

## BIOGRAPHICAL SKETCH 12,2011

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NAME James E. Faber	POSITION TITLE Professor		
eRA COMMONS USER NAME (credential, e.g., agency login) James_faber			
EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)			
INSTITUTION AND LOCATION	DEGREE (if applicable)	MM/YY	FIELD OF STUDY
University of Missouri-Columbia	BS	5/74	Biology
University of Missouri-Columbia	PhD	5/80	Physiology
University of Iowa Cardiovascular Center	Postdoc	10/82	Pharmacology

**A. Personal Statement.** My laboratory focuses on the collateral circulation (“endogenous bypass vessels”)—how these unique vessels form and persist in tissues and how to assess and augment their abundance and remodeling (lumen enlargement) in mice and ultimately in patients with or at risk for stroke, myocardial infarction, coronary artery and peripheral vascular diseases. Until our work [refs 1-8], nothing was known about when or how these unique anastomosing vessels form or the molecular mechanisms involved. Our studies show that collaterals form during a narrow window late in gestation by novel angiogenic-like mechanisms. We have also: 1) introduced several new methods, eg, modifications to laser Doppler perfusion imaging, boosting resolution by >30-fold [1]; 2) introduced a new model tissue for studying collateral vessels (mouse pial cerebral collateral circulation) that affords the highest resolution available [1-10]; 3) discovered that the extent (ie, density and diameter) of pre-existing collaterals in healthy inbred mouse strains varies dramatically from natural genetic polymorphisms, and that this variation has a major impact on tissue injury and recovery in models of the above occlusive diseases [1,4,6-8]; 4) identified 5 genes (*Vegfa*, *Clic4*, *Flik1*, *Adam10*, *Adam17*) whose expression impacts formation of the collateral circulation (2,3,13); 5) are using association mapping and other genetic approaches to identify candidate genes responsible for genetic variation in extent of the collateral circulation (8). Besides genetic factors, we are also finding that environmental factors, eg, cardiovascular risk factors and disease, reduce the extent of the native collateral circulation and impair collateral remodeling in ischemic disease, and are pursuing the molecular mechanisms. For example, we have found that eNOS-derived nitric oxide is required for maintenance of collateral density during natural growth to adulthood (5). Other work has found that collateral rarefaction occurs with aging in association with impaired NO signaling, resulting in much worse ischemic injury in brain and hindlimb after arterial obstruction (10,14,15). We are also studying new potential therapies to induce collateral formation, prevent collateral loss, and augment collateral remodeling in brain, heart and lower extremities. We also study collateral vascular biology with others at UNC and elsewhere, eg, multi-potential hematopoietic cells in recovery from acute MI (9) and LAR--IGF-1 signaling (Lee, Runge et al). We secondarily study angiogenesis (eg,11,12). We have begun translational studies at UNC and Univ of Calgary of the collateral circulation in acute stroke patients (“on-going collaborations”, below).

### **B. Positions, Employment and Other Background of the Investigator**

1983, Assistant Professor, 1989, Associate Professor, 1994, Professor, Department of Cell and Molecular Physiology, Univ N Carolina at Chapel Hill. Executive Committee, McAllister Heart Inst. Member, NIH training grants: Cellular and Molecular Biology; MD-PhD; Short-term Minority Student; Postdoctoral Clinical Fellows.

### **Selected Honors and Awards**

NIH-Research Career Development Award, 1989-94  
Hyman Battle Distinguished Excellence in Medical Teaching Award, 1996, 1997, 2000, 2002  
Medical School Best First-Year Course Award (course director) 1997, 2000  
North Carolina Governor’s Teaching Excellence Award, 1999  
Kaiser-Permanente Excellence Professor, 1999, 2000, 2001  
Ranked within top 0.3%, NIH R01 HL-062584-05 grant application, 2003  
UNC Distinguished Teaching Award for Post-Baccalaureate Education, 2004  
Faculty of the Year Award, UNC Student National Medical Association, 2004

