Hypertension In The News

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Surgical Sciences Fifteenth Annual Residents' and Fellows' Research Day

Each year, the Division of Surgical Sciences hosts a Residents' and Fellows' Research Day, an event which highlights the extensive research and training efforts by Division. Sixteen fellows and students from the Hypertension Center participated in the 15th Annual Residents' and Fellows' Research Day held November 15, 2007. As part of the day's activities, Mitchell Berger, M.D. Professor and Chair, Department of Neurological Surgery and Director, Brain Tumor Surgery Program at The University of California, San Francisco gave a lecture entitled "Maximizing the Extent of Resection for Gliomas: What Impact Has That Made on Outcome?" Following Dr. Mitchell's lecture was a poster competition during which trainees presented to a judging panel their projects in the areas of clinical and basic science. The day concluded with an awards ceremony held at The Piedmont Club in downtown Winston-Salem. The Hypertension Center's own Jyotsana Menon, D.V.M., M.S., a 5th year Physiology and Pharmacology graduate student, received the Silver Award for Students in Basic Science for her presentation "Angiotensin-(1-7) Reduces Lung Tumor Growth in a Novel Bitransgenic Ki-rasG12C Mouse Model of Lung Tumorigenesis."

Please see *Research Day* on page 3

Wake Forest University Baptist MEDICAL CENTER®
Knowledge makes all the difference.

Retirement for Dr. Ronald Smith

"After 51 years in the medical profession…he looks with eager eyes upon his life with his wife Marilyn at Holly Berry Farm..."

Quo Vadis Medicus? Were goes Medicine?

Dr. Smith assumes his gallery seat to watch, rather than participate, in the unfolding of medical science and clinical medical care in the 21st century. From afar he hopes and trusts that his past colleagues, neighbors, and friends can untangle and restore a medical system that will truly serve our country's people.

After 51 years in the medical profession as a research investigator, clinician, director, and administrator, he looks with eager eyes upon his life with his wife Marilyn at Holly Berry Farm on the edge of the Uwharrie Mountains and High Rock Lake. Time will not sit heavily on his hands with more hours spent with his violin, music, the Salisbury Symphony Orchestra, two Civic organizations in Salisbury, reading to children at the Salisbury Library, organizing a medical out reach program to his county's Latino population in coordination with five Presbyterian Churches, sailing his Highlander, and the restoration of 3 antique vehicles. In spare hours he and Marilyn will be gardening and caring for their farm, the goats, sheep, swans and geese, and also the Heritage apple and Japanese persimmon orchards. Most importantly, he will be delving into his extensive library of American history, philosophy, religion ethics, and gardening. With luck a few evenings may be left to rekindle his passion for duplicate bridge, days to travel our beautiful and bountiful country, and even lounge without guilt on the patio in front of the lake. They tell him life can be very beautiful in retirement.

Upcoming Fellows and Graduate Students Lectures

For the Hypertension Journal Club Katsunori Isa will be presenting on 3/5/08, Aaron Trask on 3/19/08, Liliya Yamaleyeva on 4/2/08, Karl Pendergrass on 4/23/08, and Jonathan Cohen on 4/30/08.
For the Department of Physiology and Pharmacology Graduate Student Seminar Series Amy Arnold will be presenting on 3/17/08.
For the Women's Health Research Day David Soto Pantoja will be presenting a poster on 4/3/08.

Recent Publications

Journal Articles

Anton L, Merrill DC, Neves LA, Brosnihan KB. Angiotensin-(1-7) inhibits in vitro endothelial cell tube formation in human umbilical vein endothelial cells through the AT(1-7) receptor. Endocrine. 2007 Oct;32(2):212-8.

Joyner J, Neves LA, Stovall K, Ferrario CM, Brosnihan KB. Angiotensin-(1-7) serves as an aquaretic by increasing water intake and diuresis in association with down-regulation of aquaporin-1 during pregnancy in rats. Am J Physiol Regul Integr Comp Physiol. 2008 Jan 9

Neves LA, Stovall K, Joyner J, Valdés G, Gallagher PE, Ferrario CM, Merrill DC, Brosnihan KB. ACE2 and ANG-(1-7) in the rat uterus during early and late gestation. Am J Physiol Regul Integr Comp Physiol. 2008 Jan;294(1):R151-61.

