department of Physiology, 1997  
University of Rochester, Department of Pharmacology, 1997  
Cleveland Clinic, Division of Anesthesiology, 1999  
University of Chicago, Department of Cell Physiology, 1999  
University of Texas, Southwestern, Department of Physiology, 2000  
Bowling Green State University, Department of Biology, 2000.  
University of Oklahoma Health Sciences Center, Department of Cell Biology, 2000  
Northeast Ohio Universities College of Medicine, Department of Physiology, 2001

### **Conferences**

FASEB, *Endothelial Cell Biology*, 1991  
Gorden Research Conference, *Atherosclerosis*, 1991  
FASEB Summer Research Conference, *Microvascular Biology*; Copper Mountain, CO, 1992  
University of California at Los Angeles, *Vascular Biology Series*, 1993  
Gordon Conference, *Calcium Signalling*, 1995  
FASEB Summer Research Conference, *Biology and Chemistry of Vision*, 1995  
University of Utah, Bristol-Myers Squibb Symposium on *Ion Channels*, 1998  
Gordon Conference, *Calcium Signalling*, 1999  
Gordon Conference, *Mycotoxins and Phycotoxins*, 2001

### **B. INTERNATIONAL**

Mexican Cardiology Society, Veracruz, Mexico, 1993  
Physiological Society, King's College, London, 1993  
IUPHAR, *Vascular Neuroeffector Mechanisms*, Kananaskis, Alberta, Canada, 1994  
University of Bath, *International Symposium on Calcium Signalling*, 1995  
Norvartis Pharmaceuticals, Horsham, UK, 1999

## **PROFESSIONAL SERVICE:**

### **A. INTERNAL**

#### **Case Western Reserve University/Rammelkamp Center for Research**

Chairman, Shared Resources Committee (Rammelkamp Center), 1995-present  
Chairman, Post-Doctoral Training Committee (Physiology, CWRU), 2002-present  
Member, Executive Faculty Committee (Rammelkamp Center), 2000-present  
Member, Faculty Recruitment Committee (Rammelkamp Center), 2000-present  
Member, Website Committee (Rammelkamp Center), 2000-2001  
Member Computer Committee (Rammelkamp Center), 2000-present  
Member, Post-Doctoral Steering Committee (Rammelkamp Center), 1995-present  
Member, Graduate Student Advisory Committees (Physiology, CWRU), 1995-present  
Member, Graduate Student Admissions Committee (Physiology, CWRU), 1996-2000  
Member, Seminar Committee (Physiology, CWRU), 1997-present  
Member, Promotions and Tenure Committee (Physiology, CWRU), 1997-1999

#### **Baylor College of Medicine**

Member, Student Promotions and Acad. Achiev. Committee (Medical School), 1990-1992.  
Member, Faculty Research & Fellowship Support Committee (Medical School), 1991-1993.  
Member, Executive Council (Graduate School), 1992-1995.  
Member, Curriculum and Policy Committee (Graduate School), 1985-1995.  
Member, SMART Program Committee (Graduate School), 1989-1992.  
Member, Graduate Advisory Committees (Graduate School), 1985-1995  
Member, Graduate Education Committee (Physiology), 1985-1995.  
Member, Shared Equipment Committee (Physiology), 1985-1995.  
Environmental Safety Supervisor (Physiology), 1985-1995.

### **B. NATIONAL**

Member, Editorial Board, *Am. J. Physiol:Heart and Circulatory Physiology*, 2000 - present  
Member, Editorial Board, *Am. J. Physiol:Cell Physiology*, 1996 - present  
Member, American Heart Association, Molecular Signaling I Study Committee, 1996 - 1999  
Member, American Heart Association, Mid-America Consortium Study Group, 1998-1999  
Member, American Heart Association-Ohio Affiliate, Research Study Group, 1997  
Member, *Ad hoc*, NIH Study Section, CBY-2, 1997  
Member, Editorial Board, *Am. J. Physiol:Heart and Circulatory Physiology*, 1990 - 1996  
Member, American Heart Association, Vascular Wall Biology Study Committee, 1991 - 1995  
Member, Am. Heart Association, TX-Affiliate, Central Research Review Committee, 1990-1993  
Member, NHLBI Program Project Grant Site Visit Committee, 1986

## C. INTERNATIONAL

### *Ad Hoc Grant Reviews for:*

The Wellcome Trust, UK.

