BIOGRAPHICAL SKETCH

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NAME: Leeper, Nicholas J

eRA COMMONS USER NAME: LEEPER.NICHOLAS

POSITION TITLE: Associate Professor of Surgery and Medicine; Chief, Vascular Medicine

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	FIELD OF STUDY
University of Chicago, Chicago, IL	BA	06/1999	Chemistry
University of Chicago, Pritzker School of Medicine	MD	06/2003	Medicine
University of California, San Francisco	Residency	06/2005	Internal Medicine
Stanford University, Stanford, CA	Fellowship	06/2009	Cardiology
Stanford University, Stanford, CA	Fellowship	06/2010	Vascular Medicine

A. Personal Statement

I am a vascular biologist and cardiologist interested in atherosclerosis and aneurysm disease. My laboratory pursues these conditions with a combination of translational approaches from the fields of human genetics, molecular biology, and murine models of vascular disease. We hope to translate our findings from bench to bedside to reduce the burden of cardiovascular disease. A specific example of this work centers in our recent discovery of the role of *efferocytosis* (the phagocytic clearance of apoptotic debris) in the heritable component of atherosclerosis (*JCI*, 2014; *Nature*, 2016). I also direct the Stanford Vascular Medicine Translational Research Program, which works towards targeting these processes in humans with cardiovascular disease.

B. Positions and Honors

Previous Positions

EMPLOYMENT/ POSITIONS	BEGINNING DATE (mm/yy)	ENDING DATE (mm/yy)	FIELD	INSTITUTION/ COMPANY	SUPERVISOR/ EMPLOYER
Research Intern	06/93	09/93	Gene Therapy	Progenitor Inc.	Douglass Given
Research Assistant	06/96	03/97	Human Genetics	University of Chicago	David Ledbetter
Research Assistant	06/98	09/98	Angiogenesis	Stanford University	Tom Quertermous
Research Assistant	06/00	06/02	Preconditioning	University of Chicago	Bruce Gewertz
Intern in Medicine	06/03	05/04	Internal Medicine	UC San Francisco	Lee Goldman
Resident Physician	06/04	06/05	Internal Medicine	UC San Francisco	Harry Hollander
Clinical Fellow	07/05	06/07	Cardiology	Stanford University	John Giacomini
Postdoctoral Fellow	07/07	06/09	Vascular Biology	Stanford University	Tom Quertermous
Instructor in Medicine	07/09	04/11	Vascular Medicine	Stanford University	John Cooke
Assistant Professor	04/11	09/15	Vascular Medicine	Stanford University	Ron Dalman
Director, Vascular Research	09/15	-	Translational Res.	Stanford University	Mary Hawn
Chief, Vascular Medicine	09/15	-	Vascular Medicine	Stanford University	Ron Dalman
Associate Professor	10/15	-	Vascular Medicine	Stanford University	Mary Hawn

Honors

1992 Eagle Scout, Boy Scouts of America
1995 Varsity Track and Field, 400 Meter Dash and Pole Vault, University of Chicago 1995-1997
1999 Graduated with Honors, University of Chicago, Department of Chemistry
2000 Charlie Huggins Research Award Recipient
2002 Calvin Fentress Research Award Recipient
2003 Alpha Omega Alpha Honors Society
2003 Graduated with Honors, University of Chicago, Pritzker School of Medicine
2010 Jay D. Coffman Young Investigator Award Winner, Society for Vascular Medicine
2011 American Heart Association Young Investigator Finalist, FGTB
2011 Northwestern Cardiovascular Young Investigators' Forum Finalist
2011 "Golden Heart Award", American Heart Association- Western Affiliates
2014 Jeremiah Stamler Award recipient, Northwestern Cardiovascular Young Investigators' Forum

Professional Societies and Public Advisory Committees

2013 Associate Editor, Vascular Medicine
2013 Steering Committee Member, Stanford Cardiovascular Institute
2013 President, American Heart Association Board, Silicon Valley
2014 Membership and Communications Committee, PVD council, AHA
2015 National Member at Large, Science Advisory and Coordinating Committee, AHA
2016 Journal Watch Editor, JACC Basic to Translational Medicine
2016 Chair ('16-'18), Early Career Committee (ECC), ATVB

Past Editorial Experience (last 5 years)

Ad hoc reviewer for: Circulation, Circulation Cardiovascular Genetics, JAMA, JACC, JAHA, ATVB, JMCC, AJC, Vascular Medicine, Mayo Clinic Proceedings, JVS, Metabolism, Atherosclerosis, IJC.