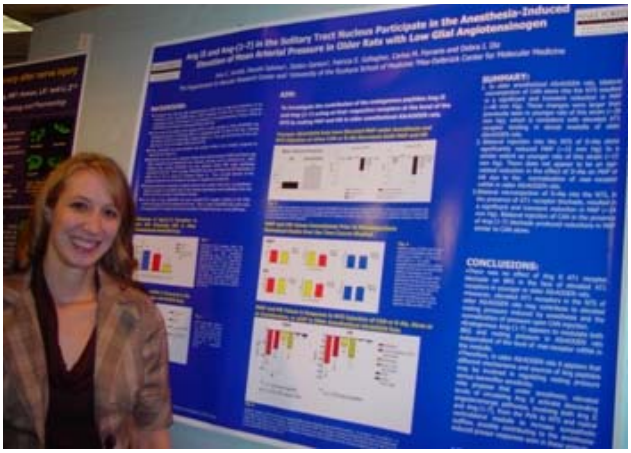
Varagic J, Frohlich ED, Susic D, Ahn J, Matavelli L, Lopez B, Diez J. AT1 receptor antagonism attenuates target organ effects of salt excess in SHR without affecting pressure. Am J Physiol Heart Circ Physiol. 2008 294(2):H853-8.

Wei Y, Sowers JR, Clark SE, Li W, Ferrario CM, Stump CS. Angiotensin II-induced skeletal muscle insulin resistance is mediated by NF-{kappa}B activation via NADPH oxidase. Am J Physiol Endocrinol Metab. 2008 294(2):E345-51.

Book Chapters

Ferrario CM, Averill DB, Brosnihan KB, Chappell MC, Diz DI, Gallagher PE, Neves LAA, and Tallant EA. Regulation of cardiovascular control mechanisms by angiotensin-(1-7) and angiotensin converting enzyme 2. Hypertension and Hormonal Mechanisms, R Carey, editor. 2007: pp 43-59.

Residents' and Fellows' Research Day (cont.)



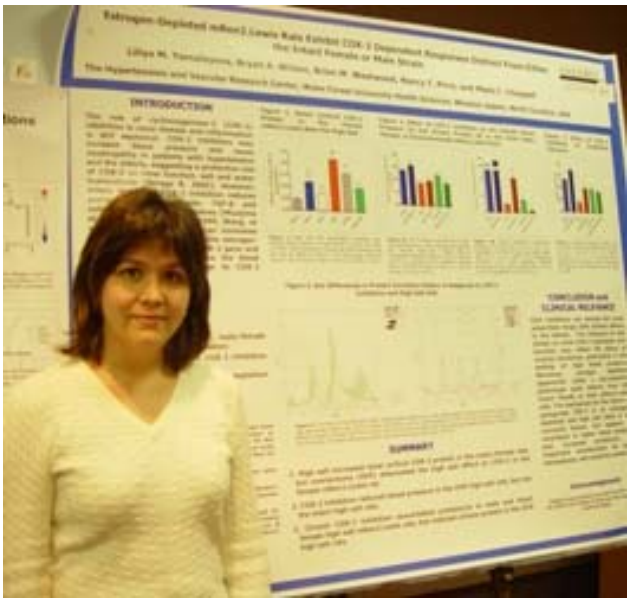
The Increased Shift of the Ang II/Ang-(1-7) Balance in the Chorionic Villi from Preeclamptic Subjects is Mediated by the AT1 Receptor. Lauren Anton, David C. Merrill, Debra Diz, Liomar A. A. Neves, Kathryn Stoval, Patricia E. Gllagher, Cheryl Moorefield, Courtney Gruver, Carlos M. Ferrario, K. Bridget Brosnihan

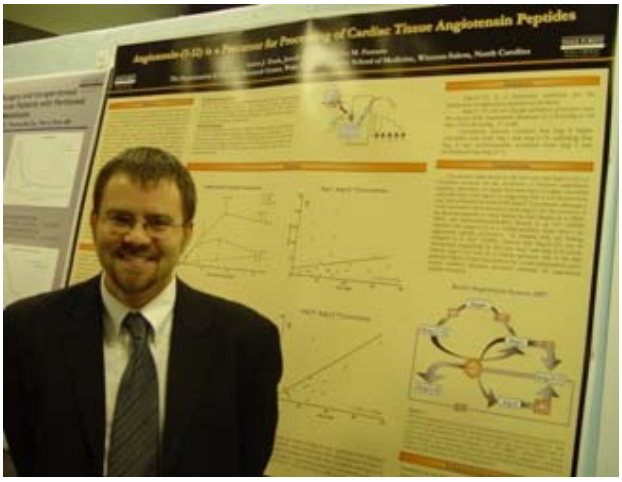
Angiotensin II and Angiotensin-(1-7) in the Solitary Tract Nucleus Participate in the Anesthesia-Induced Elevation of Mean Arterial Pressure in Older Rats with Low Glial Angiotensinogen. Amy Arnold, Atsushi Sakima, Detlev Ganten, Patricia Gallagher, Carlos M. Ferrario, Debra Diz

