LOSARTAN

A MEDICAL DICTIONARY, BIBLIOGRAPHY,
AND ANNOTATED RESEARCH GUIDE TO
INTERNET REFERENCES

JAMES N. PARKER, M.D.
AND PHILIP M. PARKER, PH.D., EDITORS

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FORWARD

In March 2001, the National Institutes of Health issued the following warning: "The number of Web sites offering health-related resources grows every day. Many sites provide valuable information, while others may have information that is unreliable or misleading."[1] Furthermore, because of the rapid increase in Internet-based information, many hours can be wasted searching, selecting, and printing. Since only the smallest fraction of information dealing with losartan is indexed in search engines, such as **www.google.com** or others, a non-systematic approach to Internet research can be not only time consuming, but also incomplete. This book was created for medical professionals, students, and members of the general public who want to know as much as possible about losartan, using the most advanced research tools available and spending the least amount of time doing so.

In addition to offering a structured and comprehensive bibliography, the pages that follow will tell you where and how to find reliable information covering virtually all topics related to losartan, from the essentials to the most advanced areas of research. Public, academic, government, and peer-reviewed research studies are emphasized. Various abstracts are reproduced to give you some of the latest official information available to date on losartan. Abundant guidance is given on how to obtain free-of-charge primary research results via the Internet. **While this book focuses on the field of medicine, when some sources provide access to non-medical information relating to losartan, these are noted in the text.**

E-book and electronic versions of this book are fully interactive with each of the Internet sites mentioned (clicking on a hyperlink automatically opens your browser to the site indicated). If you are using the hard copy version of this book, you can access a cited Web site by typing the provided Web address directly into your Internet browser. You may find it useful to refer to synonyms or related terms when accessing these Internet databases. **NOTE:** At the time of publication, the Web addresses were functional. However, some links may fail due to URL address changes, which is a common occurrence on the Internet.

For readers unfamiliar with the Internet, detailed instructions are offered on how to access electronic resources. For readers unfamiliar with medical terminology, a comprehensive glossary is provided. For readers without access to Internet resources, a directory of medical libraries, that have or can locate references cited here, is given. We hope these resources will prove useful to the widest possible audience seeking information on losartan.

The Editors

[1] From the NIH, National Cancer Institute (NCI): **http://www.cancer.gov/cancerinfo/ten-things-to-know**.

CHAPTER 1. STUDIES ON LOSARTAN

Overview

In this chapter, we will show you how to locate peer-reviewed references and studies on losartan.

The Combined Health Information Database

The Combined Health Information Database summarizes studies across numerous federal agencies. To limit your investigation to research studies and losartan, you will need to use the advanced search options. First, go to **http://chid.nih.gov/index.html**. From there, select the "Detailed Search" option (or go directly to that page with the following hyperlink: **http://chid.nih.gov/detail/detail.html**). The trick in extracting studies is found in the drop boxes at the bottom of the search page where "You may refine your search by." Select the dates and language you prefer, and the format option "Journal Article." At the top of the search form, select the number of records you would like to see (we recommend 100) and check the box to display "whole records." We recommend that you type "losartan" (or synonyms) into the "For these words:" box. Consider using the option "anywhere in record" to make your search as broad as possible. If you want to limit the search to only a particular field, such as the title of the journal, then select this option in the "Search in these fields" drop box. The following is what you can expect from this type of search:

- **Effects of Losartan on Renal and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Nephropathy**

  Source: New England Journal of Medicine. 345(12): 861-869. September 20, 2001.

  Summary: Diabetic nephropathy (diabetes associated kidney disease) is the leading cause of end stage renal disease (ESRD). Interruption of the renin angiotensin system slows the progression of renal (kidney) disease in patients with type 1 diabetes, but similar data are not available for patients with type 2, the most common form of diabetes. This article reports on a study that assessed the role of the angiotensin II receptor antagonist **losartan** in patients with type 2 diabetes and nephropathy. A total of 1,513 patients were enrolled in this randomized, double blind study comparing **losartan** (50 to 100 milligrams once daily) with placebo, both taken in addition to conventional antihypertensive treatment (calcium channel antagonists, diuretics, alpha blockers, beta

