BIOGRAPHICAL SKETCH

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NAME	POSITION TITLE
James E. Faber	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—how these unique vessels form and persist in healthy tissues, and how to assess and augment their abundance and remodeling (lumen enlargement/arteriogenesis) in models of stroke, coronary and peripheral artery disease. We do this work in mice with and without chronic cardiovascular risk factor presence, with the ultimate goal of applying our findings to human disease. A major goal of our previous work (summarized below) and studies in this proposal is to provide a genetic test to predict individual genetic variation in leptomeningeal (pial) collateral abundance to combine with image-based assessment and thus improved estimation of collateral status. This will provide a means to: 1) predict risk-severity before stroke occurs and thus aid adoption of life-style choices and treatments to prevent stroke, 2) stratify acute stroke patients for native collateral abundance to aid in clinical decision-making, 3) predict risk for and severity of hemorrhagic transformation, 4) extend the window for thrombolytic and endovascular procedures in patients with "good" collateral status, 5) stratify patients for collateral status to reduce variability in association studies and trials of new therapies. A second major goal is to define the signaling pathway that controls formation of native pial collaterals (our studies shows this occurs during embryogenesis) in order to develop rational targets to study for stimulation of new collateral formation in acute stroke; our results in mice show that new collaterals form rapidly in less than 18 hours after acute stroke[3] and myocardial infarction.[Zhang, Faber ATVB abstract, 2012] A third goal is to determine if chronic cardiovascular risk factor presence causes rarefaction of pial and other collaterals, the molecular mechanism, and how to prevent it.

Until our work,[1-8] nothing was known about when or how collaterals form or the mechanisms involved. Our studies show that pial collaterals form late in gestation by a novel "sprouting arteriolegenesis" mechanism.[5,10,12] We have also: (1) made modifications, together with Moore Inc, to laser Doppler perfusion imaging that have boosted resolution by ~30-fold;[1] (2) introduced a model tissue for studying collateral vessels in mouse that affords the highest resolution and access available (cerebral pial circulation);[1-13] (3) Discovered that the extent (ie, density and diameter) of native (pre-existing) collaterals in healthy inbred mouse strains varies dramatically from naturally occurring genetic polymorphisms, and that this variation has a major impact on tissue injury and recovery in models of stroke and peripheral artery disease;[3,5-7,9] (4) Used gene targeting to identify 5 genes (*Vegfa, Clic4, Flk1, Adam10, Adam17*) whose expression impacts formation of the collateral circulation;[1,2,12] (5) Used QTL and haplotype mapping and other genetic approaches to identify 4 loci responsible for almost all of this heritable variation in collateral extent in mice; and we have identified several candidate genes.[3,7,9] Besides genetic factors, we are also finding that "environmental" factors, eg, cardiovascular risk factors, cause rarefaction of the native collateral circulation and impair collateral remodeling in ischemic disease, and are pursuing mechanisms and ways to prevent it. For example, we have found that eNOS-derived nitric oxide is required for maintenance of collateral density during natural growth to adulthood.[4] Other work has found that collateral rarefaction occurs with aging in association with impaired eNOS signaling, resulting in more severe ischemic injury in brain and hindlimb after arterial obstruction.[8,13] We are also studying new potential therapies to induce collateral formation, prevent collateral loss, and augment collateral remodeling in brain, heart and lower extremities of adults. In addition, we study collateral vascular biology with others at UNC and elsewhere, eg, multi-potential hematopoietic cells in recovery from acute MI,[11] and have begun translational studies of the collateral circulation in acute stroke patients at UNC and Univ of Calgary ("On-going Collaborations", below).

