BIOGRAPHICAL SKETCH

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NAME: Cassis, Lisa A.

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POSITION TITLE: Professor, Department of Pharmacology and Nutritional Sciences, VPR

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
West Virginia University, Morgantown, WV	BS	05/1980	Pharmacy
West Virginia University, Morgantown, WV	Ph.D.	05/1984	Pharmacology
Univ. of Wurzburg, Wurzburg, W. Germany	Post-doc	05/1985	Pharmacology
Univ. Of Virginia, Charlottesville, VA	Post-doc	03/1988	Pharmacology

A. Personal Statement

I have broad training in cardiovascular pharmacology, from my training as a pharmacist through to serving as Chair of the Department of Pharmacology. Beginning in 1985, while a postdoctoral fellow at the University of Virginia, I began studies focused on the renin-angiotensin system (RAS), with an emphasis on AGT, the primary focal point of this project, that have continued through the course of my academic research career. I have continued studies on the RAS in cardiovascular and metabolic diseases, continuously funded by the NIH, for the last 26 years as independent investigator. As described below, I was one of the first to describe a large level of expression of AGT in adipocytes. In collaboration with Dr. Daugherty over the last 20 years, we have examined components of the RAS in vascular diseases, including atherosclerosis and abdominal aortic aneurysms (AAAs). This includes studies focused on AGT, where we were the first to demonstrate the significance of adipocyte-derived AGT to the systemic RAS in normal physiology, and in obesity-hypertension. Dr. Daugherty and I have also pioneered studies demonstrating a primary role for AngII in the development of atherosclerotic lesions, and as the original creators of the AngII models of aortic arch and abdominal aortic aneurysms. The following list of publications, representative of >139 peer reviewed articles, reflect primary findings from the Cassis laboratory.

1. **Cassis LA**, Saye J, Peach MJ. Location and regulation of rat angiotensinogen messenger RNA. *Hypertension* 11:591-6, 1988.
2. Daugherty, A., Manning, M.W., & **Cassis, L.A**. (2000). Angiotensin II promotes rapid development of atherosclerotic lesions and aneurysm formation in apolipoprotein E-/-mice. *Journal of Clinical Investigation* 105(11), 1605-1612. PMCID: PMC300860
3. Daugherty A, Rateri DL, Lu H, Inagami T, **Cassis LA**. Hypercholesterolemia stimulates angiotensin peptide synthesis and contributes to atherosclerosis through the AT1A receptor. *Circulation* 110:3849-57, 2004.
4. Yiannikouris F, Gupte M, Putnam K, Thatcher S, Charnigo R, Rateri DL, Daugherty A, **Cassis LA**. Adipocyte deficiency of angiotensinogen prevents obesity-induced hypertension in male mice. *Hypertension 60:1524-30,* 2012. PMCID: PMC3517298.

B. Positions and Honors

Positions and Employment

1980-1984 Pharmacist (part-time), Monongahela Hospital, Morgantown, WV

1984-1985	Alexander von Humboldt Postdoctoral Fellow; Department of Pharmacology, University of Wurzburg, Wurzburg, Germany
1985-1988	Postdoctoral Fellow; Dept. of Pharmacology, University of Virginia, Charlottesville, VA
1988-1994	Assistant Professor; College of Pharmacy, University of Kentucky, Lexington, KY
1994-2000	Associate Professor; College of Pharmacy, University of Kentucky, Lexington, KY
2000	Professor; College of Pharmacy, University of Kentucky, Lexington, KY
2003	Director and Chair, Graduate Center for Nutritional Sciences, University of Kentucky, Lexington, KY
2012 - 2014	Chair, Department of Pharmacology and Nutritional Sciences
2014	Interim Vice President for Research
2015	Vice President for Research