blockers, and centrally acting agents) for a mean of 3.4 years. The primary outcome was the composite of a doubling of the baseline serum creatinine concentration, end stage renal disease, or death. Secondary end points included a composite of morbidity (related illness or complications) and mortality from cardiovascular causes, proteinuria, and the rate of progression of renal disease. A total of 327 patients in the **losartan** group reached the primary end point, as compared with 359 in the placebo group. **Losartan** reduced the incidence of a doubling of the serum creatinine concentration and end stage renal disease, but had no effect on the rate of death. The benefit exceeded that attributable to changes in blood pressure. The composite of morbidity and mortality from cardiovascular causes was similar in the two groups, although the rate of first hospitalization for heart failure was signficantly lower with **losartan.** The level of proteinuria (protein in the urine) declined by 35 percent with **losartan.** The authors conclude that **losartan** conferred significant renal benefits in patients with type 2 diabetes and nephropathy, and it was generally well tolerated. 3 figure. 3 tables. 34 references.

- **Low-Sodium Diet Potentiates the Effects of Losartan in Type 2 Diabetes**

  Source: Diabetes Care. 25(4): 663-671. April 2002.

  Contact: Available from American Diabetes Association. 1701 North Beauregard Street, Alexandria, VA 22311. (800) 232-3472. Website: www.diabetes.org.

  Summary: Patients with diabetes have a high prevalence of hypertension (high blood pressure), increased total body exchangeable sodium levels, and an impaired ability to excrete a sodium load. This article reports on a study that assessed the effect of dietary sodium (salt) restriction on the efficacy of **losartan** in subjects with hypertension (high blood pressure), type 2 diabetes, and albumin (protein) excretion rates of 10 to 200 micrograms per minute. In the study, 20 subjects were randomized to **losartan** 50 milligrams per day (n = 10) or placebo (n = 10). Drug therapy was given in two 4 week phases separated by a washout period. In the last 2 weeks of each phase, patients were assigned to low or regular sodium diets, in random order. The results showed that a low-sodium diet dominates the antihypertensive and antiproteinuric effects of **losartan** in type 2 diabetes. The blood pressure reduction resulting from the addition of a low sodium diet to **losartan** was of similar magnitude to that predicted from the addition of a second antihypertensive agent. Thus, the low sodium diet optimizes the renoprotective (protective of the kidney) effects of the ANG-receptor blocker, **losartan.** In certain circumstances, the addition of a low-sodium diet should be considered as an appropriate alternative to additional pharmacological antihypertensive agents, including combination therapy with a diuretic. 5 figures. 4 tables. 41 references.

- **Losartan Reduces the Costs Associated With Diabetic End-Stage Renal Disease**

  Source: Diabetes Care. 26(3): 683-687. March 2003.

  Contact: Available from American Diabetes Association. 1701 North Beauregard Street, Alexandria, VA 22311. (800) 232-3472. Website: www.diabetes.org.

  Summary: This article reports on a study undertaken to evaluate the within-trial effect of **losartan** and conventional antihypertensive therapy (CT) compared with placebo and CT on the economic cost associated with end stage renal disease (ESRD). The study was a multinational double-blind randomized placebo-controlled clinical trial designed to evaluate the renal protective effects of **losartan** on a background of CT in patients with type 2 diabetes and nephropathy (kidney disease). The primary composite end point was doubling of serum creatinine, ESRD, or death. The results showed that **losartan** and

CT compared with placebo and CT reduced the number of days with ESRD by 33.6 days per patient over 3.5 years. This reduction in ESRD days resulted in a decrease in cost associated with ESRD of $5,144 per patient. After accounting for the cost of **losartan,** the reduction in ESRD days resulted in a net savings of $3,522 per patient over 3.5 years. The authors conclude that treatment with **losartan** in patients with type 2 diabetes and nephropathy not only reduced the incidence of ESRD, but also resulted in substantial cost savings. 1 figure. 4 tables. 13 references.

Federally Funded Research on Losartan

The U.S. Government supports a variety of research studies relating to losartan. These studies are tracked by the Office of Extramural Research at the National Institutes of Health.[2] CRISP (Computerized Retrieval of Information on Scientific Projects) is a searchable database of federally funded biomedical research projects conducted at universities, hospitals, and other institutions.

Search the CRISP Web site at **http://crisp.cit.nih.gov/crisp/crisp_query.generate_screen**. You will have the option to perform targeted searches by various criteria, including geography, date, and topics related to losartan.