## **Invited Symposia, Conference Presentations, Keynote Presentations and Editorial Series (last 5 years)**

47<sup>th</sup> Japan Angiol Conf (plenary lctr) "Collateral development in normal tissues and in ischemia" Kobe 2006  
Exp Biol "Genetic reg of col formation, capacity for remodeling, and VEGF" (speaker) Wash DC 2007  
North American Vascular Biology Organization's annual *Vasculata Workshop* "Genetic mechanisms in arteriogenesis and vascular adaptations to ischemia" (conf co-organizer, session chair, lecture) 2007  
13<sup>th</sup> Cardiovasc Revasc Therapies (CRT) "The influence of genetics on col devel" (speaker) Wash DC 2008  
AHA Arteriosclerosis, Thrombosis and Vascular Biology Meeting (session co-moderator) Atlanta 2008  
Exp Biol "Genetics of collateral formation and growth in ischemia" (co-organizer, speaker) San Diego 2008  
AHA Annual Mtg, "Collateral function in the mouse brain & periphery" (organizer, speaker) New Orleans 2008  
AHA Annual Mtg, "Angiogenesis I" (oral session co-moderator) New Orleans 2008  
14<sup>th</sup> CRT Angiomyogenesis Conference (conf co-organizer, speaker), Washington DC 2009  
NAVBO, "Genetics and Genomics of Vascular Disease", Hyannis, Cape Cod, (prog committee, speaker) 2009  
AHA Annual Mtg, "Collateral Circ: Basic Sci & Clin Perspec" (organizer, moderator, speaker) Orlando 2009  
Keystone Conf - Angiogen in Health & Dis, "Devel & Genetics of Col Formation & Remodeling" (speaker) 2010  
Exp Biol, "Formation and remodeling of the collateral vasc" (Co-moderator, speaker) Anaheim 2010  
Eur Soc of Cardiol Congress, "Genetic & environ mech's of col circ insufficiency" (speaker) Stockholm 2010  
AHA Annual Mtg, "Angiogenesis and Arteriogenesis" (oral session organizer, co-moderator) 2010  
4<sup>th</sup> International Meeting on Angiogenesis, "Genetic and environmental mechanisms of collateral formation and progression to insufficiency" (speaker), Amsterdam, 2011  
AHA Annual, "How Can We Grow Coronary Collaterals—Mechanisms & Biomarkers" (organizer, modr), 2011  
12<sup>th</sup> International Collateral Circulation Symposium, Sils-Marie, Switzerland (speaker, moderator), 2012  
University of Missouri annual Cardiovascular Day (keynote lecture), 2012  
NAVBO, "Genetics and Genomics of Vascular Disease", Asilomar, (speaker) 2012

## **Study Section, Editorial, and Advisory Service**

NIH-NHLBI, Program Project Site Visit Team 1985  
NIH-NHLBI, Experimental Cardiovascular Sciences 1989, 1990, 1991 (ad hoc)  
NIH-NHLBI, Experimental Cardiovascular Sciences 1993-96 (regular member)  
NIH-NHLBI, Cardiovascular Biology 2001 (ad hoc)  
NIH-NHLBI, Vascular Cell and Molecular Biology 2004 (ad hoc)  
NIH-NHLBI, SEP ZRG1 CVS-F Vascular Pathobiology 2009

Associate Editor: *American Journal of Physiology-Heart and Circulatory Physiology*, 1993-1999  
Editorial Boards: *American Journal of Physiology-Heart and Circulatory Physiology*, 1991-1993  
*Journal of Vascular Research*, 1991-1999  
*Journal of Pharmacology and Experimental Therapeutics*, 1999, 2000  
*Circulation Research*, 2009-present  
*Angiogenesis*, 2011-present

Am Heart Assoc: Abstract reviewer for fall meeting, 2002-present; ATVB Program Committee 2010 - present  
Am Microcirc Soc Comm's: Awards 87-89; Executive 90-93,98; Program 93-95; Liaison 95-98; Council 98-01  
American Physiological Society Committees: CV Section Nominating 92-96; CV Section Steering 93-96;  
Daggs Award Committee 99-2001 (Chair 2001); CV Section Awards Committee 00-2005  
Member, Scientific Advisory Board of the European Comprehensive Ctr for Vascular Medicine, 2010 - present

