

Scott M. O'Grady

Professor

Appointment 70% Research, 25% Teaching, 5% Service

Research Area Physiology: Mechanisms and Regulation of Epithelial Ion Transport

Appointment History

1996-present	Professor
1992-1996	Associate Professor
1987-1992	Assistant Professor

Graduate Program Affiliations

Animal Sciences – Senior Member
Biophysical Sciences & Medical Physics – Senior Member
Cellular & Integrative Physiology – Senior Member
Molecular Veterinary Biosciences – Senior Member

Professional and Honorary Societies

Member, Society of General Physiologists
Member, American Physiological Society
Member, Editorial Board, *American Journal of Physiology*
Member, Physiology Industrial Advisory Board

Five Most Significant Publications

Lee, S.Y., S. Wolff, R.A. Nicholas, and S.M. O'Grady. 2003. P2Y receptors modulate ion channel function through interactions involving their C-terminal domains. *Mol. Pharm.* 63(4):878-885, 2003.

This manuscript describes a novel mechanism for P2Y receptor regulation of an endogenous Cl channel in *Xenopus* oocytes that involves protein-protein interactions with the c-terminal tail of the P2Y₁ and P2Y₂ receptors. It is the first description of ion channel modulation by the receptor protein itself and identifies two new protein-protein sequence motifs distinct from the PDZ domain present at the end of the c-terminus of the P2Y₁ receptor. Publication of this paper was followed by an invitation to write a review paper on P2Y receptor modulation of ion channel function for *Cellular Biochemistry and Biophysics*, 39:75-88, 2003.

O'Grady, S.M. and S.Y. Lee. 2003. Chloride and Potassium channels in alveolar epithelial cells. *Am. J. Physiology (Lung Cell and Mol. Physiol.)* 284:L689-L700, 2003.

This is an invited review that presents a new model for adrenergic regulation of NaCl absorption across the alveolar epithelium. This has been a controversial issue in pulmonary physiology and has important significance in the treatment of pulmonary edema. The review includes the work of two papers published from my laboratory that defined a role for CFTR in fluid absorption across the alveolar epithelium (Jiang, et al. *Am J Physiol* 275: C1610-20, 1998) and a second study that presented the first molecular characterization of voltage-gated K channels in alveolar epithelial cells (Lee, S.Y et. al., *Am. J. Physiol.* 284: C1614-C1624, 2003).

Bankers-Fulbright, J.L., H. Kita, G. Gleich, and S.M. O'Grady. 2001. Regulation of NADPH oxidase activity in human eosinophils: A central role for PKC Δ . *J. Cell. Physiol.* 189(3):306-315, 2001.

This study describes a novel role for PKC delta in regulation of proton channel function and NADPH oxidase activity in human eosinophils. We show that both cytokine (IL-5) and Gq

coupled G protein receptors converge on a common post-receptor signaling cascade that involves the auto-phosphorylation of PKC delta and subsequent activation of NADPH oxidase and a proton channel that prevents intracellular acidification. The work described in this paper led to the development of two novel use patents that were purchased by Corus-Pharma, Inc.

Deachapunya, C., M. Palmer-Densmore, and S.M. O'Grady. 1999. Insulin stimulates transepithelial sodium transport by activation of a protein phosphatase that increases Na-K ATPase activity in endometrial epithelial cells. *J. Gen. Physiol.* 114(4):561-74, 1999.

This paper describes a mechanism for stimulation of transepithelial Na⁺ absorption that involves acute activation of the Na-K ATPase independent of an increase in apical membrane Na⁺ conductance. Previous models for regulation of Na absorption in epithelia indicated that the effects of insulin or IGF-1 were due to activation of Na channel activity and did not involve direct regulation of the pump. We developed a method for measuring pump currents in intact endometrial cell monolayers and directly showed that pump activation was dependent on the activity of a protein phosphatase associated with the basolateral membrane.

Deachapunya, C. and S.M. O'Grady. 1998. Regulation of chloride secretion across porcine endometrial epithelial cells by prostaglandin E₂. *J. Physiol.* 508: 31-47, 1998.

This was our first paper on electrolyte transport in cultured porcine endometrial gland epithelial cells. It describes the transport-related actions of PGE₂ on anion secretion. The paper describes a technique for measuring Cl channel function in the apical membrane of intact endometrial cell monolayers that is superior to whole cell patch clamp experiments with dissociated cells. The methods for isolating pure populations of endometrial epithelial cells described in this paper ultimately led to the development of an immortalized endometrial epithelial cell line by constitutive expression of the human telomerase catalytic subunit.

Refereed Journal Publications and Book Chapters (Last Five Years)

Authored or co-authored the following 15 papers in peer-reviewed journals, 3 invited reviews, 1 book chapter and 2 patents.