Recent/Ongoing Clinical and Translational Trials

- **PACE trial**: "Bone Marrow Derived ALDH Bright Cells in Intermittent Claudication". Cardiovascular Cell Therapy Research Network (CCTRN), Phase II, Sponsor: NHLBI. Co-Investigator.
- **Protocol 23848**. "Effect of Proton Pump Inhibitors on Endothelial Function". Phase I, Sponsor: Stanford (Investigator Initiated). Principle Investigator.
- **REVIVE CLI study**: "An Efficacy and Safety Study of Ixmyelocel-T in Patients With Critical Limb Ischemia (CLI) (REVIVE)", Phase III, Sponsor: Aastrom Biosciences, Site Principle Investigator.
- **EUCLID Trial**. "A randomised, double-blind, parallel group, multicentre phase IIIb study to compare ticagrelor with clopidogrel treatment on the risk of cardiovascular death, myocardial infarction and ischaemic stroke in patients with established Peripheral Artery Disease (Examining Use of tiCagreLor In paD). Phase III, Sponsor: Astra-Zeneca. Site Principle Investigator.
- **PLX-PAD 1202-02**. "Safety of Intramuscular Injection of Allogeneic PLX-PAD Cells for the Treatment of Critical Limb Ischemia". Phase I, First-in-Man; Sponsor: Pluristem. Co-Principle Investigator.
- **Protocol CY 4022.** "A Phase II, double-blind, randomized, placebo-controlled, three-way crossover, pharmacokinetic and pharmacodynamic study of CK-2017357 in patients with claudication". Phase II, Sponsor: Cytokinetics. Co-Investigator.

C. Contribution to Science

1. <u>The Role of Efferocytosis in Atherosclerosis</u>

Our most recent contribution to the field of vascular biology surrounds the role of *efferocytosis* in atherosclerotic plaque progression. *Efferocytosis* (Greek: to carry the dead to the grave) is the process by which dying and diseased tissue undergoes phagocytic clearance to prevent the accumulation of necrotic debris. Our work has shown that the top genetic locus for cardiovascular disease (the 9p21 locus) regulates SMC apoptosis (*ATVB*, 2013) and the phagocytic clearance of these cells during atherosclerosis (*JCI*, 2014). We have reported that this phenomenon contributes to expansion of the necrotic core and plaque instability. We have continued to intensely pursue these findings (via R01 HL123370), and have now found that

efferocytosis-regulating molecules (known as 'eat-me' and 'don't-eat-me' ligands) are dysregulated in atherogenesis and can be targeted by antibodies for therapeutic purposes (*Nature*, 2016). Currently we are investigating how these signaling defects occur, how they impact other aspects of vascular disease, and how we can translate these findings into human studies.

a. Kojima Y, Direnzo D, Nanda V, Volkmer JP, Weissman lL, **Leeper NJ**. *CD47 blocking antibodies restore phagocytosis and prevent atherosclerosis*. Nature. 2016 Aug 4;536(7614):86-90.

b. Kojima Y, Downing KD, Kundu R, Miller CL, Lancero H, Quertermous T, **Leeper NJ**. *The role of CDKN2B in atherosclerosis and efferocytosis*. Journal of Clinical Investigation. 2014 Mar 3;124(3):1083-97. PMCID: PMC3938254.

c. Nanda V, Downing KP, Ye J, Xiao S, Kojima Y, Spin JM, DiRenzo D, Nead KT, Connolly AJ, Dandona S, Perisic L, Hedin U, Maegdefessel L, Dalman J, Guo L, Zhao X, Kolodgie FD, Virmani R, Davis HR Jr, **Leeper NJ**. *CDKN2B Regulates TGFβ Signaling and Smooth Muscle Cell Investment of Hypoxic Neovessels.* Circulation Research. 2016 Jan 22;118(2):230-40. PMID: 26596284

d. **Leeper NJ**, Raisedana A, Kojima Y, Kundu R, Putnam K, Tsao P, Cheng H, Schadt E, Owen GK, Quertermous T. *Loss of CDKN2B promotes p53-dependent smooth muscle cell apoptosis and aneurysm formation*. Arteriosclerosis, Thrombosis, and Vascular Biology. 2013 Jan;33(1):e1-e10. PMCID: PMC3569043.