Key Collaborators: **See page 4 last paragraph.**

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)

Exp Biol "Genetic reg of col formation, capacity for remodeling, and VEGF" (leadoff speaker) 2007
NAVBO *Vasculata* "Genetic mech^{s} of arteriogenesis and vascular adap to ischemia" (conf co-org, lecture) 2007
13th Cardiovasc Revasc Therapies (CRT) "The influence of genetics on col develop" (speaker) Wash DC 2008
Exp Biol "Genetics of collateral formation and growth in ischemia" (co-organizer, leadoff speaker) 2008
AHA Annual Mtg, "Collateral function in the mouse brain & periphery" (organizer, leadoff speaker) 2008
14th CRT Angiomyogenesis Conference (conference 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) 2009
Keystone Conf - Angiogen in Health & Dis, "Devel & Genetics of Col Formation & Remodeling" (speaker) 2010
Exp Biol, "Formation and remodeling of the collateral circulation" (Co-moderator, leadoff speaker) 2010
Eur Soc of Cardiol Congress, "Genetic & environ mech's of col circ insufficiency" (leadoff spkr) Stockholm 2010
4th Intl Mtg Angiogen, "Genetic & environ mech^{s} of Col form & progression to insufficiency" (spkr), Amst^{m} 2011
AHA Annual, "How Can We Grow Coronary Collaterals—Mechanisms & Biomarkers" (organizer, modr) 2011
7th International Collateral Circulation Symposium (speaker, moderator) Sils-Marie, Switzerland 2012
University of Missouri annual Cardiovascular Day (keynote speaker) 2012
2nd NAVBO Genetics and Genomics of Vascular Disease Conference, (speaker, moderator) Asilomar, 2012
Invited Ed Series, *Circ Res*, "The COL circ: New developments in genetics, vasc biol and treatments", 2013
Eur Soc Cardiol Congress, "Formation of the collateral circ in brain and heart" (speaker) Munich 2012
1st conf on human cerebral COLs & stroke (www.collateralperfusion.org) (leadoff spkr after Intro) UCLA, 2012

Study Section, Editorial, and Advisory Service

NIH-NHLBI, PPG Site Visit Team 1985
NIH-NHLBI, Experimental Cardiovascular Sciences 1989, 1990, 1991 (ad hoc), 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. Physiol,* 1993-1999. Areas of assigned submissions: **Cerebral circulation, neural & autonomic control of circ**.

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. 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

2. 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

3. 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

4. Dai X, Faber JE (2010) eNOS deficiency causes collateral vessel rarefaction and impairs activetion 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".

5. Chalothorn D, Faber JE (2010) Formation and maturation or the murine native cerebral collateral circulation. **J Molec Cell Cardiol.** 49:251-259. http://www.ncbi.nlm.nih.gov/pubmed/20346953

6. 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

7. 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"), **featured in editorial** (S Schwartz) http://f1000biology.com/article/id/3765959/evaluation.

8. Faber JE, Zhang H, Lassance-Soares RM, Prabhakar P, 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

9. Wang S, Zhang H, Wiltshire T, Sealock R, Faber JE (2012) Genetic dissection of the *Canq1* locus governing variation in extent of the collateral circulation. **PLoS One.** 7:e31910. http://www.ncbi.nlm.nih.gov/pubmed/22412848

10. Lucitti JL, Mackey J, Morrison J, Haig J, Adams R, Faber JE (2012) Formation of the collateral circulation is regulated by vascular endothelial growth factor-A and A Disintegrin and Metalloprotease Family Members 10 and 17. **Circ Res**, epub Sept 107 (in appendix). http://circres.ahajournals.org /content/early/2012/09/10/CIRCRESAHA.112.279109.full.pdf?ijkey=DmwDoHc8Yepdx7Z&keytype=ref

Additional publications for current grant period that are of importance to the field

11. Aitsebaomo J, Srivastava S, Zhang H, Jha S, Veleva AN, Pi X, Lockyer P, Winnick S, Faber JE*, Patterson C* (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, *Co-senior authors. http://atvb.ahajournals.org/cgi/reprint/ATVBAHA.110.216986v2

12. Faber JE, Dai X, Lucitti J (2011) Genetic and environmental mechanisms controlling formation and maintenance of the native collateral circulation. *In*: **Arteriogenesis – Molecular Regulation, Pathophysi-ology and Therapeutics I.** E Deindl, W Schaper (eds), Shaker Verlag, Aachen, Ch 1, pp 1-22. (in appendix)