Binational Science Foundation, Israel

University of Melbourne, Australia, Thesis Examination

The Israel Science Foundation

Australian Research Council

Flinders University of South Australia, Thesis Examination

Medical Research Council, London, UK

## **BIBLIOGRAPHY:**

### A. ARTICLES (*electronic version: double click on PDF icon for copy of recent papers*):

Van Alstyne, E., Bartschat, D.K., Wellsmith, N.V., Poe, S.L., **Schilling, W.P.**, and Lindenmayer, G.E. Isolation of a highly enriched sarcolemma membrane fraction from canine heart. *Biochem. Biophys. Acta* **553**:338-395, 1979.

Hungerford, R.T., Lindenmayer, G.E., **Schilling, W.P.**, and Van Alstyne, E. The effects of membrane potential on sodium-dependent calcium transport in cardiac sarcolemma vesicles. *In* *Electrogenic transport: Fundamental principles and physiological implications*. (M.P. Blaustein and M.L. Lieberman, Eds.) Raven Press, New York, 1984.

**Schilling, W.P.** and Lindenmayer, G.E. Voltage-sensitive calcium flux promoted by vesicles in an isolated cardiac sarcolemma preparation. *J. Memb. Biol.* **79**:163-173, 1984.

**Schilling, W.P.**, Schuil, D.W., Bagwell, E.D., and Lindenmayer, G.E. Sodium and potassium permeability of membrane vesicles in a sarcolemma enriched preparation from canine ventricle. *J. Memb. Biol.* **77**:101-114, 1984.

**Schilling, W.P.** and Drewe, J.A. Voltage-sensitive nitrendipine binding in an isolated cardiac sarcolemma preparation. *J. Biol. Chem.* **261**:2750-2758, 1986.

Colden-Stanfield, M., **Schilling, W.P.**, Ritchie, A.K., Eskin, S.G., Navarro, L.T., and Kunze, D.L. Bradykinin-induced increases in cytosolic calcium and ionic currents in cultured bovine aortic endothelial cells. *Circ. Res.* **61**:632-640, 1987.

**Schilling, W.P.**, Ritchie, A.K., Navarro, L.T., and Eskin, S.G. Bradykinin-stimulated calcium influx and cytosolic calcium changes in bovine aortic endothelial cells. *Am. J. Physiol.* **255**:H219-H227, 1988.

**Schilling, W.P.** Effect of divalent cation chelation on dihydropyridine binding in isolated cardiac sarcolemma vesicles. *Biochem. Biophys. Acta* **943**:220-230, 1988.

Rampe, D., Poder, T., Zhao, Z.-Y., and **Schilling, W.P.** Calcium channel agonist and antagonist binding in a highly enriched sarcolemma preparation obtained from canine ventricle. *J. Cardiovas. Pharmacol.* **13**:547-556, 1989.

**Schilling, W.P.** Effect of membrane potential on bradykinin-stimulated changes in cytosolic calcium in bovine aortic endothelial cells. *Am. J. Physiol.* **257**:H778-H784, 1989.

Elliott, S.J., Eskin, S.G., and **Schilling, W.P.** Effect of t-butyl-hydroperoxide on bradykinin-stimulated changes in cytosolic  $\text{Ca}^{2+}$  in vascular endothelial cells. *J. Biol. Chem.* **264**:3806-3810, 1989.

