

**BIOGRAPHICAL SKETCH**

Give the following information for the key personnel and consultants and collaborators. Begin with the principal investigator/program director. Photocopy this page for each person.

NAME

POSITION TITLE

R. Tyler Miller

Professor of Medicine

EDUCATION (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
Harvard College, Cambridge, MA	B.A.	1975	History
Case Western Reserve University, Cleveland, OH	M.D.	1980	Medicine

**RESEARCH AND PROFESSIONAL EXPERIENCE:** Concluding with present position, list, in chronological order, previous employment, experience, and honors. Key personnel include the principal investigator and any other individuals who participate in the scientific development or execution of the project. Key personnel typically will include all individuals with doctoral or other professional degrees, but in some projects will include individuals at the masters or baccalaureate level provided they contribute in a substantive way to the scientific development or execution of the project. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. DO NOT EXCEED TWO PAGES.

Intern, Department of Medicine, UCSF, June 1980 - July 1981

Resident, Department of Medicine, UCSF, July 1981 - June 1983

Chief Resident, Department of Medicine, UCSF, July 1983 - June 1984

Fellow, Nephrology (D.G. Warnock), UCSF, July 1984 - June 1986

Fellow Pharmacology (H.R. Bourne), UCSF, July 1986 - June 1988

Visiting Researcher (J. Pouyssegur), CNRS, Nice, France, Nov 1989 - Feb 1990

Asst. Professor, Medicine, UT Southwestern Medical Center at Dallas, July 1988 - June 1995

Assoc. Professor of Medicine and Pharmacology, University of Florida, July 1995-April, 2001

Professor of Medicine and Physiology, Case-Western Reserve University, May, 2001 – Present

Chief, Nephrology Louis Stokes VAMC, Cleveland, OH May 2001 - Present

**Awards.**

Student Fellowship, Pathology - CWRU, July 1976 - June 1977, Alpha Omega Alpha 1979, Ph.D. Thesis

Comm. Claude Sardet, Univ. de Nice Feb 1990, Post Graduate Education Committee Am Soc Nephrol 1990-

1993, Ad Hoc Physiology Study Section NIH June 1992, Ad Hoc GMB Study Section Feb 1993, Member,

Council on Kidney and Cardiovascular Disease 1994 -1997, Chair Awards Committee Council on Kidney and Cardiovascular Disease, AHA. Deputy Editor, Journal of the American Society of Nephrology, 1996-2002.

Member VA Merit Review Study Section, 1997-2000. Member AHA Molecular Signaling study section, 1997 - 2000. ASN Basic Science Committee 1998 -2001, Editorial Board, AJP Renal 1/99 - 12/04.

Research Projects ongoing or completed during the last three years.

1) G protein-dependent signaling in renal epithelial cells (NIH RO1 DK41726, 8/97 - 6/02). The goal of this proposal is to understand the intracellular signaling systems that are regulated by G protein-dependent signaling systems in renal epithelial cells. The application focuses on the signaling systems regulated by the extracellular Ca-sensing receptor (CaR). The hypotheses we will test are: 1) the Ca<sub>o</sub>-R activates of multiple G proteins (G<sub>q</sub>, G<sub>13</sub>, and a G<sub>i</sub>); 2) the G proteins that couple to the Ca<sub>o</sub>-R signal by different mechanisms, and activate different sets of MAP kinases; 3) the G proteins and kinase activate different elements of the NHE-1 promoter; and 4) the signals that regulate Na/H exchange also regulate other transporters in a coordinated manner. The studies will be performed in cells that allow simultaneous genetic and biochemical analyses, freshly isolated MTAL cells to verify the genetic and biochemical studies and cultured MTAL cells to test the effects of these signaling systems on regulation of transport. Establishing the mechanisms by which the Ca<sub>o</sub>-R acts will improve our understanding of the genetic diseases linked to the Ca<sub>o</sub>-R and the electrolyte abnormalities and interstitial nephritis associated with hypercalcemia.

2) Interaction of the Ca receptor with filamin, a potential scaffolding protein. (NIH RO1, 7/02 - 6/05). We found

that the Ca receptor interacts with filamin, a cytoskeletal, actin cross-linking protein in a yeast two hybrid assay and in mammalian cells. Other investigators have shown that filamin interacts with a number of other proteins, many of which have signaling functions, suggesting that filamin may act as a scaffolding protein. The goals of these studies are to characterize the interaction of the CaR and filamin using yeast two hybrid analysis and mammalian cells, to determine which of several cell signaling systems depend on the interaction of the CaR and filamin, and to look for additional proteins that interact with filamin and the CaR that could participate in a signaling complex.