For most of the studies, the agencies reporting into CRISP provide summaries or abstracts. As opposed to clinical trial research using patients, many federally funded studies use animals or simulated models to explore losartan. The following is typical of the type of information found when searching the CRISP database for losartan:

- **Project Title: ANEMIA AND CLINICAL OUTCOMES IN DIABETIC NEPHROPATHY**

  Principal Investigator & Institution: Mohanram, Anupama; Internal Medicine; University of Texas Sw Med Ctr/Dallas Dallas, Tx 753909105

  Timing: Fiscal Year 2002; Project Start 01-DEC-2002; Project End 30-NOV-2004

  Summary: (provided by applicant): Diabetic nephropathy (DN) is the leading cause of ESRD in the U.S. and cardiovascular (CV) morbidity and mortality are excessive in this population. Preliminary data from the Reduction in Endpoints in NIDDM with the Angiotensin II Antagonist **Losartan** (RENAAL) trial indicate that anemia is a modifiable risk factor for ESRD and CV morbidity and mortality in type 2 DN. I hypothesize that hemoglobin (Hb) is an independent predictor of both renal and CV disease in this population. The specific aims of this project are to determine if anemia is an independent predictor of 1) ESRD; 2) cardiovascular morbidity (non-fatal CV events defined as hospitalization for heart failure, myocardial infarction, and unstable angina, and mortality (sudden cardiac death, death due to progressive heart failure, myocardial infarction, and other cardiac causes) and 3) hospitalization for revascularization (coronary, peripheral, cerebral, or renal), amputation, and stroke. I will use the RENAAL trial database involving 1,513 Type 2 diabetic patients with nephropathy followed on average for 3.4 years. Cox proportional hazards regression models using baseline and follow-up (Hb) will be employed as the independent variable, and renal

[2] Healthcare projects are funded by the National Institutes of Health (NIH), Substance Abuse and Mental Health Services (SAMHSA), Health Resources and Services Administration (HRSA), Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDCP), Agency for Healthcare Research and Quality (AHRQ), and Office of Assistant Secretary of Health (OASH).

disease, cardiovascular disease, and vascular disease outcomes as dependent variables. Power analysis based on observed event rates in the RENAAL trial indicate 95% power to detect a 30% reduction in risk of the primary composite endpoint of doubling serum creatinine, ESRD or death for patients in the highest compared to the lowest quartile of baseline Hb. I expect these results will establish anemia as an independent risk factor for ESRD and cardiovascular morbidity and mortality in type 2 diabetics with progressing renal disease. These data could change practice and lead to new clinical trials.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: ANG II: PERMISSIVE ROLE TO MAINTAIN VASCULAR RELAXATION**

  Principal Investigator & Institution: Lombard, Julian H.; Medical College of Wisconsin Po Box26509 Milwaukee, Wi 532260509