**Schilling, W.P.**, Rajan, L., and Strobl-Jager, E. Characterization of the bradykinin-stimulated calcium influx pathway of cultured vascular endothelial cells: Saturability, selectivity and kinetics. *J. Biol. Chem.* **264**:12838-12848, 1989.

Rani, C.S.S., **Schilling, W.P.**, and Fields, J.B. Stimulation of intracellular calcium mobilization by thyrotropin in dog thyroid cells: Comparison with the effects of carbachol and ATP. *Endocrinology* **125**:1889-1897, 1989.

Hamilton, S.L., Alvarez, R.M., Fill, M., Hawkes, M.J., Brush, K.L., **Schilling, W.P.**, and Stefani, E. [ $^3\text{H}$ ]PN200-110 and [ $^3\text{H}$ ]ryanodine binding and reconstitution of ion channel activity with skeletal muscle membranes. *Anal. Biochem.* **183**:31-41, 1989.

Elliott, S.J. and **Schilling, W.P.** Carmustine augments the effects of tert-butyl-hydroperoxide on calcium signaling in cultured pulmonary artery endothelial cells. *J. Biol. Chem.* **265**:103-107, 1990.

**Schilling, W.P.**, Zaher, M., and Rampe, D. Effect of inorganic calcium channel blockers on dihydropyridine binding in isolated cardiac sarcolemma vesicles. *Mol. Pharmacol.* **37**: 80-89, 1990.

Colden-Stanfield, M., **Schilling, W.P.**, Possani, L.D., and Kunze, D.L. Bradykinin-induced potassium current in cultured bovine aortic endothelial cells. *J. Memb. Biol.* **116**:227-238, 1990.

Liao, C.F., **Schilling, W.P.**, Birnbaumer, M., and Birnbaumer, L. Cellular responses to stimulation of the type-5 muscarinic acetylcholine receptor as seen through stable expression in murine L Cells. *J. Biol. Chem.* **265**:11273-11284, 1990.

Elliott, S.J. and **Schilling, W.P.** Oxidative stress inhibits bradykinin stimulated  $^{45}\text{Ca}^{2+}$  flux in pulmonary vascular endothelial cells. *Am. J. Physiol.* **260**:H549-H556, 1991.

Mo, M., Eskin, S.G, and **Schilling, W.P.** Flow-induced changes in calcium signalling of vascular endothelial cells: Effect of shear stress and ATP. *Am. J. Physiol.* **260**:H1698-H1707, 1991.

Elliott, S.J. and **Schilling, W.P.** The vascular endothelium in oxidant-induced lung injury. *In* Free radical mechanisms of tissue injury. Eds. M.T. Moslen and C.V. Smith, CRC Press, Boca Raton, 1992.

**Schilling, W.P.**, Mo, M., and Eskin, S.G. Effect of shear stress on cytosolic  $\text{Ca}^{2+}$  of calf pulmonary artery endothelial cells. *Exp. Cell Res.* **198**:31-35, 1992.

Elliott, S.J. and **Schilling, W.P.** Oxidant-stress alters  $\text{Na}^+$  pump and  $\text{Na}^+\text{-K}^+\text{-Cl}^-$  cotransporter activities in vascular endothelial cells. *Am. J. Physiol.* **263**:H96-H102, 1992.

**Schilling, W.P.** and Elliott, S.J.  $\text{Ca}^{2+}$  signaling mechanisms of vascular endothelial cells and their role in oxidant-induced endothelial cell dysfunction. (Invited Review) *Am. J. Physiol.* **262**:H1617-H1630, 1992.

**Schilling, W.P.**, Cabello, O. and Rajan, L. Depletion of the inositol-1,4,5-trisphosphate-sensitive intracellular  $\text{Ca}^{2+}$  store in vascular endothelial cells activates the agonist-sensitive  $\text{Ca}^{2+}$  influx pathway. *Biochem. J.* **284**:521-530, 1992.