### **PUBLICATIONS - Peer-Reviewed Articles**

1. Miller, R.T., J.G. Douglas, and M.J. Dunn. Dissociation of aldosterone and prostaglandin biosynthesis in the rat adrenal glomerulosa. *Prostaglandins* 20:449-62, 1980.
2. Miller, R.T. and A.S. Pollock. Modification of the internal pH sensitivity of the Na/H antiporter by parathyroid hormone in a cultured renal cell line. *J. Biol. Chem.* 262:9115-9120, 1987.
3. Miller, R.T., A.S. Pollock, and D.G. Warnock. Cycloheximide effects on the Na/H antiporter in cultured opossum kidney cells. *BBA*, 900:157-159, 1987.
4. Chambers, H.F., R.T. Miller, and M. Newman. Right sided staphylococcus aureus endocarditis in intravenous drug abusers: Two week combination therapy. *Ann. Int. Med.* 109:619-624, 1988.
5. Sullivan, K.A., R.T. Miller, S.B. Masters, B. Beiderman, W. Heideman, and H.R. Bourne. Identification of receptor contact site involved in G protein-receptor coupling. *Nature* 330: 758-760, 1987.
6. Masters, S.B., K.A. Sullivan, R.T. Miller, B. Beiderman, N.G. Lopez, J. Ramachandran, and H.R. Bourne. Carboxyl terminal domain of G<sub>s</sub> specifies coupling of receptors to adenylyl cyclase. *Science*, 241: 448-451, 1988.
7. Miller, R.T., S.B. Masters, K.A. Sullivan, B. Beiderman, and H.R. Bourne. A mutation that prevents GTP-dependent activation of the  $\gamma$  chain of G<sub>s</sub>. *Nature*, 334: 712-715, 1988.
8. Masters, S.B., R.T. Miller, H.-H. Chi, F.-H. Chang, B. Beiderman, N.G. Lopez, and H.R. Bourne. Mutations in the GTP binding site of  $\gamma$ s alter stimulation of adenylyl cyclase. *J. Biol. Chem.* 264:15467-15474, 1989.
9. Miller, R.T., L. Counillon, G. Pages, C.R. Lifton, C. Sardet, and J. Pouyssegur. Structure of the 5' flanking regulatory region and gene for the human growth factor activatable Na/H exchanger NHE-1. *J. Biol. Chem.* 266:10813-10819, 1991.
10. Moe, O.W., R.T. Miller, and R.J. Alpern. Differential regulation of the Na/H antiporter by acid. *J. Clin. Invest.* 88:1703-1708, 1991.
11. Horie, S., O.W. Moe, R.T. Miller, and R.J. Alpern. Long term activation of protein kinase C causes chronic Na/H antiporter stimulation in cultured proximal tubule cells. *J. Clin. Invest.* 89:365-372, 1992.
12. Horie, S., O.W. Moe, Y. Yamaji, R.T. Miller, and R.J. Alpern. Protein kinase C and AP-1 mediate acid-induced increases in Na/H antiporter. *PNAS*, 89:5236-5340, 1992.
13. Moe, O.W., K. Ujiie, R.A. Star, R.T. Miller, J. Widell, R.J. Alpern, and W.L. Henrich. Renin Expression in renal Proximal Tubule. *J. Clin. Invest.* 91:774-779, 1992.
14. Cano, A., R.T. Miller, R.J. Alpern, and P.A. Preisig. Angiotensin II stimulation of Na/H antiporter activity is c-AMP-independent in OK cells. *A.J.P. Cell*, 266:C1603-C1608, 1994.
15. Kitamura, K., and R.T. Miller. Regulation of hormone-sensitive Ca influx by the adenylyl cyclase system in renal epithelial cells. *J. Clin. Invest.* 94:328-336, 1994.
16. Singer, W., R.T. Miller, and P.C. Sternweis. Purification and characterization of the  $\gamma$  subunit of G<sub>13</sub>. *J. Biol. Chem.* 269:19796-19802, 1994.
17. Yamaji, Y., O.W. Moe, R.T. Miller, and R.J. Alpern. Acid activation of immediate early genes. *J. Clin. Invest.* 94:1297-1303, 1994.
18. Kitamura, K., W.D. Singer, A. Cano, and R.T. Miller. Regulation of NHE-1 by distinct G protein  $\gamma$  chains in renal epithelial cells. *Am. J. Physiol.* 268:C101-110, 1995.
19. Yamaji, Y., Moe, O.W., Amemiya, M., Cano, A., Miller, R.T., and R.J. Alpern. Overexpression of CSK inhibits acid-induced activation of NHE-3. *PNAS*, 92:6274-6278, 1995.
20. Kugi, M., K. Kitamura, G.L. Cottam, and R.T. Miller. G $\gamma_{12}$  mimics the effect of bacterial lipopolysaccharide priming on PAF-induced intracellular Ca mobilization and arachidonic acid release in cultured murine macrophages. *J. Inflammation*, 45:175-182, 1995.