Professional Memberships and Honors

1986	National Research Service Award Postdoctoral Fellowship
1991	IBM Supercomputer Competition, First Place, Near IR Imaging of Atherosclerosis Lesions of Living Arteries, Lisa Cassis and Robert Lodder
1992	Research Career Development Award, NIHLBI
1996-2003	National American Heart Association Grant Reviewer, Co-Chair
1997-2001	Pharmacology Study Section Member, NIH
2010-2012	Associate Editor, Gender Medicine
2010	Leadership Council, Council of High Blood Pressure Research, American Heart Association
2010-2012	College of CRS Reviewers, NIH
2011-2016	Standing member, Vascular Cell and Molecular Biology Study Section, NIH
2012	Women's Mentor of the Year, Council on Arteriosclerosis, Thrombosis, and Vascular Biology, American Heart Association
2012	Mentor of the year, Center for Clinical and Translational Sciences, University of Kentucky
2012	Council for High Blood Pressure Research Harriett Dustan Award for Excellence in Hypertension Research, American Heart Association
2014	Fred and Marcielle de Beer Barnstable Brown Diabetes and Obesity Award

C. **Contribution to Science**

1. In 1985, while a postdoctoral fellow at the University of Virginia working with Dr. Michael Peach, a leader in the RAS, I initiated a project focused on defining the role of locally synthesized AngII in blood vessels on the regulation of peripheral vascular tone. Little did I know that this would set the stage for my independent research program over the next 26 years. My approach at the time focused on AGT, the only known component of the RAS that had been sequenced, and the required precursor for synthesis of AngII. In examining rat aorta as a model blood vessel for components of the RAS, I detected AGT mRNA expression, but could not find expression of the AGT gene in cultured vascular endothelial or smooth muscle cells. This confused me. One day, as I contemplated the aorta while cleaning it of residual material, I decided to explore the material that I was carefully cleaning from the vessel for the expression of AGT. To my surprise, this material, which I soon discovered was brown fat, had a high level of AGT expression. I quickly examined all other sources of white and brown adipose tissue in rats, and demonstrated that each adipose depot expressed abundant AGT. We then confirmed this finding in human adipocytes. To put this finding into perspective, our first publication in this area was in 1988. At that time, adipocytes were thought to do nothing more than store and release lipid, and obesity was at a low prevalence in the US. Our finding of AGT expression in adipocytes, one of the first of now over 50 adipokines, raised considerable skepticism in both the adipocyte world and certainly the cardiovascular world of the RAS. Recently, we demonstrated that in mice, adipocytes contribute 25% to the circulating AGT pool. Notably, we then demonstrated that deficiency of AGT in adipocytes totally prevented obesity-induced elevations in plasma AngII concentrations and the development of obesity-induced hypertension.

a. **Cassis LA**, Saye J, Peach MJ. Location and regulation of rat angiotensinogen messenger RNA. *Hypertension* 11:591-6, 1988.
b. **Cassis LA**, Lynch KR, Peach MJ. Localization of angiotensinogen messenger RNA in rat aorta. *Circ Res* 62:1259-62, 1988.
c. Yiannikouris F, Karounos M, Charnigo R, English VL, Rateri DL, Daugherty A, **Cassis LA**. Adipocyte-specific deficiency of angiotensinogen decreases plasma angiotensinogen concentration and systolic blood pressure in mice. *Amer J Physiol* 302:R244-51, 2012. PMCID: PMC3349391.

d. Yiannikouris F, Gupte M, Putnam K, Thatcher S, Charnigo R, Rateri DL, Daugherty A, **Cassis LA**. Adipocyte deficiency of angiotensinogen prevents obesity-induced hypertension in male mice. *Hypertension 60:1524-30,* 2012. PMCID: PMC3517298.

2. In 1998, I began collaborations with Dr. Alan Daugherty, who had recently been recruited to UK. We initiated our collaboration to respond to an NIH RFA for grants studying inter-relationships between atherosclerosis and hypertension. Dr. Daugherty brought to the collaboration a strong understanding of atherosclerosis, and I contributed expertise on the RAS in the control of blood pressure. We initiated studies infusing AngII to hypercholesterolemic mouse models of atherosclerosis to define inter-relationships between hypertension and atherosclerosis. I will focus on scientific outcomes of these studies, but I point out that additional contributions to science included establishing the methodologies for chronically infusing AngII by osmotic minipump to mice, a commonly employed method for RAS and cardiovascular researchers. We found that AngII had a profound effect to augment the development of new atherosclerotic lesions, and that this effect was un-related to blood pressure regulating effects of the peptide. Rather, AngII promoted macrophage infiltration to developing lesions, the initial demonstration of pro-inflammatory effects of the RAS. Unexpectedly, we demonstrated that a 1 month infusion of AngII to male hypercholesterolemic mice resulted in the development of large aneurysms in the supra-renal region of mouse aorta. This mouse model has been used by other 50 laboratories to study mechanisms of AAA formation in the pursuit of developing effective therapeutic strategies for this insidious vascular disease.