Inhibition of Glioblastoma Growth by Angiotensin-(1-7). Kyle A. Carver, E. Ann Tallant, Steven J. Newton, Glenn J. Lesser, Patricia E. Gallagher

Chronic Intracerebroventricular AT1 Receptor Blockade, but not Renin Inhibition, Normalizes Blood Pressure in (mRen2)27 Transgenic Rats. Maria Antonia Garcia-Espinosa, Katsunori Isa, Mark C. Chappell, Detlev Ganten, Carlos M. Ferrario, Debra Diz

Residents' and Fellows' Research Day (cont.)





Elevated Angiotensin I and Creatinine Excretion Precede the Increase in Proteinuria during Aging in Sprague-Dawley Rats. Shea Gilliam-Davis, Mark Chappell, Debra I. Diz

Nuclear Angiotensin II-Receptor Subtype, AT2, is Differentially Expressed in the Cortical and Medullary Regions of the Sheep Kidney. TanYa Gwathmey, Nancy T. Pirro, Debra I. Diz, Jorge P. Figueroa, James C. Rose, Mark C. Chappell

Chronic Intracerebroventricular Immunoneutralization of the Novel Angiotensin Peptide, Angiotensin-(1-12), Lowers Blood Pressure in Transgenic Hypertensive Rats. Katsunori Isa, Maria Antonia Garcia-Espinosa, Amy C. Arnold, Nancy Pirro, Ellen Tommasi, Carlos Ferrario, Mark C. Chappell, Debra I. Diz

Localization of the Novel Angiotensin Peptide, Angiotensin-(1-12), in Heart and Kidney of Hypertensive and Normotensive Rats. Jewell A. Jessup, Aaron J. Trask, Mark C. Chappell, Carlos M. Ferrario

Vasorelaxation by Estrogen is Enhanced in Salt-Sensitive Female mRen2. Lewis Rats. Sarah H. Linday, Mark C. Chappell

The Role of the PI3 Kinase Signal Transduction Pathway in Nucleus Tractus Solitarii of mRen2.Lewis and (mRen2)27 Transgenic Hypertension. Exazevia Logan, Debra Diz, David Averill

Angiotensin-(1-7) Reduces Lung Tumor Growth in a Novel Bitransgenic Ki-rasG12C Mouse Model of Lung Tumorigenesis. Jyotsana Menon, Ann Tallant, Mark S. Miller, Michael Callahan, Mark J. Cline, Patricia E. Gallagher

Differential Expression of Neprilysin and Angiotensin Converting Enzyme 2(ACE2) may Contribute to the Gender Disparity in the Hypertensive mRen2.Lewis Strain. Karl D. Pendergrass, Brian Westwood, Mark Chappell

Gender Differences in the Development of Insulin Resistance in Adult Sheep as Result of Antenatal Betamethasone. Hossam A. Shaltout, Mark C. Chappell, David B. Averiall, Jorge P. Figueroa, James C. Rose, Debra I. Diz

Angiotensin-(1-7) Inhibits the Growth of Human Triple Negative Breast Tumors in an Orthotopic Model. David R. Soto-Pantoja, Patricia E. Gallagher, E. Ann Tallant

Angiotensin-(1-12) is a Novel Precursor for the Processing of Cardiac Tissue Angiotensin Peptides. Aaron J. Trask, Jewell A. Jessup, Carlos M. Ferrario

Estrogen-Depleted mRen2.Lewis Rats Exhibit COX-2 Dependent Responses Distinct From Either the Intact Female or Male Strain. Liliya M. Yamaleyeva, Bryan Wilson, Brian M. Westwood, Nancy T. Pirro, Mark C. Chappell

The following Publications were listed incorrectly in Vol 1 Issue 1:

Awumey EM, Howlett AC, Putney JW Jr, Diz DI, Bukoski RD. Ca(2+) mobilization through dorsal root ganglion Ca(2+)-sensing receptor stably expressed in HEK293 cells. *Am J Physiol Cell Physiol* 2007 May; 292(5):C1895-905.