  Timing: Fiscal Year 2003; Project Start 01-MAR-2003; Project End 28-FEB-2008

  Summary: Elevated dietary salt intake in normotensive animals leads to impaired relaxation of resistance arteries in response to a variety of vasodilator stimuli. This appears to be mediated by suppression of the renin-angiotensin system (RAS), since it can be prevented by i.v. infusion of a low dose of angiotensin II (ANGII). This project will study the response of the middle cerebral artery (MCA) to vasodilator stimuli in four novel inbred genetic rat strains: 1) Dahl salt sensitive (Dahl S; SS/Mcw) rats, a genetic model of salt sensitive hypertension that exhibits impaired relaxation to vasodilator stimuli and an impaired ability to regulate plasma ANGII levels in response to changes in dietary salt intake; 2) normotensive Brown Norway (BN/Mcw) rats; 3) SS.BN13 consomic rats, with chromosome 13 of BN rat on the Dahl S background; and 4), renin congenic rats, with the Dahl R renin gene on the Dahl S genetic background. These rat strains will be used to test two fundamental hypotheses related to the role of ANGII in maintaining normal vascular relaxation mechanisms. The first hypothesis is that ANGII, acting through its specific receptor subtypes, plays a role in the maintenance of vascular relaxation mechanisms in middle cerebral arteries under normal physiological conditions. The second hypothesis is that the impaired relaxation of the middle cerebral artery to vasodilator stimuli that occurs in Dahl S rats on a low salt diet is due to defective regulation of plasma ANGII levels in these animals. In Aim 1, we will compare the response of isolated middle cerebral arteries to a variety of vasodilator stimuli acting via different signal transduction mechanisms in inbred normotensive BN/Mcw rats, SS/Mcw rats, and SS.BN13 consomic rats on a low salt diet, in order to demonstrate that SS/Mcw rats on low salt diet exhibit impaired relaxation mechanisms that are not shared by BN/Mcw rats, SS.BN13 rats, or other normotensive rat strains e.g., Sprague-Dawley rats, that have been extensively characterized in studies by our laboratory and others. Aim 2 will utilize pharmacological tools, endothelial removal, and measurement of key biochemical mediators of vascular relaxation in order to determine the mechanisms that mediate vascular relaxation in response to vasodilator stimuli in isolated middle cerebral arteries of SS.BN13 consomic rats on a low salt diet, and to identify vascular relaxation mechanisms that are impaired in vessels of SS/Mcw rats on low salt diet. Aim 3 will utilize i.v. infusions of the ANGII receptor antagonists **losartan** (ATI) and PD123319 (AT2) to determine the role of specific ANGII receptor subtypes in maintaining vascular relaxation mechanisms in the middle cerebral artery under normal physiological conditions in SS.BN13 rats and in renin congenic rats, and to assess the role of specific ANGII receptor subtypes in mediating any protective effect of low dose ANGII infusion to restore normal responses of the middle cerebral artery to vasodilator stimuli in

SS/Mcw rats on a low salt diet. The demonstration that ANGII may have a permissive role in maintaining vascular relaxation mechanisms in normotensive animals is a completely new aspect of ANGII's complex physiological role that has only recently been described and is largely unexplored. In this respect, the studies proposed in this project address a conceptually innovative aspect of the physiological role of ANGII in regulating vascular function. When completed, these studies will not only enhance our understanding of the role of ANGII and its receptors in regulating vascular reactivity under normal physiological conditions, but will also provide insight into the mechanisms of the impaired reactivity of resistance vessels to vasodilator stimuli in SS/Mcw rats, a genetic model of salt sensitive hypertension that has many similarities to the salt sensitive forms of hypertension that develop in humans, particularly in African-Americans.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: ANGIOTENSIN II AND DIABETIC RETINOPATHY**

  Principal Investigator & Institution: Scicli, Alfonso G.; Senior Staff Research Investigator; Molecular Biology; Case Western Reserve Univ-Henry Ford Hsc Research Administraion Cfp-046 Detroit, Mi 48202

  Timing: Fiscal Year 2003; Project Start 01-JAN-2003; Project End 30-NOV-2006

  Summary: (provided by applicant): Clinical trials suggest that Angiotensin Converting Enzyme inhibitors (ACEi) slow the progression of diabetic retinopathy. However, there is little experimental evidence that Angiotensin II (Ang II) is a critical pathogenetic factor in the development of diabetic retinopathy. ACEi's act systemically decreasing blood pressure (BP) and may also act by decreasing local Ang II effects or by non-Ang-dependent mechanisms. Vascular Endothelial Growth Factor (VEGF) is responsible for retinal neovascularization and stimulates expression of Intercellular Adhesion Molecule-1 (ICAM-1), causing leukostasis, capillary plugging and vasopermeability. Reactive oxygen species (ROS) may mediate in part Ang II effects. We have found that Ang II is angiogenic, and that this effect is supressed by SU5416, a highly selective inhibitorof VEGF receptor (VEGF R) responses, suggesting that Ang II can act via VEGF R. In addition, intravitreal Ang II induces retinal leukostasis in vivo. We hypothesize that: a) inhibitionof Ang II ameliorates diabetic retinopathy by mechanisms independent of BP reduction and b) Ang II acts via ROS and VEGF R to increase the expression of retinal leukocyte adhesion molecules, leukostasis, capillary plugging and vasopermeability. Our specific aims are: Aim 1: To compare the effects of chronic treatment with a Ca- Channel blocker, (nifedipine), an ACEi (ramipril), and a AT1 receptor antagonist (Iosartan), on diabetic retinopathy in streptozotocin-induced diabetes (SZD), a rat model of type 1 diabetes (12 months treatment), and in a novel model of retinal neovascularization, the Koletsky rat, a hypertensive model of type 2 diabetes, (10 months treatment). All treatments may lower BP but nifedipine does not inhibit the renin angiotensin system (RAS). We expect that retinopathy is decreased by ramipril and perhaps Iosartan but not nifedipine. Aim 2: To determine whether retinal leukostasis, capillary plugging, vasopermeability and adhesion molecules: a) decrease after treatment with either an ACEi or an Ang II ATl inhibitor in SZD rats (1-2 weeks), and in normal rats 48 hrs after ivt VEGF, and b) increase after ivt Ang II, and whether anti-oxidants or SU5416 inhibit these responses. In Aim 3 we will study in retinal endothelial cells in vitro if Ang II increases adhesion molecules and leukocyte adhesion via ROS and VEGF R and the role of NF-kB. These studies will help understand the role of the RAS in diabetic retinopathy.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: ANGIOTENSIN II BLOCKADE**

