

EXECUTIVE SUMMARY

Education:

BA Chemistry, University of Rochester

PhD Biochemistry, University of Maryland

Current Positions at Georgetown University:

Director, Center for the Study of Sex Differences in Health, Aging and Disease

Associate Vice-Chair for Research, Department of Medicine

Professor, Departments of Medicine and Physiology & Biophysics

Leadership and Initiative:

Chair, New Lectureship Subcommittee and established the first NIH Directors Margaret Pittman Lectureship (1994)

North American Editor, Cell Biology International (1994-1995)

Founded and Chaired a New Gordon Conference on Ligand Recognition (1997)

Co-Chair, American Heart Association, Mid-Atlantic Consortium Peer Review (1999)

Chair, Nation's Capital Research Committee, National Kidney Foundation (2002)

Consultant to the Dean of Research at Texas Tech University School of Pharmacy, Health Sciences Center in Amarillo during which time, grant income (direct costs) increased by 200% (2002-2004)

Chaired, National American Heart Association Molecular Signaling Peer Review Committee (2003-2004)

Founder and Director, Georgetown University Center for the Study of Sex Differences in Health, Aging and Disease (CSD), which currently includes over 50 faculty members in diverse departments across the university (csd.georgetown.edu). The CSD has a broad focus encompassing sex differences in cell biology and oncology; endocrinology, obesity and diabetes; immunology and infection; neuroscience and cognition; and, vascular biology and hypertension.

Since its inception in the spring of 2003, the CSD has instituted the following:

- **CSD Annual Symposium**, which brings together internationally recognized investigators from the USA and abroad in the field of sex-based biology and gender-specific medicine for a day long symposium on a yearly basis;
- **CSD Grand Rounds**, which is published in the journal *Gender Medicine* (<http://www.gendermedjournal.com>) and brings outstanding investigators to Georgetown on a monthly basis to speak on sex-based biology and gender-specific medicine that is relevant to health and healthcare;
- **CSD Visiting Professor Seminar Series**, which brings sex-based biology and gender-specific medicine to individual departments as a department-CSD co-sponsored event;
- **CSD Interdisciplinary Workshop Series**, which combines two faculty from diverse departments across the University, Washington Hospital Center and MedStar Research Institute for brainstorming sessions on interdisciplinary approaches to new research and grant opportunities;
- **CSD Community Outreach Program**, which serves to educate the public about the importance of sex based biology/gender-specific medicine to their health and healthcare;
- **CSD Quarterly**, a newsletter that focuses on CSD faculty and their research as well as highlighting relevant upcoming events;
- **CSD Educational Initiatives**, which include the establishment of two new graduate courses entitled, "Sex Differences in Physiology and Pathophysiology" and "The Endocrine Basis of Sex Differences in Physiology" as well as a Pharmacology Minicourse Selective for medical students as part of a CSD initiative to better integrate gender-specific medicine into the medical school core curriculum.

Major research findings:

Over her career, Dr. Sandberg has published extensively on the renin angiotensin aldosterone system (RAAS). She was one of the first to clone the type 1b angiotensin receptor (AT_{1b}R) through expression cloning in the *Xenopus* oocyte¹. During this endeavor, she discovered that the amphibian possesses an angiotensin receptor (xAT_aR) on follicular cells surrounding the oocyte which binds angiotensin II (Ang II) and mobilizes intracellular calcium through gap junctions² using the inositol trisphosphate signaling cascade³. By cloning the xAT_aR⁴ and taking advantage of the striking pharmacological differences she discovered between these receptors⁵ – xAT_aRs bind angiotensin *peptide* ligands with high affinity but have low affinity for *nonpeptide* AT₁R antagonists – she identified 13 amino acids that are critical determinants of the AT₁R nonpeptide binding pocket by using site-directed mutagenesis and ultimately creating a gain-of-function xAT_aR that binds the nonpeptide, losartan with affinity equivalent to the AT₁R⁶. Her structure function studies also identified key residues required for AT₁R signal transduction and ligand-mediated receptor internalization. These studies revealed residues necessary for receptor internalization that were *independent* of those critical for signaling and thereby demonstrated that AT₁R internalization does not require receptor signal transduction. More recently, Dr. Sandberg's studies have centered on RAAS-mediated mechanisms underlying sex differences in susceptibility, severity and rate of disease progression in hypertension and renal and vascular disease. She has shown that 17β-estradiol replacement attenuates age-induced salt-sensitive hypertension in the ovariectomized Dahl salt-sensitive rat⁷ and that 17β-estradiol attenuates while dihydrotestosterone aggravates indices of renal damage in the renal wrap model of hypertension⁸. Her lab has also demonstrated that estrogen attenuates AT₁R-mediated aldosterone release via modulating adrenal levels of Ang II⁹ and by inhibiting translation of adrenal AT₁ receptors¹⁰. In addition, AT₁R translation was found to be regulated by E₂ modulation of RNA binding proteins that interact with a hairpin loop within exon 2 of the 5' leader sequence of the AT₁R mRNA¹¹. Two upstream AUGs in exon 2 were shown to mediate exon 2 repression of translation and alternative splicing of exon 2 was demonstrated to contribute to tissue-specific expression of the AT₁R¹². Her laboratory has also found that translational regulation of AT₁Rs contributes to the regulation of AT₁R densities by osmolality in the renal medulla¹³, by uninephrectomy in the renal cortex¹⁴ and during vascular smooth cell proliferation¹⁵.

Grants

Dr. Sandberg has a long-standing record of grant support starting in 1996 from foundations, pharmaceutical companies and the NIH. She currently is Principal Investigator (PI) on two NIH R01 grants (*Translational Control of Angiotensin Receptors* and *Hormonal Regulation of Angiotensin Receptors*), and on two NIH R01 subcontracts (*Estrogen and Sodium Modulate Hypertension in Aging Rats* and *Investigation of Angiotensin Type-1 Receptors with Positron Emission Tomography*). Dr. Sandberg is also Director of the Molecular Biology and Genotyping Core in an NIH Program Project Grant entitled, *Hypertension and Oxidative Stress* and Director of Basic Science in the NICHD Obstetric Pharmacology Research Unit network on the *Pharmacokinetics and Pharmacodynamics of Drugs in Pregnancy*. In addition, she is PI on a pharmaceutical grant from Genzyme and is a Fogarty Mentor on an NIH R03 entitled, *Association between the Y Chromosome and Androgens in Hypertension*.

Editorial Boards and Key Committees

Editorial Boards including *American Journal of Hypertension* (1992-1999; 2002-2004); *Molecular and Cellular Biochemistry* (1992-1999); *Molecular and Cellular Endocrinology* (1993-1996); *American Journal of Physiology: Renal Physiology* (2002 – 2006); *Advances in Chronic Kidney Disease* (2002-present); and *Hypertension* (2004-2006)

Section Editor, Sex-Based Biology, *Journal of Women's Health* (2005 – present)

Associate Editor, *Journal Gender Medicine* (2005 - present)

Member, NIH Hypertension and Microcirculation Study Section (2004-2007)

Elected Member, Leadership Committee, Council on High Blood Pressure Research (2006-2008)

Member, Programming Committee, American Society of Nephrology (2005-2006)

Member, Awards Committee, American Physiological Society (2006-2008)