Benter IF, Yousif MH, Cojocel C, Al-Maghrebi M, Diz DI. Angiotensin-(1-7) prevents diabetes-induced cardiovascular dysfunction. *Am J Physiol Heart Circ Physiol* 2007 Jan; 292(1):H666-72.

Benter IF, Yousif MH, Dhaunsi GS, Kaur J, Chappell MC, Diz DI. Angiotensin-(1-7) prevents activation of NADPH oxidase and renal vascular dysfunction in diabetic hypertensive rats. *Am J Nephrol* 2008;28(1):25-33.

Chappell MC. Emerging evidence for a functional Angiotensin-converting enzyme 2-angiotensin-(1-7)-Mas Receptor Axis: more than regulation of blood pressure? *Hypertension* 2007;50:596-599.

De Mello WC, Ferrario CM, Jessup JA. Beneficial versus harmful effects of Angiotensin (1-7) on impulse propagation and cardiac arrhythmias in the failing heart. *J Renin Angiotensin Aldosterone Syst* 2007 Jun; 8(2):74-80.

Diz DI, Kasper SO, Sakima A, Ferrario CM. Aging and the brain renin-angiotensin system: insights from studies in transgenic rats. *Cleve Clin J Med* 2007 Feb;74 Suppl 1:S95-98.

Gilliam-Davis S, Payne VS, Kasper SO, Tommasi EN, Robbins ME, Diz DI. Long term AT1 receptor blockade improves metabolic function and provides renoprotection in Fischer 344 rats. *Am J Physiol Heart Circ Physiol* 2007 Jul;293:H1327-33.

Gironacci MM, Brosnihan KB, Ferrario CM, Gorzalczany S, Verrilli MA, Pascual M, Taira C, Pena C. Increased hypothalamic angiotensin-(1-7) levels in rats with aortic coarctation-induced hypertension. *Peptides* 2007 Aug; 28(8):1580-85.

Grigore D, Ojeda NB, Robertson EB, Dawson AS, Huffman CA, Bourassa EA, Speth RC, Brosnihan KB, Alexander BT. Placental insufficiency results in temporal alterations in the renin angiotensin system in male hypertension growth restricted offspring. *Am J Physiol Regul Integr Comp Physiol* 2007 Aug; 292(2):R801-11.

Joyner J, Neves LA, Granger JP, Alexander BT, Merrill DC, Chappell MC, Ferrario CM, Davis WP, Brosnihan KB. Temporal-spatial expression of ANG-(1-7) and angiotensin-converting enzyme 2 in the kidney of normal and hypertensive pregnant rats. *Am J Physiol Regul Integr Comp Physiol* 2007 July;293(1):R169-77.

Lakoski SG, Li L, Langefeld CD, Liu Y, Howard TD, Brosnihan KB, Xu J, Bowden DW, Herrington DM. The association between innate immunity gene (IRAK1) and C-reactive protein in the Diabetes Heart Study. *Exp Mol Pathol* 2007 Jun; 82(3):280-83.

Lakoski SG, Liu Y, Brosnihan KB, Herrington DM. Interleukin-10 concentration and coronary heart disease (CHD) event risk in the estrogen replacement and atherosclerosis (ERA) study. *Atherosclerosis* 2007, Aug 10.

Matavelli LC, Zhou X, Varagic J, Susic D, Frohlich ED. Salt loading produces severe renal hemodynamic dysfunction independent of arterial pressure in spontaneously hypertensive rats. *Am J Physiol Heart Circ Physiol* 2007 Feb;292(2):H814-19.

Menon J, Soto-Pantoja DR, Callahan MD, Cline JM, Ferrario CM, Tallant EA, Gallagher PE. Angiotensin-(1-7) inhibits growth of human lung adenocarcinoma xenografts in nude mice through a reduction in cyclooxygenase-2. *Cancer Res* 2007 Mar 15;67(6):2809-15.

Oudit GY, Kassiri Z, Patel MP, Chappell M, Butany J, Backx PH, Tsushima RG, Scholey JW, Khokha R, Penninger JM. Angiotensin II-mediated oxidative stress and inflammation mediate the age-dependent cardiomyopathy in ACE2 null mice. *Cardiovasc Res* 2007 Jul 1;75(1):29-39.

Corrected Publications (cont.)