  Principal Investigator & Institution: Ibrahim, Hassan N.; Medicine; University of Minnesota Twin Cities 200 Oak Street Se Minneapolis, Mn 554552070

  Timing: Fiscal Year 2002; Project Start 05-SEP-2002; Project End 30-JUN-2007

  Summary: (provided by applicant): Renal transplant loss due to chronic allograft nephropathy (CAN) is widely acknowledged as a major problem that has increased in relative importance as the incidence of early graft loss from acute rejection has declined. Studies from various centers, including the University of Minnesota, suggest that, after excluding patients dying with a functioning graft, as many as 80% of patients who will return to dialysis do so because of CAN. At the present time there are no therapeutic options once the clinical manifestations of CAN have developed. Testing measures to prevent CAN have not been addressed. The overall purpose of this project is to investigate the role of the renin-angiotensin-aldosterone system (RAAS) in the development of CAN. This system plays an important role in the progression of many experimental and clinical renal diseases. Furthermore, blockade of this system with angiotensin converting enzyme inhibitors and angiotensin II receptor blockers has yielded beneficial results in retarding injury and progression in numerous intrinsic renal diseases. This study specifically investigates the long term benefit of the angiotensin II receptor blocker, Iosartan, in the prevention of cortical interstitial volume expansion (an accurate predictor of long term graft function) and graft loss from biopsy proven CAN in a 5 year, randomized, double masked, placebo controlled study of kidney transplant recipients. This clinical trial will directly test the hypothesis that blockade of the renin angiotensin aldosterone system will provide a substantial benefit through blood pressure lowering independent mechanisms, namely, interruption of tibrogenic pathways, anti-proteinuric actions, amelioration of hyperfiltration and possibly some immunomodulatory effects. The proposed studies will also characterize the interstitial ultrastructural compositional changes that occur in the renal allografts with CAN, the effects of treatment on these changes and provide a complete description of the incidence and predictors for the development of transplant glomerulopathy. These studies will also determine the impact of angiotensin II receptor blockade on the rate of decline of glomerular filtration rate, as well as the impact of glomerular size on the rate of graft loss from CAN, the incidence and the progression of post transplant proteinuria, the nature of the permselectivity defects responsible for the proteinuria and will also explore the association of proteinuna with graft loss from CAN. This trial will also help construct a profile for the RAAS in the transplant recipients and explore the relationship between two genes polymorphisms, ACE and TGF-b and CAN. These studies should help to describe the natural history, nature and pathogenesis of CAN, elucidate early markers and predictors of this important disorder and, perhaps, define a safe and useful preventative strategy.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: ANGIOTENSIN II, OXIDATIVE STRESS, AND ATHEROSCLEROSIS**

  Principal Investigator & Institution: Cohen, Richard A.; Associate Professor; Boston Medical Center Gambro Bldg, 2Nd Fl, 660 Harrison Ave, Ste a Boston, Ma 02118