## **C. Selected Peer-reviewed Journal Publications (limit 15)**

### **Most relevant to the current application**

1. Chalothorn D, Clayton JA, Zhang H, Pomp D, Faber JE (2007) Collateral density, remodeling and VEGF-A expression differ widely between mouse strains. **Physiol Genomics** 30:179-191.  
<http://physiolgenomics.physiology.org/content/30/2/179.full.pdf+html>

#### **Journal cover article.**

2. Clayton JA, Chalothorn D, Faber JE (2008) Vascular endothelial growth factor-A specifies formation of native collaterals and regulates collateral growth in ischemia. **Circ Res** 103(9):1027-36.  
<http://circres.ahajournals.org/cgi/content/full/103/9/1027>

**Featured in editorial:** Chilian WM “Vascular endothelial growth factor and the collateral circulation—the story continues”. <http://circres.ahajournals.org/cgi/content/full/103/9/905>

3. Chalothorn D, Zhang H, Smith JE, Edwards JE, Faber JE (2009) Chloride intracellular channel-4 is a determinant of native collateral formation in skeletal muscle and brain. **Circ Res** 105:89-98. <http://circres.ahajournals.org/cgi/content/full/105/1/89>

**Journal cover article, “featured article”, and featured in editorial:** Waltenberger J “Limits to growth of native collateral vessels. Just one mouse CLIC away from unlimited collateral perfusion?” p9-11 <http://circres.ahajournals.org/cgi/content/full/105/1/9>

4. Zhang H, Prabhakar P, Sealock RW, Faber JE (2010) Wide genetic variation in the native pial collateral circulation is a major determinant of variation in severity of stroke. **J Cere Blood Flow Metab** 30:923-934. <http://www.nature.com/jcbfm/journal/v30/n5/full/jcbfm201010a.html>
5. Dai X, Faber JE. (2010) eNOS deficiency causes collateral vessel rarefaction and impairs active-tion of a cell cycle gene network during arteriogenesis. **Circ Res** 106:1870-81. <http://circres.ahajournals.org/cgi/content/full/106/12/1870>

**Journal Cover Article and “featured article”.**

6. Chalothorn D, Faber JE (2010) Formation and maturation of the murine native cerebral collateral circulation. **J Molec Cell Cardiol** 49:251-259. <http://www.ncbi.nlm.nih.gov/pubmed/20346953>
7. Chalothorn D, Faber JE (2010) Strain-dependent variation in native collateral function in mouse hindlimb. **Physiol Genomics** 42:469-79. <http://physiolgenomics.physiology.org/content/42/3/469.long>
8. Wang S, Zhang H, Dai X, Sealock R, Faber JE (2010) Genetic architecture underlying variation in extent and remodeling of the collateral circulation. **Circ Res** 107:558-568. <http://circres.ahajournals.org/cgi/reprint/107/4/558>

**Selected for Faculty of 1000 Biology – rated “10 - Exceptional”.**

<http://f1000biology.com/article/id/3765959/evaluation>. Editorial by Stephen Schwartz: “This may well be the seminal paper in one of the most important mysteries in vascular biology: the mechanisms controlling collateral formation in the arterial tree.”

9. Aitsebaomo J, Srivastava S, Zhang H, Jha S, Veleva AN, Pi X, Lockyer P, Winnick S, Faber JE<sup>\*</sup>, Patterson C<sup>\*</sup> (2011) Recombinant human interleukin-11 mobilizes CD34+/VEGFR2+ mononuclear cells and enhances collateral vessel growth after femoral artery ligation. **Arterioscler Thromb Vasc Biol** 31:306-12 <sup>\*</sup>Co-senior authors. <http://atvb.ahajournals.org/cgi/reprint/ATVBAHA.110.216986v2>
10. Faber JE, Zhang H, Prabhakar, RM Lassance-Soares, Burnett MS, Epstein SE (2011) Aging causes collateral rarefaction and increased severity of ischemic injury in multiple tissues. **Arterioscler Thromb Vasc Biol** 31:1748-56. <http://atvb.ahajournals.org/content/31/8/1748.full.pdf+html>

