BIOGRAPHICAL SKETCH

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NAME: Cooke, John P

eRA COMMONS USER NAME (credential, e.g., agency login): COOKE.JOHN

POSITION TITLE: Professor of Medicine and Chair, Dept. of Cardiovascular Sciences

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)*	Start Date MM/YYYY	Completion Date MM/YYYY	FIELD OF STUDY
Cornell University, Ithaca, NY	BA	09/1972	06/1976	Biology
Wayne State University, Detroit, MI	MD	09/1976	06/1980	Medicine
Mayo Graduate School of Medicine, Rochester, MN	PhD	01/1983	06/1985	Physiology
Mayo Graduate School of Medicine, Rochester, MN	Res/Fellow	06/1980	12/1986	Cardiovascular Medicine

A. Personal Statement

I have 30 years of experience in generating fundamental insights into endothelial biology and vascular diseases, and in translating these fundamental insights toward transformative therapies, with over 30 patents and >30,000 citations; h index = 96 (Scopus 9-11-20). Relevant to the current proposal, we have studied the mechanisms of nuclear reprogramming during alterations in cell fate. We discovered that innate immune signaling through pattern recognition receptors (PRRs) induces global epigenetic changes that increase DNA accessibility to alter cell fate and function. We have shown that activation of PRRs changes the expression and/or post-translational modification of epigenetic enzymes, as well as their substrates, to increase DNA accessibility and cellular plasticity.

B. Positions and Honors

Positions and Employment

1987-90 Assistant Professor of Medicine, Harvard Medical School, Boston, MA
1990-95 Assistant Professor of Medicine, Stanford University School of Medicine, Stanford, CA
1995-2004 Associate Professor of Medicine, Stanford University School of Medicine
2004-2013 Professor of Medicine, Stanford University School of Medicine
2013- Professor and Chair, Dept. of Cardiovascular Sciences, Houston Methodist Research Institute
2013- Director, Center for Cardiovascular Regeneration
2014- Executive Committee, Houston Methodist Research Institute
2015- Director, CPRIT RNA Core
2015- Director, Board of Directors, Houston Methodist Research Institute

Other Experience and Professional Memberships

2005-07 President, Society for Vascular Medicine
2006-2009 Director, American Board of Vascular Medicine
2006-2010 Chair, Young Investigator Award, Accreditation Coordinating Committee
2006-2010 Chair, Zipes Distinguished Young Scientist Award Committee

Honors

1988 Milton Award, Harvard Medical School
1990 First Place, Young Investigator Competition, American College of Cardiology
1990 Henry Christian Award, American Federation for Clinical Research
1991 Vascular Academic Award, National Institutes of Health
1996 Established Investigator Award, American Heart Association
2001 Departmental Teaching Award, Stanford University School of Medicine
2008 "2008 Best PAD Research Award", Peripheral Arterial Disease Coalition
2009 Master of the Society for Vascular Medicine
2010 Election to the Association of American Physicians
2013 Award for Excellence in Peer Reviewed Publication, Houston Methodist Institute for Academic Medicine (Ghebremariam Y et al, Circulation. 2013 Aug 20;128(8):845-53)
2015 President's Award for Transformational Excellence, Houston Methodist Research Institute
2015 Outstanding Inventor Award, Stanford University
2016 Best Manuscript Award from Circulation Research
2016 Award for Excellence in Peer Reviewed Publication, Houston Methodist Institute for Academic Medicine (Yepuri et al, Circ Res. 2016 Jun 10;118(12):e36-42)
2019 Award for Excellence in Peer Reviewed Publication, Houston Methodist Institute for Academic Medicine (Chanda P et al, Circulation. 2019 Sep 24;140(13):1081-1099)
2019 Election to Fellowship in the National Academy of Inventors
2020 Award for Excellence in Peer Reviewed Publication, Houston Methodist Institute for Academic Medicine (Boada C et al Circ Res. 2020 Jan 3;126(1):25-37.)
2020 Mayo Clinic Distinguished Alumnus of 2020

C. Contributions to Science (see also **Personal Statement)**

1. ***Transflammation mediates nuclear reprogramming.*** We were the first to recognize the importance of inflammatory signaling in cell fate determination (Lee et al, Cell 2012). This work revealed that innate immune signaling causes global changes in epigenetic modifiers to facilitate nuclear reprogramming of cell fate. More recently, we have shown the importance of reactive oxygen and nitrogen species, as well as a glycolytic shift, in nuclear reprogramming. We coined the term ***"Transflammation"*** to describe the process by which inflammatory signaling increases DNA accessibility to facilitate nuclear reprogramming. Notably, based on these insights, we have now systematically manipulated innate immune signaling to facilitate the process of transdifferentiation of one somatic cell to another. This has permitted us to develop a small molecule based methodology to induce human fibroblasts to transdifferentiate into endothelial cells. We have comprehensively characterized the endothelial nature of these cells by transcriptional and functional profiling.