Major Honors and Awards

Merlin Bumpus Award for Most Promising Young Investigator, Gordon Conference on Angiotensin (1994)
 Young Investigator of the Year Award, COSEHC-Hoechst Marion Roussel (1995)
 Geoffrey D. Spinks Young Investigator Award, National Kidney Foundation (1995)
 Established Investigator Award, American Heart Association (1996)
 John F. Maher, MD Memorial Research Award, National Kidney Foundation (1997)
 Jocelyn Beard Memorial Award, American Heart Association (2001)
 Estelle Ramey Mentorship of the Year Award, Georgetown University (2004)
 Elected President, Women in Nephrology (2003-2004)
 Virendra B. Mahesh Lectureship, Medical College of Georgia (2006)
 Elected President, Organization for the Study of Sex Differences (2006-2008)

Selected Citations

1. Sandberg, K., Ji, H., Clark, A.J., Shapira, H. and K.J. Catt. Cloning and expression of a novel rat angiotensin II receptor subtype. *J. Biol. Chem.* **267**, 9455-9458 (1992).
2. Sandberg, K., Bor, M., Ji, H., Markwick, A.J., Millan, M.A. and K.J. Catt. Angiotensin II-induced calcium mobilization in oocytes by signal transfer through gap junctions. *Science* **249**, 298-301 (1990).
3. Sandberg, K., Ji, H., Iida, T. and K.J. Catt. Intercellular communication between follicular angiotensin II receptors and *Xenopus laevis* oocytes: mediation by an inositol 1,4,5-trisphosphate-dependent mechanism. *J. Cell. Biol.* **117**, 157-167 (1992).
4. Ji, H., Sandberg, K., Zhang, Y. & Catt, K.J. Molecular cloning, sequencing and functional expression of an amphibian angiotensin II receptor from myocardium. *Biochem. Biophys. Res. Comm.* **194**, 756-762 (1993).
5. Sandberg, K., Ji, H., Millan, M.A. and K.J. Catt. Amphibian myocardial angiotensin II receptors are distinct from mammalian AT₁ and AT₂ receptor subtypes. *FEBS Lett.* **284**, 281-284 (1991).
6. Ji, H., Zheng, W., Zhang, Y., Catt, K.J. & Sandberg, K. Genetic transfer of a nonpeptide binding site to a previously unresponsive angiotensin II receptor. *Proc. Natl. Acad. Sci. USA* **92**, 9240-9244 (1995).
7. Hinojosa-Laborde, C. et al. Ovariectomy augments hypertension in aging female Dahl salt-sensitive rats. *Hypertension* **44**, 1-5 (2004).
8. Ji, H. et al. Gonadal steroid regulation of renal injury in renal wrap hypertension. *Am J Physiol Renal Physiol* **288**, F513-20 (2005).
9. Wu, Z., Zheng, W. & Sandberg, K. Estrogen regulates adrenal angiotensin type 1 receptors by modulating adrenal angiotensin levels. *Endocrinology* **144**, 1350-6 (2003).
10. Wu, Z. et al. Estrogen regulates adrenal angiotensin AT₁ receptors by modulating AT₁ receptor translation. *Endocrinology* **144**, 3251-61 (2003).
11. Ji, H. et al. Translational regulation of angiotensin type 1a receptor expression and signaling by upstream AUGs in the 5' leader sequence. *J Biol Chem* **279**, 45322-8 (2004).
12. Zhang, Y. et al. Translational control of the rat angiotensin type 1a receptor by alternative splicing. *Gene* **341**, 93-100 (2004).
13. Lee, S., Wu, Z., Sandberg, K., Yoo, S.E. & Maric, C. Posttranscriptional mechanisms contribute to osmotic regulation of angiotensin type 1 receptors in cultured rat renomedullary interstitial cells. *Am J Physiol Regul Integr Comp Physiol* (2005).
14. Mok, K.Y. et al. Growth hormone regulation of glomerular AT₁ angiotensin receptors in adult uninephrectomized male rats. *Am J Physiol Renal Physiol* **285**, F1085-91 (2003).
15. Lee, S. et al. Translational regulation of angiotensin II type 1 receptors in proliferating vascular smooth muscle cells. *Am J Physiol Regul Integr Comp Physiol* (2005).