a. Daugherty A, **Cassis L**. Chronic angiotensin II infusion promotes atherogenesis in low density lipoprotein receptor -/- mice. Ann NY Acad Sci 18:108-18, 1999.
b. Daugherty, A., Manning, M.W., & **Cassis, L.A**. (2000). Angiotensin II promotes rapid development of atherosclerotic lesions and aneurysm formation in apolipoprotein E-/-mice. *Journal of Clinical Investigation* 105(11), 1605-1612. PMCID: PMC300860
c. Daugherty A, Rateri DL, Lu H, Inagami T, **Cassis LA**. Hypercholesterolemia stimulates angiotensin peptide synthesis and contributes to atherosclerosis through the AT1A receptor. *Circulation* 110:3849-57, 2004.
d. **Cassis LA**, Rateri DL, Lu H, Daugherty A. Bone marrow transplantation reveals that recipient AT1a receptors are required to initiate angiotensin II-induced atherosclerosis and abdominal aortic aneurysms. *Arterioscler Thromb Vasc Biol* 27:380-6, 2006.

3. Male gender is the largest non-modifiable risk factor for AAAs. Similarly, the AngII model of AAA development exhibits profound sex differences, with males exhibiting 2-3 fold higher AAA incidences compared to females. The underlying mechanisms for sexual dimorphism of AAA are unclear. Therefore, we set out to define mechanisms for sex differences in AngII-induced AAAs. We first thought that estrogen would be protective against AAA formation in females, but were surprised to find that ovariectomy of female mice did not promote AngII-induced AAAs. Thus, we performed orchiectomy in male mice and demonstrated that removal of male sex organs reduced AAA incidence to the level of females. Interestingly, administration of testosterone to female mice converted them to a male phenotype in terms of AAA susceptibility. We focused on the target(s) of androgen to promote AngII-induced AAAs, and demonstrated interesting regional localization of the angiotensin type 1a receptor (AT1aR) in a manner consistent with AAA formation. Specifically, abdominal aortas express high AT1aR mRNA abundance (compared to thoracic) in male, but not in female mice, and this regional difference is dictated by testosterone. We used a very novel approach to study sexual dimorphism of the vasculature, in essence, we androgenized female mice during development and examined their adult AAA susceptibility. Fascinating results from these studies demonstrated that a single injection of testosterone to 1 day old female mice resulted in a high level of adult AAA susceptibility, similar to males. We are continuing this area of investigation focusing on the interplay between sex hormones and sex chromosomes in the regulation of vascular diseases.

a. Henriques TA, Huang J, D'Souza SS, Daugherty A, **Cassis LA**. Orchidectomy, but not ovariectomy, regulates angiotensin II-induced vascular diseases in apolipoprotein E deficient mice. *Endocrinology* 145:3866-72, 2004.
b. Henriques T, Zhang X, Yiannikouris FB, Daugherty A, **Cassis LA**. Androgen increases AT1a receptor expression in abdominal aortas to promote angiotensin II-induced AAAs in apolipoprotein E-deficient mice. *Arterioscler Thromb Vasc Biol* 28(7)1251-6, 2008. PMCID: PMC2757112.
c. Zhang X, Thatcher SE, Rateri DL, Bruemmer D, Charnigo R, Daugherty A, **Cassis LA**. Transient exposure of neonatal female mice to testosterone abrogates the sexual dimorphism of abdominal aortic aneurysms. *Circ Res* 110:e73-85, 2012. PMCID: PMC3518797.

d. Zhang X, Thatcher S, Wu C, Daugherty A, **Cassis LA**. Castration of male mice prevents the progression of established angiotensin II-induced abdominal aortic aneurysms. *J Vasc Surg* S0741-5214, 2014. PMCID: PMC4099302.