21. Xu, X, K. Kitamura, K. Lau, S. Muallem, and R.T. Miller. Differential regulation of Ca release activated Ca influx (CRAC) by heterotrimeric G proteins. *J. Biol. Chem.* 270:29169-29175, 1995.
22. Kitamura, K., W.D. Singer, R.A. Star, and R.T. Miller. Induction of iNOS by the Heterotrimeric G protein, G $\nabla_{13}$ . *J. Biol. Chem.* 271:7412-7415, 1996.
23. Khair-El-Din, T., S.C. Sicher, M.A. Vazquez, G.W. Chung, K.A. Stallworth, K. Kitamura, R.T. Miller, and C.Y. Lu. Transcription of the murine iNOS gene is inhibited by docosahexaenoic acid, a major constituent of fetal and neonatal sera as well as fish oils. *J. Exp. Med.* 183:1241-1246, 1996.
24. Henrich, W.L., E.A. McAllister, A. Eskue, R.T. Miller, and O.W. Moe. Regulation of the renin-angiotensin system in cultured proximal tubule cells. *Hypertension*, 27:1337-1340, 1996.
25. Kitamura, K., K. Tomita, and R.T. Miller. Inhibition of G $\nabla_{13}$ -induced Ca influx and NO production by cAMP in renal epithelial cells. *J. Am. Soc. Nephrol* 8: 558-568, 1997.
26. Kitamura, K., T. Tomita, and R.T. Miller. Inhibition of G $\nabla_{13}$ -induced Ca influx and NO production by cAMP in renal epithelial cells. *J. Am. Soc. Nephrol.* 8:558-568, 1997.
27. Williams, R.C., Malone, C.C., Miller, R.T., and Silvestris, F. Urinary loss of IgG anti-F(ab')<sub>2</sub>, and anti-DNA antibody in systemic lupus erythematosus nephritis. *J. Lab. Clin. Med.* 132: 210-222, 1998.
28. Kitamura, K., N. Shiraishi, W.D. Singer, K. Tomita, and R.T. Miller. Activation of G $\nabla_{13}$  by endothelin B receptors. *AJP Cell* 276:C930-C937, 1999.
29. Shiraishi, N., F. Shiraishi, M.E. Handlogten, I.D. Weiner, and R.T. Miller. Stimulation of Cl/HCO<sub>3</sub> exchange by G $\nabla_q$  and G $\nabla_{13}$  in renal epithelial cells. In revision.
30. Handlogten, M.E., N. Shiraishi, H. Awata, and R.T. Miller. The extracellular Ca-sensing receptor is a promiscuous divalent cation sensor. *AJP Renal* 279:F1083-F1091, 2000.
31. Handlogten, M.E., C. Huang, N. Shiraishi, H. Awata, and R.T. Miller. The Ca receptor activates cPLA<sub>2</sub> via a MAP kinase independent pathway. *J. Biol. Chem.* 276:13941-13948, 2001.
32. Awata, H., C. Huang, M.E. Handlogten, and R.T. Miller. Interaction of the Ca receptor with filamin, a potential scaffolding protein. *J. Biol. Chem.* 276: 34871-34879, 2001.
33. Huang, C., M.E. Handlogten, and R.T. Miller. Parallel activation of PI-4 kinase and phospholipase C by the extracellular Ca-sensing receptor. *J. Biol. Chem.* 277: 20293-20300, 2002.
34. Vargas-Poussou, R., C. Huang, P. Hulin, P. Houillier, X. Jenunmaitre, M. Paillard, G. Planelles, M. Dechaux, R.T. Miller, and C. Antignac. Functional characterization of a calcium-sensing receptor mutation in severe autosomal dominant hypocalcemia with a Bartter-like syndrome. *JASN* 13: 2259 – 2266, 2002.
35. Yamakaw, K., K. Kitamura, H. Nonoguchi, N. Takasu, R.T. Miller, and K. Tomita. G $\alpha_{13}$  induces preproET-1 gene expression via JNK. *Hypertension Res.* 25:427-432, 2002.
36. Shiraishi, N., K. Kitamura, Y. Kohda, T. Narikiyo, Adachi, M. Miyoshi, T., K. Iwashita, H. Nonoguchi, R.T. Miller, and K. Tomita. Increased endothelin-1 expression in the kidney in hypercalcemic rats. *Kidney Int.* 63:835-852, 2003.
37. Verlander, J.W., R.T. Miller, M.N. Cash, A.E. Frank, and I.D. Weiner. Localization of the ammonium transporter proteins, Rh B glycoprotein and Rh C glycoprotein, in the mouse kidney. *Am. J. Physiol.(Renal)* 284:F323-F337, 2003.
38. Wu, K.L., S. Kahn, L. Wang, G. Jarad, R.T. Miller, M. Konieczkowski, J.R. Sedor, and J.R. Schelling. Renal tubular epithelial cell apoptosis is associated with caspase cleavage of the NHE1 Na/H exchanger. *Am. J. Physiol. (Renal)* 284:F829-F839, 2003.
39. Weiner, I.D., R.T. Miller, and J.W. Verlander. Localization of the ammonium transporters, Rh B glycoprotein and Rh C glycoprotein, in the mouse liver. *Gastroenterology* 124: 1432-1440, 2003.
40. Huang, C., K.M. Hujer, Z. Wu, and R.T. Miller. The Ca<sup>2+</sup>-sensing receptor couples to G $\alpha_{12/13}$  to activate phospholipase D in MDCK cells. *Am. J. Physiol. (Cell)* 286:C22-C30, 2004.
41. Wang, W., C. Li, T.-K. Kwon, R.T. Miller, M.A. Knepper, J. Frokiaer, and S. Nielsen. Reduced expression of renal Na transporters in rats with PTH-induced hypercalcemia. *Am. J. Physiol. (Renal)*, F534-F545, 2003.