Vaca, L., **Schilling, W.P.** and Kunze, D.L. G-protein-mediated regulation of a  $\text{Ca}^{2+}$ -dependent  $\text{K}^+$  channel in cultured vascular endothelial cells. *Pflügers Arch.* **422**:66-74, 1992.

Elliott, S.J., Meszaros, J.G. and **Schilling, W.P.** Effect of oxidant-stress on calcium signaling in vascular endothelial cells. (Invited Review) *Free Rad. Biol. Med.* **13**:635-650, 1992.

Hanson, G.L., **Schilling, W.P.**, and Michael, L.H. Developmental changes in canine cardiac sarcolemmal activities of  $\text{Na}^+$ ,  $\text{K}^+\text{-ATPase}$  and  $\text{Na}^+$ ,  $\text{Ca}^{2+}$  exchange. *Am. J. Physiol.* **264**:H320-H326, 1993.

Alevriadou, B.R., Eskin, S.G., McIntire, L.V., and **Schilling, W.P.** Effect of shear stress on  $^{86}\text{Rb}^+$  efflux from calf pulmonary artery endothelial cells. *Ann. Biomedical Eng.* **21**:1-7, 1993.

Elliott, S.J., Doan, T.N. and **Schilling, W.P.** Role of lipid peroxidation in tert-butylhydroperoxide-induced inhibition of endothelial cell calcium signaling. *J. Pharmacol. Exp. Therap.* **264**:1063-1070, 1993.

Cabello, O.A. and **Schilling, W.P.** Vectorial  $\text{Ca}^{2+}$  flux from the extracellular space to the endoplasmic reticulum via a restricted cytoplasmic compartment regulates inositol 1,4,5-trisphosphate-stimulated  $\text{Ca}^{2+}$  release from internal stores in non-excitable cells. *Biochem. J.* **295**:357-366, 1993.

Cabello, O.A. and **Schilling, W.P.** Calcium signaling processes in endothelial cells. In *Functionality of endothelium in Health and Disease: A comprehensive review.* (G. Pastelin, R. Rubio, G. Ceballos, J.Suarez, Eds.) Sociedad Mexicana de Cardiologia, Veracruz, 1994.

Tian, P., Hu, Y., **Schilling, W.P.**, Lindsay, D.A., Eiden, J. and Estes, M.K. The nonstructural glycoprotein of rotavirus affects intracellular calcium levels. *J. Virology* **68**:251-257, 1994.

Hu, Y., Rajan, L. and **Schilling, W.P.**  $\text{Ca}^{2+}$  signaling in Sf9 insect cells and the functional expression of a rat brain  $\text{M}_5$  muscarinic receptor. *Am. J. Physiol. (Cell Physiol.)* **266**:C1736-C1743, 1994.

Hu, Y., Vaca, L., Zhu, X., Birnbaumer, L., Kunze, D.L. and **Schilling, W.P.** Appearance of a novel  $\text{Ca}^{2+}$  influx pathway in Sf9 insect cells following expression of the transient receptor potential-like (trpl) protein of *Drosophila*. *Biochem. Biophys. Res. Comm.* **201**:1050-1056, 1994.

Vaca, L., Sinkins, W.G., Hu, Y., Kunze, D.L. and **Schilling, W.P.** Activation of recombinant *Trp* by thapsigargin in Sf9 insect cells. *Am. J. Physiol. (Cell Physiol.)* **267**:C1501-C1505, 1994.

Hu, Y. and **Schilling, W.P.** Receptor-mediated activation of recombinant *Trp1* expressed in Sf9 insect cells. *Biochem. J.* **305**:605-611, 1995.

Daniels, E.E., van Breemen, C., **Schilling, W.P.**, and Kwan, C.-Y. Regulation of vascular tone: cross-talk between sarcoplasmic reticulum and plasmalemma. *Can. J. Physiol. Pharmacol.* **73**:551-557, 1995.

