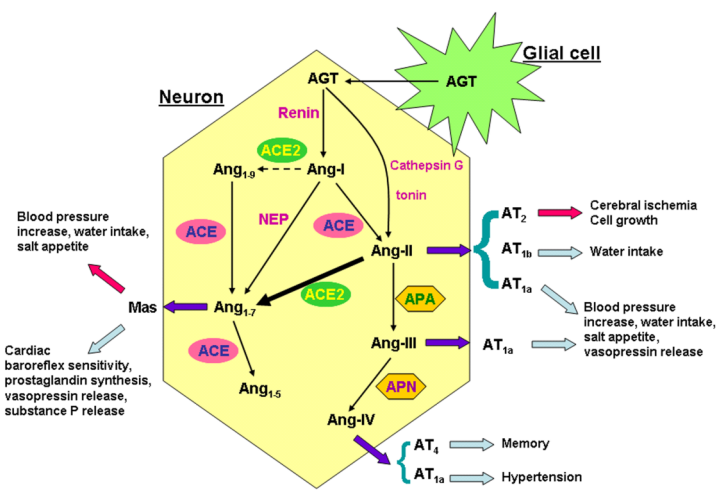
Lazartigues' Laboratory

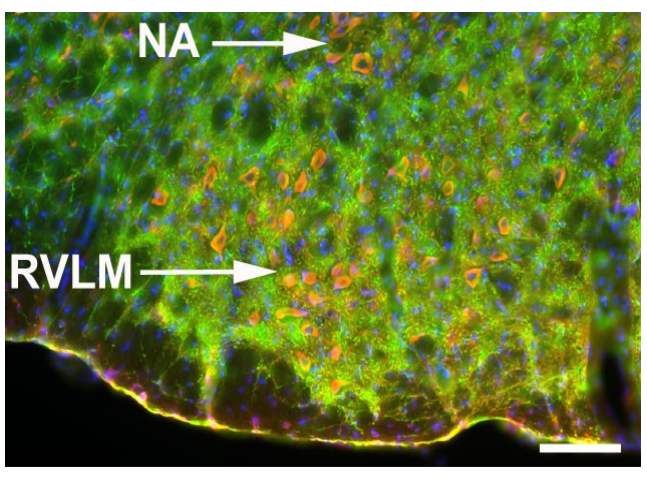
"From Gene to Function: Sculpting the Genome to Unravel the Role of the Renin-Angiotensin System in the Regulation of Cardiovascular Function".

ACE2 and the brain Renin-Angiotensin System

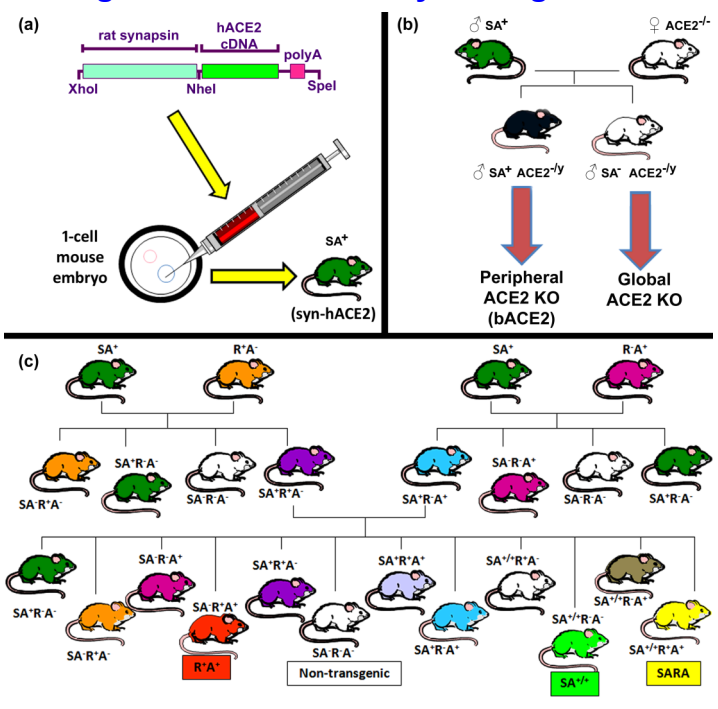


Schematic of the brain renin-angiotensin system (RAS) emphasizing the role of ACE2 in opposing the effects of Ang-II in cardiovascular function and volume homeostasis. According to this model, ACE2 in the brain is in a position to counterbalance the effects of Ang-II in the central regulation of cardiovascular function by decreasing the levels of this peptide and promoting the formation of the vasodilatory peptide Ang-(1-7).