Pignone A. Del Rosso A, Brosnihan KB, Perfetto F, Livi R, Fiori G, Guiducci S, Cinelli M, Rogai V, Tempestini A, Bartoli F, Generine S, Ferrario CM, Matucci Cerinic M. Reduced circulating levels of angiotensin (1-7) in systemic sclerosis: a new pathway in the dysregulation of endothelial dependent vascular tone control. *Ann Rheum Dis* 2007;66:1305-1310.

Prime DD, Brosnihan KB, Herrington DM. Effects of hormone therapy on blood pressure and the renin-angiotensin system in postmenopausal women. *Minerva Cardioangiol* 2007 Aug; 55(4):477-85.

Sakima A, Averill DB, Kasper SO, Jackson L, Ganter D, Ferrario CM, Gallagher PE, Diz DI. Baroreceptor reflex regulation in anesthetized transgenic rats with low glia-derived angiotensinogen. *Am J Physiol Heart Circ Physiol* 2007 Mar;292(3):H1412-19.

Schindler C, Bramlage P, Kirch W, Ferrario CM. Role of the vasodilator peptide angiotensin-(1-7) in cardiovascular drug therapy. *Vasc Health Risk Manag* 2007; 3(1):125-37.

Schindler C, Brosnihan KB, Ferrario CM, Bramlage P, Maywald U, Koch R, Oertel R, Kirch W. Comparison of inhibitory effects of irbesartan and atorvastatin treatment on the renin angiotensin system (RAS) in veins: a randomized double-blind crossover trial in healthy subjects. *J Clin Pharmaco*l 2007 Jan; 47(1):112-20.

Shaltout HA, Westwood BM, Averill DB, Ferrario CM, Figueroa JP, Diz, DI, Rose JC, Chappell MC. Angiotensin metabolism in renal proximal tubules, urine, and serum of sheep: evidence for ACE2-dependent processing of angiotensin II. *Am J Physiol Renal Physiol* 2007 Jan; 292(1):F82-91.

Strawn WB, Ferrario CM. Angiotensin II AT(1) receptor blockade normalizes CD11b(+) monocyte production in bone marrow of hypercholesterolemic monkeys. *Atherosclerosis* 2008 Feb;196(2):624-3*2.*

Susic D, Varagic J, Ahn J, Matavelli L, Frohlich ED. Long-term mineralocorticoid receptor blockade reduces fibrosis and improves cardiac performance and coronary hemodynamics in elderly SHR. *Am J Physiol Heart Circ Physiol* 2007 Jan;292(1):H175-79.

Trask AJ Averill DB, Ganten D, Chappell MC, Ferrario CM. Primary role of angiotensin-converting enzyme-2 in cardiac production of angiotensin-(1-7) in transgenic Ren-2 hypertensive rats. *Am J Physiol Heart Circ Physiol* 2007 Jun;292(6):H3019-24.

Trask AJ, Ferrario CM. Angiotensin-(1-7): pharmacology and new perspectives in cardiovascular treatments. *Cardiovasc Drug Rev* 2007 Summer; 25(2):162-74.

Wei Y, Whaley-Connell AT, Chen K, Habibi J, Uptergrove GM, Clark SE, Stump CS, Ferrario CM, Sowers JR. NADPH oxidase contributes to vascular inflammation, insulin resistance, and remodeling in the transgenic (mRen2) rat. *Hypertension* 2007 Aug; 50(2):384-91.

Westwood BM , Chappell MC. Application of correlate summation to data clustering in the estrogen- and salt-sensitive female mRen2.Lewis Rat. In *Proceedings of the 1st International Workshop on Text Mining in Bioinformatics* (Arlington, Virginia, USA, November 10, 2006). TMBIO '06. ACM Press, New York, NY, 21-26.

Yamaleyeva LM, Gallagher PE, Vinsant S, Chappell MC. Discoordinate regulation of renal nitric oxide synthase isoforms in ovariectomized m Ren2.Lewis rats. *Am J Physiol Regul Integr Comp Physiol* 2007 Feb;292(2):R819-26.

Yamaleyeva LM, Pendergrass KD, Pirro NT, Gallagher PE, Groban L, Chappell MC. Ovariectomy is protective against renal injury in the high salt fed older mREN2.Lewis rat. *Am J Physiol Heart Circ Physiol* 2007 Jul 13.

Zhao W, Diz DI, Robbins ME. Oxidative damage pathways in relation to normal tissue injury. *Br J Radiol* 2007 Sep; 80 Spec No 1:S23-31.