13. 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**. 4:779-89. http://www.ncbi.nlm.nih.gov/pubmed/21538183

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://www.ncbi.nlm.nih.gov/pubmed/21398592

15. Faber JE (2012) Reprogrammed endothelial cells: Cell therapy for coronary collateral growth? **Circ Res**. 110:192-194, Invited editorial. http://circres.ahajournals.org/content/110/2/192.full.pdf+html

D. Research Support. Ongoing research support

R01 HL111070-01, 10/2012-6/2016. "Maintenance and Rarefaction of the Native Collateral Circulation". Project investigates whether and how cardiovascular risk factors cause collateral rarefaction and how to inhibit it, and tests the hypothesis that mural cells of collaterals vessels have a unique cellular and molecular phenotype compared to other vessels of the general arterial-venous circulation. Role: Principal Investigator.

R01 HL062584-13, 7/99-6/13. "α-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. Role: Principal Investigator.

R01 HL096597-01, 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. Role: Principal Investigator-Subcontract.

R01 HL######-01, 7/1/13-6/30/18 (submitted). "Targeting of the Pial Collateral Circulation for Mitigation of Cerebral Ischemia". Project uses congenic analysis, RNA-Seq, FAIRE/ChIP-Seq and gene targeting to identify the genetic element at *Candqr1* (the major locus controlling collaterogenesis) and its effectors. Role: PI.

Completed research support (last 3 years)

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".

On-going Collaborations ($, key collaborator; *collaborator on grant; **subcontract on grant)

**Diana Ramirez, Case Western Reserve U Physiol. ARNT and VEGF in collaterogenesis. (RO1 subcontract)
*Anne Hamik, Case WRU Med. KLF4 in formation/growth of collateral circ & angiogen. (RO1 subc in revision)
*Leslie Parise, UNC Biochemistry. CIB1 in neovascularization in ischemia. **2 publications resulted**
*John Edwards, St. Louis U. CLIC proteins in collatero- and angio-genesis in ischemia. **1 publication**
*Julius Aitsebaomo, UNC Medicine. IL-11 in neovascularization in ischemia.
Stephen Epstein, MedStar Res Inst, Wash DC. Collateral function in aging. (RO1 subc in review). **3 pubs
*Marshall Runge, Nageswara Madamanchi, UNC Medicine. LAR in neovascularization. **Paper in review**
*Oliver Smithies, Noboyuki Takayashi, UNC Pathol. sFlt-1 and sEng mechanisms in pre-eclampsia. **1 pub**
*Jun Yu, William Sessa, Yale. NOGO-B in collaterogenesis and arteriogenesis. **Paper in preparation.**
Zofia Zukowska (deceased), Georgetown, NPY and collateral remodeling in ischemia. **Paper in review.**
William Arendshorst, UNC Physiology. ADP ribosyl cyclase in renal vasc reg and remod. **Paper in review.**
Zoltan Arani, Harvard. PGC1α in vascular development and ischemic neovascularization.
P Quax, AY Nossent, Leiden Univ. P300/CBP Association Factor in collateral formation. **Paper in review.**
$ UNC Depts of Cell Molec Physiol[1], Neurology[2], Neuroradiology[3], Ophthalmology[4] – translational pilot study – Assessing collateral extent in acute stroke patients (J Faber[1] PI), P Prabhakar[1], Y Lee[3], J Lowe[1], T Jones[1], M Waddell[1], P Chtcteprov[1], D Huang[2], K Smith[2], S Solander[2], H An[3], S Moyer[4], S Garg[4]). **Paper in review.**
$ *Univ of Calgary Stroke Ctr. Assessing COL extent and genetic polymorphisms in acute stroke patients. BK Menon, AM Demchuk, JE Faber, MD Hill, M Goyal, R Frayne, E Smith, W Misik. **Paper & CIHR grant in rev.**