We previously showed for the first time the presence of the ACE2 protein in the mouse brain in regions involved in the central regulation of cardiovascular function (Doobay et al.; Am. J. Physiol. Regul. Integr. Comp. Physiol. 2006). Immunohistochemistry staining showing ACE2 (red) expression on neurons (green) of the rostral ventrolateral medulla (RVLM) and nucleus ambiguus (NA), two brain regions involved in the control of sympathetic and parasympathetic tones, respectively.



Transgenic models to study the regulation of cardiovascular function



Our laboratory is using several transgenic mouse models with alterations of different components of the RAS. Some of these models exhibit neuron-targeted expression of AT1 receptors (NSE-AT1a mouse), ACE2 (Syn-hACE2) or multiple genes over-expression (R^+A^+ mouse); while others have been nullified for specific genes ($ACE2^{-/y}$ mice). In addition, combination of these different models with state-of-the-art injection (Sinnayah et al., Circ. Res. 2006) and recording techniques but also classic hypertension models (Lazartigues et al., Circ. Res. 2004; Zimmerman et al., Circ. Res. 2004) is an excellent tool to study the role of the brain RAS in the regulation of cardiovascular function.

We recently designed additional transgenic mouse models amenable to study the role of central ACE2 in the regulation of cardiovascular function (Xia and Lazartigues, J. Neurochem. 2008; Xia et al., Hypertension 2009; Feng et al., Circ. Res. 2010).

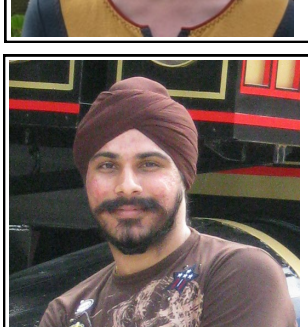
Selected Publications (2007-2010): (for a complete list click here)

- Differential expression of neuronal ACE2 in transgenic mice with overexpression of the brain renin-angiotensin system. Doobay MF, Talman LS, Obr TD, Tian X, Davisson RL, Lazartigues E. Am J Physiol Regul Integr Comp Physiol. 2007;292 (1):R373-81.
- The two fACEs of the tissue renin-angiotensin systems: implication in cardiovascular diseases. Lazartigues E, Feng Y, Lavoie JL. Curr Pharm Des. 2007;13(12):1231-45. Review.
- Angiotensin-converting enzyme 2 overexpression in the subfornical organ prevents the angiotensin II-mediated pressor and drinking responses and is associated with angiotensin II type 1 receptor downregulation. Feng Y, Yue X, Xia H, Bindom SM, Hickman PJ, Filipeanu CM, Wu G, Lazartigues E. Circ Res. 2008;102(6):729-36. Editorial in Circ Res. 2008 Mar 28;102 (6):628-9.
- The sweeter side of ACE2: physiological evidence for a role in diabetes. Bindom SM, Lazartigues E. Mol Cell Endocrinol. 2009;302(2):193-202. Review.
- Angiotensin-converting enzyme 2 in the brain: properties and future directions. Xia H, Lazartigues E. J Neurochem. 2008;107(6):1482-94. Review.
- The angiotensin converting enzyme 2/Ang-(1-7) axis in the heart: a role for MAS communication? Stewart JA Jr, Lazartigues E, Lucchesi PA. Circ Res. 2008;103(11):1197-9. Editorial.
- Angiotensin II type 1 receptor-mediated reduction of angiotensin-converting enzyme 2 activity in the brain impairs baroreflex function in hypertensive mice. Xia H, Feng Y, Obr TD, Hickman PJ, Lazartigues E. Hypertension. 2009;53(2):210-6. (Cover of the Issue).
- Editorial Focus: A role of the (pro) renin receptor in neuronal cell differentiation. Lazartigues E. Am J Physiol Regul Integr Comp Physiol. 297(2):R248-249. Editorial.
- ACE2: A new target for neurogenic hypertension. Feng Y., Xia H., Speth R.C., Santos R.A. & Lazartigues E. Exp Physiol. 2009 Nov 18. [Epub ahead of print]. PMID: 19923158
- Brain-selective over-expression of human Angiotensin Converting Enzyme 2 attenuates neurogenic hypertension. Feng Y., Xia H., Cai Y., Halabi C.M., Becker L.K., Santos R.A.S., Speth R.C., Sigmund C.D. & Lazartigues E. Circ. Res. 2009 Nov 19. [Epub ahead of print]. (Cover of the Issue).