Zhao W, Payne V, Tommasi E, Diz DI, Hsu FC, Robbins ME. Administration of the peroxisomal proliferator-activated receptor gamma agonist pioglitazone during fractionated brain irradiation prevents radiation-induced cognitive impairment. *Int J Radiat Oncol Biol Phys* 2007 Jan 1; 67(1):6-9.

COSEHC Distinguished Fellow Award

Carlos Ferrario, M.D. receiving recognition as the *first* COSEHC Distinguished Fellow

On October 13, 2007, the COSEHC Board of Directors recognized Carlos Ferrario, M.D. for his vision, courage, and leadership as President of the organization since its inception. Ferrario, who retired as President in January 2008, founded COSEHC in 1993 upon his recognition of the deplorable high morbidity and mortality rates of cardiovascular disease in the Southeastern United States. During his 15 year tenure as President, Ferrario developed a regional organization with networked cardiovascular centers of excellence and provided educational and research initiatives that have accelerated the translation of research to clinical practice and improved cardiovascular care throughout the Southeastern United States. The COSEHC mission, which is succeeding in reducing cardiovascular morbidity and mortality in the southeastern United States, especially in minority and underserved populations, is evidence that his leadership as founder and the first President of COSEHC has improved the health and welfare of Americans.

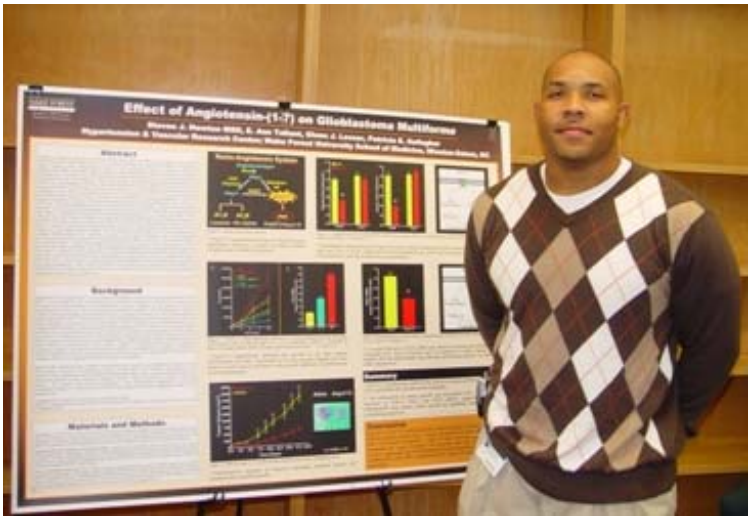
Clinical Contract Awards

Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Trial of HMR1766 Assessing the Efficacy and Safety of 3 Doses of HMR1766 (25, 100, 200 Mg OD) versus Placebo with Cilostazol, 100 Mg BID as a Calibrator, Administered for 26 weeks in Patients with Peripheral Arterial Disease (PAD) Fontaine Stage II
PI: Dr. Levy
Sponsor: Sanofi-Aventis U.S. Inc.
IRB# 00001672

Title: A Double-Blind, Placebo-Controlled, Randomized, Parallel, Clinical Trial to Study the Effect of Losartan Potassium on Endothelial Dysfunction and Insulin Resistance in Obese Patients with Impaired Fasting Glucose
PI: Drs. Ferrario and Smith
Sponsor: Merck & Co., Inc.
IRB# 00000569

Title: Effects of Losartan Therapy on Endothelial Progenitor Cell Function in Patients peripheral Arterial Disease (PAD)
PI: Dr. Levy
Sponsor: Merck & Co., Inc.
IRB# 00000266

Recognition Awards



Medical student Steven Newton was awarded 1st Place for Clinical and Translational Science Research for his poster presentation at the Medical Students' Research Day 2007. Steve's work with Drs. Tallant and Gallagher led to a phase 1 clinical trial for Angiotension–(1-7).

Research fellow Hossam Shaltout was awarded The Women's Health Center of Excellence Award at the Annual WNCSN Pizza/Poster Session on December 3, 2007. Hossam's work was on gender differences in insulin sensitivity with Drs. Diz and Chappell.

Travel Awards

Graduate Student, Lauren Anton, and Dr. JaNae Joyner received the Merck Travel Award at the American Heart Association Council of High Blood Pressure meeting in September 2007.

SAVE the DATE!!!!!

COSEHC 2008 ANNUAL Scientific Sessions

Hyatt Regency on the Inner Harbor

Baltimore, Maryland

September 24-27, 2008

How You Can Help

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