4. Investigators at our institution have developed an NIEHS Superfund Basic Science Research Program focused on polychlorinated biphenyls (PCBs). These environmental toxins were used in manufacturing as lubricants, and were banned in the 1970's because of health-related effects. In 2007, I joined this group of investigators to study the interplay between PCBs, adipose tissue, and type 2 diabetes (T2D). My interest was spurred by reports from Vietnam War veterans showing high levels of T2D. Exposures of veterans to dioxin, a prototype ligand of the aryl hydrocarbon receptor (AhR), were associated with increased prevalence of diabetes in this population. Coplanar PCBs are also ligands of the AhR. My interest was also spurred by the pharmacokinetics of these lipophilic toxins, as they concentrate up to 1000-fold in adipose tissue, but at the time, relatively little was known of their effects (if any) on adipocyte biology. We initiated studies examining effects of various congeners of PCBs on adipocyte differentiation, and on the expression of pro-inflammatory adipokines in 3T3-L1 adipocytes. Our results were the first to demonstrate that AhR ligand PCBs promote adipocyte differentiation and the expression of a variety of pro-inflammatory cytokines. We then turned *to in vivo* effects of these compounds, and demonstrated that AhR ligand PCBs promote insulin resistance in lean mice. Interestingly, as these compounds are released from adipose lipids during lipolysis and weight loss, we found that exposures of obese mice to PCBs blunted the beneficial effects of weight loss to improve glucose homeostasis. These results suggest that beneficial effects of weight loss may be blunted in the obese population harboring greater quantities of lipophilic PCBs. We recently demonstrated that adipocyte AhR mediate effects of PCBs to promote T2D in mice, and are currently exploring novel effects of adipocyte AhR deficiency on the development of obesity.

a. Arsenescu V, Arsenescu RI, King V, Swanson H, **Cassis LA**. Polychlorinated biphenyl-77 induces adipocyte differentiation and proinflammatory adipokines and promotes obesity and atherosclerosis. *Environ Health Perspect* 116:761-8, 2008. PMCID: PMC2430232.
b. Baker NA, Karounos M, English V, Fang J, Wei Y, Stromberg A, Sunkara M, Morris AJ, Swanson HI, **Cassis LA**. Coplanar polychlorinated biphenyls impair glucose homeostasis in lean C57BL/6 mice and mitigate beneficial effects of weight loss on glucose homeostasis in obese mice. *Environ Health Persp* 121:105-10, 2013. PMCID: PMC3553436.
c. Baker NA, English V, Larian N, Shoemaker R, Sunkara M, Morris AJ, Walker M, Yiannikouris F, **Cassis LA**. Deficiency of adipocyte aryl hydrocarbon receptor prevents polychlorinated biphenyl-induced disruptions in glucose homeostasis. *Environ Health Perspect*, in press, 2015.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/14s_g6CxOraQw/bibliography/40706282/public/?sort=date&direction=ascending.

D. **Research Support.**

Ongoing Research Support

R01 HL073085-09 Cassis (PI) 05/01/14 – 04/31/18
Angiotensin: A Link Between Obesity and Hypertension
The proposed studies will determine the role of adipose-derived angiotensin peptides in obesity-hypertension.
Role: PI

P42 ES007380-16 Hennig (PI) 04/01/14 – 03/31/19
The Impact of Obesity on PCB Toxicity
The proposed studies will define the role of polychlorinated biphenyls (PCBs) on angiotensin II-induced vascular diseases. This grant is in a no cost extension.
Role: Co-Investigator, PI – Project 4

8P20GM103527-05 Cassis (Program Director) 9/15/13 – 7/31/18
Center of Research in Obesity and Cardiovascular Disease
The proposed research will develop a center for the study of obesity and cardiovascular disease, and consists of 5 junior investigators and mentors.
Role: Program Director

R01 HL107326-01A1 Cassis (PI) 04/01/12 - 03/31/16

Sex differences in angiotensin II-induced vascular diseases

The proposed research will investigate the relative role of sex hormones versus sex chromosomes as mediators of increased aneurysm susceptibility in male mice.