2. <u>Investigating the Genetic Component of Vascular Disease</u>

The other major aspect of research in our laboratory surrounds the use of unbiased, genome-wide genetic approaches to explore the root cause of cardiovascular disease. To date, we have used the GWAS (genome-wide association study) and cDNA microarray approach to make important advances in the areas of atherogenesis, vascular remodeling and aneurysm disease. Specific examples of areas to which we contributed include the study of: 1. Neointimal hyperplasia (i.e. miR-26a; *JCP*, 2011); 2. Pathological angiogenesis (i.e. Hif-1α; *PNAS*, 2014); 3. Ischemic cardiomyopathy (i.e. Apelin; *JCI,* 2008); 4. AAA disease (i.e. miR-21and 29b; *JCI*, 2012, *Sci Trans Med,* 2012); and 5. Vascular SMC biology (i.e. CDKN2B; *ATVB*, 2013, 2015). These efforts are now mainly focused on the role of the vascular SMC in cardiovascular disease, and are pursued via a separate NIH grant (R01 HL125224).

a. Kullo I, **Leeper NJ**. The Genetic Basis of Peripheral Arterial Disease: Current Knowledge, Challenges and Future Directions. Circulation Research, 2015 Apr 24;116(9):1551-60. PMID: 25908728.

b. **Leeper NJ**, Raiesdana A, Kojima Y, Chun HJ, Quertermous T, Tsao P, Spin J. *MicroRNA 26-a regulates vascular smooth muscle differentiation via antagonism of the TGF-Beta pathway.* The Journal of Cellular Physiology. 2011 Apr;226(4):1035-43. PMCID: PMC3108574.

c. **Leeper NJ**, Tedesco MM, Kojima Y, Schultz GM, Kundu RK, Ashley EA, Tsao PS, Dalman RL, Quertermous T. *Apelin prevents aortic aneurysm formation by inhibiting macrophage inflammation.* American Journal of Physiology- Heart Circulatory Physiology. 2009 May; 296 (5): H1329-35. PMCID: PMC2685356.

d. Maegdefessel L, Azuma J, Toh R, Deng A, Merk DR, Raiesdana A, **Leeper NJ**, Raaz U, Schoelmerich AM, McConnell MV, Dalman RL, Spin JM, Tsao PS. *MicroRNA-21 Blocks Abdominal Aortic Aneurysm Development and Nicotine-Augmented Expansion*. Science Translational Medicine. 2012 Feb 22;4(122):122ra22. PMID: 22357537.

3. Using 'Big Data' and Translational Studies to Advance the Field of Vascular Medicine

In addition to the fundamental genomic and vascular biology efforts described above, we also lead a major clinical and translational Vascular Medicine research effort at Stanford. Here we attempt to improve the health of patients with vascular disease by: 1. Performing genomic, metabolomics and proteomic discovery studies aimed at improving disease diagnosis and risk stratification; 2. Conducting "Big Data" bioinformatic studies using the electronic health record; and 3. Performing early phase clinical trials geared towards enhancing vascular regeneration and vascular physiology. This work is conducted in a collaborative fashion, and is supported by several multi-PI grants (including the NIH CCTRN network and R01 GM10143003).

a. Shah NH, LePendu P, Bauer-Mehren A, Gherbremariam YT, Iyer SV, Marcus J, Nead KT, Cooke JP, **Leeper NJ**. *Proton pump inhibitor usage and the risk of myocardial infarction in the general population.* PLoS One. 2015 Jun 10;10(6):e0124653.

b. Nead KT, Zhou M, Caceres R, Olin J, Cooke JP and **Leeper NJ**. *Alternative ankle-brachial index method accurately identifies additional at-risk individuals*. Journal of the American College of Cardiology. 2013 May 22. doi:pii: S0735-1097(13)01987-6. PMCID: PMC3732795.

c. Downing KP, Nead KT, Kojima Y, Assimes T, Maegdefessel L, Quertermous T, Cooke JP, **Leeper NJ**. *The combination of 9p21.3 genotype and proteomic biomarker profile improves a peripheral artery disease risk prediction model*. Vascular Medicine. 2014 Feb;19(1):3-8.

d. **Leeper NJ**, Hunter AL, Cooke JP. *Stem cell therapy for vascular regeneration: Adult, Embryonic, and Induced Pluripotent Stem Cells*. Circulation. 2010 Aug 3;122(5):517-26. PMCID: PMC2920605.