Tian, P., Estes, M.K., Hu, Y., Ball, J.M., Zeng, C.Q.-Y., and **Schilling, W.P.** The rotavirus nonstructural glycoprotein NSP4 mobilizes  $\text{Ca}^{2+}$  from the endoplasmic reticulum. *J. Virology*, **69**:5763-5772, 1995.

Dong, Y., Kunze, D.L., Vaca, L. and **Schilling, W.P.** Inositol 1,4,5-trisphosphate activates the *Drosophila* cation channel *Trpl* in recombinant baculovirus-infected Sf9 insect cells. *Am. J. Physiol. (Cell Physiol.)* **269**: C1332-C1339, 1995.

Chen, X., Earley, K., Luo, W., Lin, S.-H., and **Schilling, W.P.** Functional expression of a human thrombin receptor in Sf9 insect cells: Evidence for an active tethered ligand. *Biochem. J.*, **314**:603-611, 1996.

Sinkins, W.G., Hu, Y., Vaca, L., Kunze, D.L., and **Schilling W.P.** The COOH-terminal domain of *Drosophila* *Trp* channels confers thapsigargin sensitivity. *J. Biol. Chem.* **271**:2955-2960, 1996.

Kunze, D.L., Sinkins, W.G., Vaca, L. and **Schilling W. P.** Properties of single *Drosophila trpl* channels expressed in Sf9 insect cells. *Am. J. Physiol.* **272**:C27-C34, 1997.

Garcia, R.L. and **Schilling, W.P.** Differential expression of mammalian *trp* homologues across tissues and cell lines. *Biochem. Biophys. Res. Comm.* **239**:279-283, 1997.

Chang, A.S., Chang, S.M., Garcia, R.L. and **Schilling W.P.** Concomitant and hormonally regulated expression of *trp* genes in bovine aortic endothelial cells. *FEBS Lett.* **415**: 335-340, 1997.

Sinkins, W.G., Estacion, M. and **Schilling, W.P.** Functional expression of TRPC1: A human homologue of the *Drosophila* TRP channel. *Biochem. J.* **331 (Pt. 1)**: 331-339, 1998.

Estacion, M., Sinkins, W.G., and **Schilling, W.P.** Activation of *Drosophila* TRPL by capacitative  $\text{Ca}^{2+}$  entry. *Biochem. J.* **341**: 41-49, 1999.

**Schilling, W.P.** and Sinkins, W.G., and Estacion, M. Maitotoxin activates a non-selective cation channel and a P2z/P2x7-like cytolytic pore in human skin fibroblasts. *Am.J.Physiol.*, **277**:C755-765, 1999.

**Schilling, W.P.**, Wasylyna, T., Dubyak, G., Humphreys, B. and Sinkins, W.G. Maitotoxin and P2z/P2x7 receptor stimulation activate a common cytolitic pore. *Am. J.Physiol.*, **277**:C766-776, 1999.

Estacion, M., Sinkins, W.G., and **Schilling, W.P.** Regulation of *Drosophila* TrpL channels by phospholipase C-dependent mechanisms. *J. Physiol. (Lond)*, **530.1**: 1-19, 2001.

**Schilling, W.P.** TRP Proteins: Novel therapeutic targets for regional blood pressure control? (Invited Editorial) *Circ. Res.* **88**: 256-259, 2001.