- Lee, S.Y., P.J. Maniak, R. Rhoads, D.H. Ingbar, and **S.M. O'Grady**. 2003. Basolateral Cl transport is stimulated by terbutaline in adult rat alveolar epithelial cells. *J. Memb. Biol.* 191:133-139.
- Lee, S.Y., S. Wolff, R.A. Nicholas, and **S.M. O'Grady**. 2003. P2Y receptors modulate ion channel function through interactions involving their C-terminal domains. *Mol. Pharm.*,63(4): 878-885.
- Green, B.T., A. Calvin, **S.M. O'Grady**, and D.R. Brown. 2003. Opioid and cannabinoid inhibition of kinin-induced neurogenic anion-dependent secretion in porcine ileum. *J. Pharm. Exp. Ther.* 305 (2):733-739.
- Lee, S.Y., P.J. Maniak, D.H. Ingbar, and **S.M. O'Grady**. 2003. Adult alveolar epithelial cells express multiple subtypes of voltage-gated K⁺ (K_v) channels that are located in the apical membrane. *Am. J. Physiol. [Cell physiology]*, 284(6):C1614-C1624.
- Boland, L.M., M. Jiang, S. Y. Lee, S.C. Fahrenkrug, M.C. Harnett, and **S.M. O'Grady**. 2003. Functional properties of a brain-specific N-terminally spliced modulator of Kv4 channels. *Am. J. Physiol. [Cell Physiology]* 285:C161-C171.
- Bankers-Fulbright, J.L., G.J. Gleich, G. Kephart, H. Kita, and **S.M. O'Grady**. 2003. Regulation of membrane depolarization during NADPH oxidase activation in human eosinophils. *J. Cell Sci.* 116(15):3221-3226.
- O'Grady, S.M.**, X. Jiang, P.J. Maniak, W. Birmachu, L.R. Scribner, B. Bulbulian, and G.W. Gullikson. 2002. Cyclic AMP-dependent Cl secretion is selectively regulated by multiple phosphodiesterase subtypes in human colonic epithelial cells. *J. Memb. Biol.* 185(2):137-144.

- Kim, H., J. Farris, S.A. Christman, L.K. Foster, **S.M. O'Grady**, and D.N. Foster. 2002. Events in the immortalizing process of primary human mammary epithelial cells by catalytic subunit of human telomerase. *Biochem. J.* 365:765-772.
- Palmer-Densmore, M., C. Deachapunya, M. Kannan, and **S.M. O'Grady**. 2002. UTP-dependent inhibition of Na⁺ absorption requires activation of PKC in endometrial epithelial Cells. *J. Gen. Physiol.* 120:897-906.
- Bankers-Fulbright, J.L., H. Kita, G. Gleich, and **S.M. O'Grady**. 2001. Regulation of NADPH oxidase activity in human eosinophils: A central role of PKC. *J. Cell. Physiol.* 189(3):306-315.
- Deachapunya, C. and **S.M. O'Grady**. 2001. Epidermal growth factor regulates the transition from basal sodium absorption to anion secretion in cultured endometrial epithelial cells. *J. Cell Physiol.* 186:243-250.
- Jiang, X, D.H. Ingbar, and **S.M. O'Grady**. 2001. Adrenergic regulation of ion transport across alveolar epithelial cells: Effects on Cl channel activation and transport function in cultures with an apical air interface. *J. Memb. Biol.* 181(3), 195-204.
- O'Grady, S.M.**, P.J. Maniak, S.Y. Lee, and J.A. Dranoff. 2001. Properties of a voltage-dependent inward current associated with expression of the skate P2Y receptor in *Xenopus* oocytes. *MDIBL Bulletin* 40:19-21.
- Jiang, X, D.H. Ingbar, and **S.M. O'Grady**. 2000. Selectivity properties of a Na⁺-dependent amino acid cotransport system in the apical membrane of cultured adult alveolar epithelial cells. *Am. J. Physiol.* [Lung Cell and Molecular Physiology] 279:L911-L915.
- Deachapunya, C., M. Palmer-Densmore, and **S.M. O'Grady**. 1999. Insulin stimulates transepithelial sodium transport by activation of a protein phosphatase that increases Na-K ATPase activity in endometrial epithelial cells. *J. Gen Physiol.* 114(4):561-74.

Invited reviews:

- O'Grady, S.M.** and S.Y. Lee. 2003. Chloride and potassium channels in alveolar epithelial cells. *Am J. Physiology (Lung Cell and Molecular. Physiology)* 284:L689-L700, 2003.
- Lee, S.Y. and **S.M. O'Grady**. 2003. Modulation of ion channel function by P2Y receptors. *Cell. Biochem. Biophys.* 39:75-88.
- O'Grady, S.M.**, X. Jiang, and D.H. Ingbar. 2000. Cl channel activation is necessary for stimulation of amiloride-sensitive Na transport in cultured adult rat alveolar epithelial cells. *Am. J. Physiol.* [Lung Cell and Molecular Physiology] 278:L239-L244.