Additional information and complete list of peer-reviewed publications (>50 total) available at: http://med.stanford.edu/leeperlab/

D. Research Support

Ongoing Support:

1R01 HL123370 (**PI: Leeper**) 04/10/15 – 03/31/19
- NIH/NHLBI – The role of CDKN2B in efferocytosis and atherosclerosis
- This award investigates the role of phagocytosis in cardiovascular disease and necrotic core growth

1R01 HL125224 (**PI: Leeper**) 11/01/14 - 10/30/19
- NIH/NHLBI – The paradoxical role of CDKN2B in blood vessel sprouting and maturation
- This award investigates the role of a top GWAS locus in angiogenesis and pericyte recruitment

Voyager Study (**Site PI: Leeper**) 10/16/15 – 10/15/18
- Bayer – An international, multicenter, randomized, double-blind, placebo-controlled phase 3 trial investigating the efficacy and safety of rivaroxaban to reduce the risk of major thrombotic vascular events in patients with symptomatic peripheral artery disease undergoing lower extremity revascularization procedures

5UM1 HL113456 (PI: Yang) 04/01/12 - 03/31/19
NIH
- Cell Characterization and Imaging for Regenerative Therapies in Ischemic Diseases.
- The major goal of this project is to contribute to the clinical effort of CCTRN through our innovative approaches to in vivo imaging and cell characterization for the treatment of CAD and PAD.

1R01 GM10143003 (PI: Shah) 09/01/13 - 04/30/18

- NIH - Mining health data for drug safety profiles
- The major goal of this project is to develop and utilize novel machine learning and natural language processing algorithms to characterize drug safety profiles in the field of cardiovascular medicine.

Mentored Grants (current):

- 1T32HL098049-01A1; Mentor to award recipient: Gyang E; 12/01/2013-11/30/2015
  NIH/NHLBI – Stanford T32: Mechanisms and Innovations in Vascular Disease.

- 15POST21310005; Mentor to award recipient: Nanda V**;** 1/01/2015-12/30/2017
  AHA/Western States Affiliate: - The role of CDKN2B in TGFB-dependent SMC recruitment to ischemic blood vessels.

Completed Support (last three years):

15GRNT22970033 (**PI: Leeper**) 07/01/15 -6/30/17
AHA, Grant-in-Aid
- American Heart Association, Western States Affiliate
- Western Affiliates - Inducing atherosclerotic plaque regression by stimulating the phagocytic clearance of apoptotic debris (Turned down due to excessive funding)

10BGIA3290011; (**PI: Leeper**)
AHA, Beginning Grant-in-Aid 07/01/10 - 06/30/12
- American Heart Association, Western States Affiliate
- Goal: To perform early studies on the role of CDKN2B in the remodeling carotid artery.

No number (**PI: Leeper**)
Jeremiah Stamler Distinguished Young Investigator Award 01/15/14 - 01/14/15
- Astra Zeneca - CDKN2B Regulates Efferocytosis and Atherosclerosis.

K12 HL087746; (PI: Cooke) 04/01/09 - 03/31/12
- NIH/NHLBI
- Goal: To train translational scientists in the field of Vascular Medicine. Dr. Leeper's clinical and basic research training in peripheral vascular diseases was funded by this grant.

EUCLID trial. (**PI: Leeper**) 12/19/12 - 06/18/14
- Astra-Zeneca: A randomized, double-blind, parallel group, multicenter phase IIIb study to compare ticagrelor with clopidogrel treatment on the risk of cardiovascular death, myocardial infraction and ischaemic stroke in patients with established peripheral artery disease.

K08 HL103605-01 (**PI: Leeper**) 05/15/12 - 05/14/15
NIH
- The role of CDKN2B in AAA disease.
- Goal: to investigate the genetics underlying the 9p21 variants and their link to aneurysm disease.