Estacion, M. and **Schilling, W.P.** Maitotoxin-induce cell death and membrane blebbing in vascular endothelial cells. *BMC:Physiology*, 2001, **1**:2. (download movies at [www.biomedcentral.com](http://www.biomedcentral.com))

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## **B. RECENT ABSTRACTS (not represented in bibliography)**

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## **RESEARCH INTERESTS:**

The long range goal of my research is to understand the molecular mechanisms associated with agonist-induced  $\text{Ca}^{2+}$  signaling in mammalian non-excitable cells and in particular, in vascular endothelial cells. In a variety of cell types, stimulation of membrane receptors causes the release of  $\text{Ca}^{2+}$  from internal stores and the concomitant influx of  $\text{Ca}^{2+}$  from the extracellular space. Although the mechanisms responsible for inositol-1,4,5-trisphosphate( $\text{Ins}(1,4,5)\text{P}_3$ )-induced  $\text{Ca}^{2+}$  release from internal stores are well established, the molecular mechanisms associated with  $\text{Ca}^{2+}$  entry remain unknown. In many cells,  $\text{Ca}^{2+}$  influx appears to be secondary to the depletion of internal  $\text{Ca}^{2+}$  store, i.e. the so-called capacitative  $\text{Ca}^{2+}$  entry (CCE) hypothesis. The membrane current generated by depletion of the store has been recorded, but our ability to understand the biochemical mechanisms associated with activation of CCE is hampered by our lack of knowledge concerning the molecular identity of the channels involved. A clue to their identity derived from studies of *Drosophila* phototransduction. Stimulation of isolated *Drosophila* photoreceptor cells by light causes an increase in membrane conductance that requires phospholipase C (PLC) and reflects the activity of both the *transient receptor potential* channel (Trp) and the Trp-like channel (TrpL). It was originally thought that the light-activated channels were localized in the photoreceptor cell to the base of the microvilli of the rhabdomere, the specialized plasma membrane structure containing the photopigment, rhodopsin. Close proximity of the Trp channels to the submicrovilli cisternae (SMC), i.e., the internal  $\text{Ca}^{2+}$  storage compartment, led to the suggestion that  $\text{Ins}(1,4,5)\text{P}_3$ -induced  $\text{Ca}^{2+}$  release activated Trp and TrpL via a mechanism analogous to CCE in mammalian non-excitable cells. Recent studies however, have shown that Trp, TrpL, and PLC are located along the entire length of the microvilli, placing most of the ion channels at a considerable distance from the nearest internal  $\text{Ca}^{2+}$  store. Furthermore, it has been found that mutant flies lacking the  $\text{Ins}(1,4,5)\text{P}_3$  receptor have a photoresponse that is indistinguishable from wild type. Thus, it would appear that an  $\text{Ins}(1,4,5)\text{P}_3$ -induced release of  $\text{Ca}^{2+}$  from the SMC is not the primary mechanism of light-induced activation of Trp and TrpL. In recent studies, we consider an alternative model for the activation of the Trp family of ion channels that requires PLC, but is independent of the internal  $\text{Ca}^{2+}$  stores. Specifically, we propose that it is not the release of  $\text{Ins}(1,4,5)\text{P}_3$  *per se*, but rather the light-induced hydrolysis of  $\text{PIP}_2$  that is responsible for activation of Trp. This hypothesis is based on our recent findings that single TrpL channels are activated in excised membrane patches by PLC and inhibited by  $\text{PIP}_2$ . We have identified a highly conserved region of the Trp family of ion channels that is rich in basic residues and may represent the  $\text{PIP}_2$  binding domain. Thus,  $\text{PIP}_2$  may play an important role in the regulation of mammalian Trp homologues found in a variety of cell types, including vascular endothelial cells.

A second major research project involves the identification of ion channels that appear to trigger cell death. One of the earliest detectable events associated with both apoptotic and necrotic (oncotoc) cell death appears to be a rise in cytosolic  $\text{Ca}^{2+}$ . The channels responsible for this rise in  $\text{Ca}^{2+}$  and the subsequent mechanisms involved in cell lysis remain unknown. Originally cell lysis was thought to occur by a rather non-specific, ill-defined mechanism ending in ‘membrane perturbation’ or ‘membrane breakdown’ and osmotic lysis. However, recent studies on the P2Z purinergic receptor show that necrotic cell death can reflect an ordered sequence of permeability changes. The P2Z receptor is a member of the P2X ionotropic purinergic receptor family recently cloned and identified as P2X<sub>7</sub>. This receptor is found predominantly in mononuclear phagocytes, macrophages and microglial