Book chapter:

- Palmer-Densmore, M. and **S.M. O'Grady**. 2002. Calcium-dependent anion secretion in endometrial epithelial cells. *In: Calcium-activated Cl Channels*, C.M. Fuller ed. Chapter 14, pp. 309-326.

PATENTS

- Bankers-Fulbright, J.L., G. Gleich, and **S.M. O'Grady**. Topical anesthetics useful for the treatment of cancer, US patent #: 687, 389, 10/13/32001. Status: *Allowed*
- Bankers-Fulbright, J.L., G. Gleich, and **S.M. O'Grady**. Treatment of Eosinophil associated pathologies by modulating PKC-delta activity, US patent #: 687, 291, 10/12/32001. Status: *Allowed*

Awards

- Teaching Incentive Award, 2001, College of Veterinary Medicine, University of Minnesota
- Teaching Incentive Award, 2000, College of Veterinary Medicine, University of Minnesota
- Melissa Palmer-Densmore (MS student advisee) received the Proctor & Gamble Outstanding Student Presentation Award for her paper on Cl⁻ channel function in porcine endometrial epithelial cells from the Cell and Molecular Physiology Section, American Physiological Society.

Invited Lectures (Last Five Years)

Identification of K⁺ channels involved in K⁺ recycling in winter flounder enterocytes. Mount Desert Island Biological Laboratory Conference, July, 2004.

UTP activates apical Cl⁻ channels or basolateral K⁺ channels depending on P2Y receptor localization. Purines 2004: University of North Carolina, Chapel Hill, NC, June, 2004.

Role of CFTR in alveolar electrolyte and fluid absorption. Department of Anatomy and Physiology, Wright State University, February, 2004.

Alveolar epithelial cell chloride transport and the resolution of pulmonary edema. Inaugural Ion Channel Retreat, Whistler, B.C., Canada, June, 2003.

Alveolar electrolyte transport and the resolution of pulmonary edema. Comparative Biomedical Sciences Seminar Series, University of Minnesota, May, 2002.

The role of proton transport in eosinophil attack. Department of Physiology, University of Minnesota, October, 2002.

Growth factor regulation of epithelial Na⁺ transport in endometrial epithelial cells. 3M Company, 2000.

Ionotropic properties of P2Y receptors. Department of Physiology, Kansas State University, 2000.

Purinergic receptors and ion channel function. Mount Desert Island Biological Laboratory Conference, 2000.

Funding (Last Five Years) – \$796,729

Mayo Foundation/NIH. Prime regulation of degranulation of human eosinophils. 2001-06. \$564,323.

UMN Academic Health Center. Development of a transgenic cystic fibrosis pig. C. Steer (PI). 2004-05. \$249,921.

NIH Scor Project. D. Ingbar (PI). 1993-04. \$2,677,292.

Mayo Foundation/NIH. Prime eosinophils in human disease. 1997-01. \$232,406.

Dissertations and Theses (Last Five Years)

Name	Program	Degree	Thesis Title
Xinpo Jiang	Molecular Vet Biosci	Ph.D.	Beta-adrenergic regulation of alveolar epithelial ion transport.
So Yeong Lee	Cellular/Integrative Phys	Ph.D.	P2Y receptor regulation of ion channel function in xenopus oocytes.
Melissa L. Palmer-Densmore	Animal Sciences	M.S.	Plan B

Pre-doctoral Supervision - Current Advisees

Melissa Palmer-Densmore Ph.D. Cellular & Integrative Physiology

Post-doctoral Supervision - Current Advisees

Jennifer Bankers-Fulbright, Ph.D.

Courses Taught (last 5 yrs)

Designator	Name	Cr	% Effort	Term	Years
CVM 6130	Veterinary Physiology	4	25	Spring	2000-2003
AnSc 2301	Systemic Physiology	4	25	Fall	2000
PHSL 8310	Advanced Cellular Phys	1	25	Fall	2001

Service

Reviewer: *Journal General Physiology*, *American Journal of Physiology* (Lung Cellular and Molecular Physiology), *American Journal of Physiology* (Cell Physiology), *Journal of Cell Science*. *Journal of Membrane Biology*.

Elected as Member of the Steering Committee (2004-2007), Cell and Molecular Section: American Physiological Society.

Elected as Cell and Molecular Physiology Section Representative, Committee on Committees, American Physiological Society.

Chairman, *Epithelial Na⁺ and K⁺ channel Featured Topic Symposium*, Cell and Molecular Physiology Section, American Physiological Society.