  Timing: Fiscal Year 2002; Project Start 01-SEP-1997; Project End 31-AUG-2005

  Summary: (Adapted from the Investigator's Abstract): Oxidative stress is thought to participate in vascular dysfunction and remodeling that accompanies angiotensin II (AII)-induced hypertension, but the source and cellular sources of oxidant species and their precise role is poorly understood. Recent studies in the laboratories of the two PI's

have elucidated a novel role for the aortic adventitia as the site of elaboration of both superoxide anion (O2-) and nitric oxide (NO) radicals, indicating that the adventitia is a major site of oxidative stress. New studies indicate that the increased elaboration of O2- by AII is indicated by prominent nitrotyrosine staining of the adventitia, likely as a result of production of the reaction product of O2- and NO, peroxynitrite (OONO-). There are many sources of O2- in the vascular wall, but recent studies indicate that multiple subunits of the neutrophil NAD(P)H oxidase are present in the adventitia where O2- is greatest. Preliminary studies in which AII was infused into mice that are deficient in one NADPH oxidase subunit, gp91phox, show a blunted aortic O2-, hypertrophic, and proliferative response to AII compared with wild type mice, despite a similar hypertensive response. Proposed studies in rats and mice will elucidate the hypothesis that oxidative stress mediated by adventitial NAD(P)H oxidase-derived O2- participates in the myogenic, hypertrophic, and proliferative vascular response in AII-induced hypertension. The proposed studies will also take advantage of preliminary work on Apo E deficient mice (EKO) to determine the significance of AII-induced oxidative stress in atherosclerosis. Preliminary studies in these mice indicate that captopril and **losartan** reduce atherosclerosis (suggesting a role for AII), and that hypothetically under the influence of AII, there is increased production of O2- and OONO-, as indicated in preliminary studies by nitrotyrosine. Studies in Apo E deficient mice that overexpress human Cu/Zu SOD and double knockouts deficient in Apo E and gp91 phox or the AII type receptor, will help to elucidate the hypothesis that AII-induced oxidative stress contributes significantly to vascular dysfunction and remodeling in atherosclerosis.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: AT2 MEDIATED ANGIOTENSIN II SIGNALING**

  Principal Investigator & Institution: Mauch, Teri J.; Associate Professor; Pediatrics; University of Utah Salt Lake City, Ut 84102

  Timing: Fiscal Year 2003; Project Start 01-JUN-2003; Project End 30-APR-2005

  Summary: (provided by applicant): Fetuses deprived of the vasoactive peptide and potent growth factor Angiotensin II (Ang II) are born with renal dysplasia, and they require dialysis and transplantation for long term survival. Ang II binds at least two receptors, AT1, and AT2. AT1 mediates cell growth and division, vasoconstriction, and salt retention. Decreased AT1 activation likely mediates some of the fetotoxicity in Ang U -deprived babies. AT2, however, is the predominant Ang II receptor in the fetal kidney, and its expression declines at birth. In mediating cell death, vasodilation, and salt excretion, AT2 seems to oppose AT1 action, but its downstream signaling pathways have yet to be identified, and its role in fetal nephrogenesis has not been delineated. In preliminary studies using cultured rat metanephroi, isolated from confounding variables, we found that a) Ang II stimulated ureteric bud (UB) branching, b) AT1 blockade decreased UB branching, whereas c) AT2 antagonism increased UB branching. Normal nephrogenesis involves tightly controlled reciprocal interactions between the metanephric mesenchyme and the invading UB. Excessive UB branching results in abnormal and ectopic induction of mesenchyme, whereas insufficient UB branching causes renal hypoplasia. We hypothesize that AT2 activation inhibits UB branching, and we seek to identify changes in downstream gene expression associated with this process.Specific Aim 1: To further test the hypothesis that AT2 inhibits UB branching in cultured fetal rat kidneys. a. Using confocal microscopy and lectin staining we will examine UB branching under conditions that specifically activate or antagonize AT2.b. We will optimize culture conditions that maximally activate or suppress AT2 signaling

for subsequent subtraction cloning studies.Specific Aim 2: To identify which genes are differentially expressed following AT2 activation or suppression.a. Subtraction cloning will be performed between kidneys at 2 time points following AT2 activation or antagonismb. Hybridization analysis will be used to confirm differentially expressed clones.c. Differentially expressed cDNAs will be sequenced to identify candidate genes. NCBI BLAST searches and bioinformatics will be used to sort differentially expressed genes into structural and functional categories.d. Quantitative RT-PCR will confirm the magnitude of change of selected clones.e. The spatial expression of differentially expressed clones will be assessed using in situ hybridization.The ability of candidate genes identified by this screen to influence ureteric bud branching will be tested in future studies.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: BRAINSTEM NEURONS IN NEUROGENIC HYPERTENSION**