**Some additional publications for current grant period of importance to the field**

11. Zayed MA, Yuan W, Chalothorn D, Leisner T, McFadden A, Faber JE, Parise LV (2007) CIB1 regulates endothelial cell function and ischemia-induced angiogenesis **Circ Res** 101:1185-1193. <http://circres.ahajournals.org/cgi/content/full/101/11/1185>
12. Zayed MA, Yuan W, Chalothorn D, Faber JE, Parise LE (2010) Tumor growth and angiogenesis Is impaired in CIB1 knockout mice. **J Angiogenesis Res.** 2:17-27. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2941741/?tool=pubmed>
13. Faber JE, Dai X, Lucitti J (2011) Genetic and environmental mechanisms controlling formation and maintenance of the native collateral circulation. *In: **Arteriogenesis – Molecular Regulation, Pathophysiology and Therapeutics I.*** E Deindl, W Schaper (eds), Shaker Verlag, Ch 1, pp 1-22.
14. Peng X, Wang J, Lassance-Soares RM, Najafi AH, Sood S, Aghili N, Alderman LO, Panza JA, Faber JE, Wang S, Epstein SE, Burnett MS. (2011) Gender differences affect blood flow recovery in a mouse model of hindlimb ischemia. **Am J Physiol Heart Circ.** 300:H2027-34. <http://ajpheart.physiology.org/content/300/6/H2027.long>

15. Wang J, Peng X, Lassance-Soares RM, Najafi AH, Alderman LO, Sood S, Zhuang Z, Simons M, Xue Z, Chan R, Faber JE, Epstein SE, Burnett MS. (2011) Aging-induced collateral dropout: role of dysfunctional eNOS signaling and increased susceptibility of endothelial and smooth muscle cells to apoptosis. **J Cardiovasc Transl Res** May 3. [Epub ahead of print] <http://www.ncbi.nlm.nih.gov/pubmed/21538183>

#### **D. Research Support. Ongoing research support**

R01 HL090655-03, JE Faber PI, 9/2008-8/2012. "Mechanisms of Collateral Formation and Collateral Growth in Ischemia". Project investigates how collaterals form in normal tissues, the role of VEGF and other genes in this process and in collateral remodeling in adult ischemic disease, and the genetic basis for variation in collateral density and remodeling among healthy individuals.

R01 HL062584-12, JE Faber PI, 7/1/99-6/31/12. " $\alpha$ -Adrenoceptors in Vascular Wall Growth and Remodeling". Project investigates: 1) the role of catecholamines in several in vivo adaptive and pathological models of arterial remodeling (flow-mediated carotid remodeling, pulmonary hypertension, collateral artery growth), 2) how the disposition of vascular wall norepinephrine is altered by injury and adaptive remodeling, 3) the trophic adrenergic intracellular signaling pathways.

R01 HL096597-01, JE Faber PI- SUBCONTRACT, 5% effort, 2/1/11-12-31-16 (DL Ramirez-Bergeron, PI, Case Western Univ) "The role of ARNT in endothelial cells." Subcontract provides expertise to investigate the role of ARNT in native collateral formation and in collateral remodeling and angiogenesis in ischemia.

#### **Completed research support (last 3 years)**

R01 HL088632, E Tzima PI (JE Faber co-investigator), 12/1/07 – 12/31/08. Endothelial Cell Junctions in Mechanotransduction. Project examines signaling mechanisms of endothelial cell transduction of shear stress in cell culture and the role of PECAM-1 in in vivo flow-mediated arterial remodeling.

P01-AG024282, D Clemmons, C Patterson, M Runge, PIs (JE Faber Histology Core Leader, 7/1/04-6/30/09. Mechanisms of vascular wall aging and disease. Project investigates ubiquitination, hsp's, ROS and IGF-1 mechanisms in vascular wall aging.

K99 HL093609-01, JE Faber PI, 4/1/09-3/31/10. Pathway to Independence Award (D Chalothorn PhD; JE Faber, mentor). "Genetic Determinants of Collateral Wall Specialization and Ischemic Remodeling".

T32 HL083828-2, JE Faber mentor, 7/1/08-6/30-10. Clinician-Scientist Training Program in Cardiovascular Medicine (Xuming Dai MD PhD, fellow; R Stouffer, PI). "Role of eNOS/NO Signaling in Collateral Formation and Remodeling in Ischemia.