Current Lab Members:

Huijing Xia, Ph.D. (Postdoctoral Fellow 2006-present)

Ping Xu, MD-Ph.D. (Postdoctoral Fellow 2009-present)



Kavaljit Chhabra, M. Pharm. (Graduate Student 2009-present)

Yanhui Cai, M.S. (Graduate Student 2009-present)

Former Lab Members:

- **Dr. Yumei Feng, MD-Ph.D. (2006-2010).** Currently Assistant Professor of Physiology at Tulane University.
- **Dr. Sharell M. Bindom, Ph.D. (2006-2009).** Currently enrolled in 3rd year of Medical School at LSUHSC.

News from the Lab:

- **Dr. Yumei Feng**' s work on ACE2 over-expression in the brain of syn-hACE2 transgenic mice is featured on the cover of the February 5th issue of Circulation Research. On the cover: The co-localization of the human ACE2 (Red) and mouse MAP2 (Green), a marker for neurons, in the syn-hACE2 transgenic mouse rostral ventrolateral medulla, detected by immunofluorescence, indicating that the human ACE2 transgene expression is specifically targeted to neurons. Magnification: 60X. **Dr. Feng** recently accepted a position of Assistant Professor in the Department of Physiology at Tulane University in New Orleans.
- **Dr. Huijing Xia** was recently awarded an American Autonomic Society Travel Fellowship Award to attend the 20th International Symposium on the Autonomic Nervous System held in St. Thomas, US Virgin Islands, November 11-14th 2009.
- **Dr. Sharell M Bindom** successfully defended her Ph.D. thesis project entitled "Role of ACE2 in glycemic homeostasis in diabetic mice". She graduated on May 16th, 2009 and returned to LSU Medical School to complete her degree.

Job Opportunities:

POSTDOCTORAL RESEARCHER
Louisiana State University Health Sciences Center

A postdoctoral research position in physiological genomics is available within the Department of Pharmacology and Experimental Therapeutics at Louisiana State University Health Sciences Center, New Orleans, LA. The position is available to investigate the molecular and physiological roles of components of the renin-angiotensin system in the regulation of cardiovascular function in vivo and in vitro. Our laboratory takes a multidisciplinary approach to investigate autonomic nervous function and to determine the cellular and molecular mechanisms of RAS components in normal and transgenic mice, and the resulting effects on blood pressure regulation. Among those approaches are: cardiovascular and neurophysiological techniques (mouse telemetry, baroreflex analysis, cardiovascular function assessment, central microinjections), real-time PCR, gene therapy tools including but not limited to siRNA and viral transfection, molecular and recombinant DNA methodology, immuno-histochemistry and biochemical methods (e.g. *Circ Res*, 2008, 102(6):729-736; *Hypertension* 2009, 53(2):210-216). Qualified applicants will be motivated individuals, capable to design hypothesis-driven experiments, with a strong background in molecular biology (cloning, gene mutation, promoter analysis, virus generation). Additional expertise in physiology and cardiovascular biology is a plus. The Louisiana State University Health Sciences Center (www.medschool.lsuhsc.edu) is a state-of-the-art facility with well-equipped imaging and molecular core facilities. A competitive salary is available to successful applicants. LSUHSC is an AA/EOE employer**.** Applicants should send their CV (e-mail preferably) and the names of three references to **Dr. Eric Lazartigues (elazar@lsuhsc.edu), Assistant Professor of Pharmacology and Experimental Therapeutics, Louisiana State University Health Sciences Center.**

STUDENT WORKER
Louisiana State University Health Sciences Center

A student worker position is available in the laboratory of Dr. Eric Lazartigues, within the Department of Pharmacology and Experimental Therapeutics at Louisiana State University Health Sciences Center, New Orleans, LA. Qualified applicants will be motivated individuals, in charge of maintaining the lab supplies and performing basic tasks including but not limited to preparing multi-purpose buffers and solutions, record keeping, orderings. Knowledge of Microsoft Access is a plus. LSUHSC is an AA/EOE employer**.** Applicants should verify their eligibility by visiting the folowing address (http://www.lsuhsc.edu/no/administration/hrm/jobs/policies.aspx) and send their CV (e-mail preferably) to **Dr. Eric Lazartigues (elazar@lsuhsc.edu), Assistant Professor of Pharmacology and Experimental Therapeutics, Louisiana State University Health Sciences Center.**