cells suggesting that it plays an important role in the inflammatory reaction. Activation of P2Z/P2X<sub>7</sub> is thought to be responsible for ATP-induced cytolysis. High concentrations of ATP (3-5 mM) in the presence of physiological concentrations of Mg<sup>2+</sup> cause a rapid increase in [Ca<sup>2+</sup>]<sub>i</sub> followed in time by a progressive increase in permeability of the membrane to molecules with molecular weight up to ~900 Da. The initial change in [Ca<sup>2+</sup>]<sub>i</sub> is associated with Ca<sup>2+</sup> influx via ATP-activated ion 'channels' and the subsequent increase in permeability to larger molecules is equated to 'pore' formation. The ultimate consequence of pore formation is cell death by oncosis, however, recent studies have shown that activation of the P2Z/P2X<sub>7</sub> channel and pore gives rise to both apoptosis and necrosis in some cell types. The molecular mechanisms associated with channel activation by ATP and subsequent steps involved in pore formation remain unknown. Likewise, the biochemical link between P2Z/P2X<sub>7</sub> channel/pore formation and apoptosis/necrosis has not been identified. Natural toxins and poisons (e.g., cholera toxin, pertussis toxin, tetrodotoxin, conotoxin, digitalis, ryanodine, thapsigargin) have proved useful in the identification and dissection the role of specific proteins in biochemical pathways critical for cell homeostasis and signaling. In general, these compounds are potent, specific, and highly selective agents that are derived from plant, bacterial, or animal sources. Maitotoxin or MTX, isolated from the dinoflagellate *Gambierdiscus toxicus*, is one of the most potent toxins known. MTX causes a profound increase in [Ca<sup>2+</sup>]<sub>i</sub> in all cells tested. Originally it was thought the MTX was a specific activator of voltage-gated Ca<sup>2+</sup> channels since the rise in [Ca<sup>2+</sup>]<sub>i</sub> could be attenuated by Ca<sup>2+</sup> channels antagonists. However, it was later discovered that MTX activates non-selective cation channels in all cell examined including both excitable and non-excitable cells. In non-excitable cells, activation of these channels by MTX allows the influx of Ca<sup>2+</sup> and the subsequent secondary effects such as activation of phospholipase C and release of arachidonic acid. In excitable cells, MTX-induced activation of non-selective cation channels causes membrane depolarization, activation of voltage-gated channels and secondary effects such as contraction of cardiac and smooth muscle, and the release of neurotransmitters from nerve terminals. In most cell types, MTX ultimately causes cell lysis. The identity of the MTX-activated channels and the downstream events leading to oncotic cell death remain unknown. In recent studies, we examined the effect of MTX on plasmalemma permeability of human skin fibroblasts. The results show that MTX activates a P2Z/P2X<sub>7</sub>-like cytolytic pore suggesting two possibilities: 1) MTX activates the P2Z/P2X<sub>7</sub> receptor directly, or 2) MTX and purinergic agonists activate distinct channels, but a common pore. To distinguish between these two possibilities, the effect of MTX was examined on cells in which the expression of functional P2Z/P2X<sub>7</sub> channels and pores could be varied either by alterations in the growth conditions or by heterologous expression. The results suggest that MTX activates channels that are distinct from P2Z/P2X<sub>7</sub>, but that MTX-activated pores are indistinguishable from those activated by P2Z/P2X<sub>7</sub> receptor stimulation. We have proposed a physical model in which MTX-activated channels and P2Z/p2x7 receptor-activated channels compete for a common cytolytic pore. Future studies will focus on identification of the proteins that comprise the pore structure and determination of the molecular mechanisms by which channel activation is linked to pore formation.