## Chapters and Review.

1. Bourne, H.R., S.B. Masters, R.T. Miller, K.A. Sullivan, and G.W. Heideman. Mutations probe structure

- and function of G protein alpha chains. Cold Spring Harbor Symposium on Quantitative Biology, 53, pp. 221-228, 1989.
2. Miller, R.T. and H.R. Bourne. Structure and Function of G Proteins, in Receptor Subunits and Complexes. Barnard, E.A., Burgen, A.S.V., and G.C.K. Roberts Eds. Cambridge Univ. Press. 1991, pp. 209-227.
  3. Miller, R.T. Transmembrane signalling through G proteins. *Kidney Int.* 39, pp. 421-429, 1991.
  4. Miller, R.T. ASN Conference: "Transcriptional Control and Differentiation". *JASN* 3, pp. 1025-1027, 1992.
  5. Miller, R.T. The Impact of Molecular Biology on Understanding Renal Signal Transduction. in *Seminars in Nephrology*, S. Gluck Ed. 12, pp. 516-523, 1992.
  6. Schoolwerth, A.C., R.T. Miller, and W.E. Mitch. The Kidney Council of the American heart Association needs support to maintain a good thing. *JASN* 8:1624-1625, 1997.
  7. Miller, R.T. and A.B. Little, Endocrine disease in dialysis patients, Chapter 21, in *The Principles and Practice of Dialysis*, W.L. Henrich, Ed. Williams and Wilkins, Baltimore, MD, pp 315-327, 1999.
  8. Miller, R.T., Endocrine disease in dialysis patients, Chapter 22, in *The Principles and Practice of Dialysis Second Ed.*, W.L. Henrich, Ed. Williams and Wilkins, Baltimore, MD. In press, 2003.
  9. Miller, R.T. Aquaporins and the heart – for water only? In Press. *Cellular and Molecular Cardiology*.