  Principal Investigator & Institution: Sved, Judith C.; Neurology; University of Pittsburgh at Pittsburgh 350 Thackeray Hall Pittsburgh, Pa 15260

  Timing: Fiscal Year 2004; Project Start 01-FEB-2004; Project End 31-JAN-2006

  Summary: (provided by applicant): The overall objective of this proposal is to evaluate a central neural mechanism involved in the long term regulation of cardiovascular function that may ultimately be involved in the pathogenesis of certain forms of hypertension. Selective disruption of central nervous system function can produce acute as well as chronic elevations in arterial blood pressure (AP) and influence cardiovascular reflexes. The rostra ventral lateral medulla (RVLM) is important for the maintenance of baseline AP and its reflexive regulation and is comprised of two neurochemically distinct neuronal cell populations, the C1 cell population that contains the enzyme phenylethanolamine-N-transferase (PNMT) and those cells that do not contain PNMT. Recently a technique has been developed to selectively destroy the C1 cell population in rats that has allowed the evaluation of the role of these neurons in cardiovascular regulation. The proposed studies will examine the effect of C1 RVLM lesions in two strains of genetically hypertensive rats (spontaneously hypertensive rats, SHR and Dahl salt-sensitive rats, DS) using radio telemetry to monitor AP and heart rate in freely moving rats prior to and during an extended time course following destruction of C1 neurons. Responses to stressful stimuli and anti-hypertensive drugs will also be tested. These experiments will test the hypothesis that C1-RVLM neurons are important for the maintenance of hypertension in these two models, extending acute studies in anesthetized rats suggesting that the RVLM is important in these forms of hypertension and further our understanding of how the central nervous system is involved in the pathogenesis of hypertension.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: CARDIAC SYMPATHETIC AFFERENT RELEX IN HEART FAILURE**

  Principal Investigator & Institution: Wang, Wei; University of Nebraska Medical Center Omaha, Ne 681987835

  Timing: Fiscal Year 2002

  Summary: Heart failure (HF) is characterized by an elevation in sympathetic tone. The mechanisms responsible for the sympatho-excitation of HF are not completely understood. Recent studies from this laboratory have shown that the cardiac "sympathetic afferent" reflex is enhanced in dogs with pacing-induced HF. The mechanisms by which this enhancement occurs are unclear. There is an enhancement in

afferent fiber sensitivity to bradykinin and capsaicin. Preliminary evidence from this laboratory suggests that an enhanced central gain of this reflex is, in addition, responsible for the augmentation of this reflex. Furthermore, we have shown that central angiotensin II (Ang II) is at least one mediator for this enhancement. A second mechanism which may explain the increased gain of he cardiac sympathetic afferent reflex in HF is a decrease in nitric oxide (NO) production in several central sites which regulate sympathetic outflow. We hypothesize that both an increase in central Ang II and a decrease in central NO contributes to the increase in the sensitivity of the cardiac sympathetic afferent reflex and to the tonic sympatho-excitatory state in dogs with HF. Therefore, the specific aims of this project are to: 1) determine if the central gain of the cardiac sympathetic afferent reflex in dogs with HF is related to increased levels of central Ang II or to changes in Ang II type1 receptor density or both, 2) determine if acute and chronic central administration of the Ang II receptor antagonist, **losartan** and L-158,809 and/or NO donors prevent or reduce the enhancement of the cardiac sympathetic afferent reflex in dogs with HF, 3) determine if bradykinin prostaglandins and NO are mediators of the enhanced sensitivity of cardiac sympathetic sensory endings in dogs with HF, and 4) determine if chronic thoracic sympathetic deafferentation alters the time course and/or magnitude of the sympatho-excitatory response during the development of pacing-induced HF. These studies integrate into the overall scope of this Program Project in that the regulation of sympathetic outflow in HF is likely to be mediated by a variety of peripheral inputs with important modulation from central substances. The cardiac sympathetic understanding of neuro-humoral regulation in this disease state should include this potentially potent reflex.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: COMPARATIVE EFFECTS OF RAMIPRIL & LOSARTAN ON FIBRINOLYSIS**

  Principal Investigator & Institution: Vaughan, Douglas E.; Chief, Division of Cardiovascular Medici; Vanderbilt University 3319 West End Ave. Nashville, Tn 372036917

  Timing: Fiscal Year 2002; Project Start 01-DEC-2001; Project End 30-NOV-2002

  Summary: This abstract is not available.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: CONCOMITANT CYP3A4 & CYP2C9 INHIBITION ON LOSARTAN PHARMACOKINETICS**

  Principal Investigator & Institution: Parnell, Kimberly J.; University of North Carolina Chapel Hill Aob 104 Airport Drive Cb#1350 Chapel Hill, Nc 27599

  Timing: Fiscal Year 2002

  Summary: This abstract is not available.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: CORTICAL OSTEOPONTIN EXPRESSION IN HYDRONEPHROSIS**

  Principal Investigator & Institution: Scaduto, Russell C.; Medicine; Pennsylvania State Univ Hershey Med Ctr 500 University Dr Hershey, Pa 17033

  Timing: Fiscal Year 2002; Project Start 01-FEB-1999; Project End 31-DEC-2003

  Summary: (Adapted from Investigator's Abstract): This application studies the mechanisms accounting for inflammation and fibrosis in the model of tubulointerstitial

disease following obstruction of the urinary tract. The principal investigator hypothesizes that within hours of ureteral obstruction there is increased expression of the renin angiotensin system within the renal cortical proximal tubules. The increased epithelial production of angiotensin II stimulates the angiotensin II type I receptor and this increases the proximal tubule production of osteopontin. This is a potent chemoattractant for macrophages and this leads to the infiltration of macrophages and such macrophage-dependent mechanisms of inflammation and injury as is dependent on TGFbeta1. There are three specific aims: The first specific aim will investigate the critical role of increased osteopontin expression after urinary tract obstruction via its capacity to attract macrophages to increase cortical TGFbeta1 expression. This specific aim will utilize an osteopontin knockout mouse in which the effects of obstruction in this knockout model will be examined from the standpoint of evolution of interstitial disease assessed histologically, and by immunohistochemistry and by in situ hybridization. These studies would be complemented by in vitro studies in which primary cultures of proximal tubular suspensions from osteopontin knockout and wild-type mice will be studied for their ability to induce attraction of macrophages. The second specific aim is to determine proximal tubular angiotensinogen, angiotensin-converting enzyme, and angiotensin II type 1 receptor mRNA and protein, and ACE activity during the initial as well as during the sequential time points for up to 168 hours post-ligation. The third specific aim will mechanistically determine the roles for ACE and angiotensin II type 1 receptor activation in the expression and macrophage attraction, effects of osteopontin using an in vivo rat model of experimental hydronephrosis, and an osteopontin knockout mouse model. In these studies the renin angiotensin system will be manipulated with the use of an ACE inhibitor, enalapril, and an AT-1 blocker, **losartan.**

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: DETERMINANTS OF MAXIMAL O2 TRANSPORT**

  Principal Investigator & Institution: Wagner, Peter D.; Professor of Medicine & Bioengineering; University of California San Diego 9500 Gilman Dr, Dept. 0934 La Jolla, Ca 920930934

  Timing: Fiscal Year 2002

  Summary: Chronic diseases (COPD, heart failure, renal failure) are marked by reduced exercise capacity. There is increasing evidence that skeletal muscle structure and function may be intrinsically abnormal in such conditions. The present proposal continues work from the current cycle to better understand the mechanisms of exercise limitation in both health and disease, in particular the role of skeletal muscle. Physiological approaches already developed under the PPG involving muscle O2 transport analysis (large versus small muscle mass exercise, femoral blood flow, blood gas sampling, magnetic resonance spectroscopy to measure intracellular P02, morphology to assess diffusion distances and capillary surface area) will be combined with molecular-level studies focused on genes associated with muscle angiogenic responses to exercise, since the amount of capillary surface appears critical to O2 transport limitation. This integrated approach will be applied in both animal and human studies, the latter in both health and chronic disease (heart failure, chronic obstructive pulmonary disease). Animal work will use mechanistic interventions not possible in man to complement human experiments, and in both, the molecular approaches will be applied in intact physiological systems. Major goals include: 1) separating O2 transport-based exercise limitation from that due to intrinsic muscle abnormalities in chronic diseases; 2) determining if VEGF is essential to angiogenesis using Cre/loxP targeted