a) Lee J, Sayed N, Hunter A, Au KF, Wong WH, Mocarski E, Reijo Pera R, Cooke JP: Activation of innate immunity is required for efficient nuclear reprogramming. ***Cell*** 151, 547–558, 2012

b) Sayed N, Wong WT, Ospino F, Meng S, Lee J, Jha A, Dexheimer P, Aronow BJ, Cooke JP. Transdifferentiation of Human Fibroblasts to Endothelial Cells: Role of Innate Immunity. ***Circulation*****.** 2015 Jan 20;131(3):300-9. PMID: 25359165

c) d) Meng S, Zhou G, Gu Q, Chanda PK, Ospino F, Cooke JP. Transdifferentiation Requires iNOS Activation: Role of RING1A S-Nitrosylation. ***Circulation Research****.* 2016 Oct 14;119(9):e129-e138.PMID:27623813

d) Lai L, Reineke E, Hamilton DJ, Cooke JP. Glycolytic Switch Is Required for Transdifferentiation to Endothelial Lineage. ***Circulation***. 2019 Jan 2;139(1):119-133.

2. Discovery of novel pathways in vascular development, angiogenesis and atherosclerosis. We discovered the angiogenic pathway mediated by endothelial nicotinic acetycholine receptors (nAChR). Nicotine is a potent angiogenic agent that promotes pathological neovascularization in atherosclerosis, cancer and age related macular degeneration (AMD). Based on this work we developed an antagonist of the nAChR to treat AMD which has been tested in clinical trials. Most recently, we described a novel regulator of the hemogenic endothelium that regulates the generation of HSCs from the endothelium of the AGM region during development.

a. Heeschen C, Jang J, Hoai-Ky V, Kaji S, Yang P, Hu RS, Cooke JP: Nicotine is an agent of angiogenesis. Nicotine stimulates angiogenesis and promotes tumor growth and atherosclerosis. ***Nature Med*** 2001 Jul; 7(7):833-9.

b. Heeschen C, Weis M, Cooke JP: A novel angiogenic pathway mediated by non-neuronal nicotinic acetylcholine receptors. ***J Clin Invest*** 2002 Aug;110(4):527-36
c. Zhu B, Heeschen C, Sievers RE, Karliner JS, Parmley WW, Glantz SA and Cooke JP: Second Hand Smoke Stimulates Tumor Angiogenesis and Growth, ***Cancer Cell* 2003**; 4(3):191-6
d. Gu Q, Yang X, Lv J, Zhang J, Xia B, Kim JD, Wang R, Xiong F, Meng S, Clements TP, Tandon B, Wagner DS, Diaz MF, Wenzel PL, Miller YI, Traver D, Cooke JP, Li W, Zon LI, Chen K, Bai Y, Fang L. AIBP-mediated cholesterol efflux instructs hematopoietic stem and progenitor cell fate. **Science**. 2019 Mar 8;363(6431):1085-1088

3. Novel mechanism by which CV Risk Factors impair NOS. We identified the mechanism by which cardiovascular risk factors increase ADMA levels and impair endothelial function. The enzyme dimethylarginine dimethylaminohydrolase (DDAH) degrades ADMA. We discovered that DDAH is oxidant-sensitive, as it contains a reactive sulfhydryl in its catalytic site. We showed that high levels of glucose and cholesterol increase EC oxidative stress and impair DDAH activity and increase plasma and tissue ADMA levels. Overexpression of DDAH reduced ADMA levels; increased NO synthesis; reduced blood pressure; and reduced vascular lesions in disease models.
a) Ito A, Tsao PS, Adimoolam S, Kimoto M, Ogawa T, Cooke JP. Novel mechanism for endothelial dysfunction: dysregulation of dimethylarginine dimethylaminohydrolase. ***Circulation***. 1999;99(24):3092-5. PubMed PMID: 10377069.
b) Lin KY, Ito A, Asagami T, Tsao PS, Adimoolam S, Kimoto M, Tsuji H, Reaven GM, Cooke JP. Impaired nitric oxide synthase pathway in diabetes mellitus: role of asymmetric dimethylarginine and dimethylarginine dimethylaminohydrolase. ***Circulation***. 2002;106(8):987-92. PubMed PMID: 12186805.
c) Dayoub H, Achan V, Adimoolam S, Jacobi J, Stuehlinger M, Wang B, Tsao PS, Kimoto M, Vallance P, Patterson AJ, Cooke JP: DDAH Regulates NO Synthesis: Genetic and physiological evidence. ***Circulation*** 2003; 108: 1043-1048
d) Jacobi J, Sydow K, von Degenfeld G, Zhang Y, Dayoub H, Wang B, Patterson AJ, Kimoto M, Blau HM, Cooke JP: Overexpression of Dimethylarginine Dimethylaminohydrolase (DDAH) Reduces Tissue ADMA Levels and Enhances Angiogenesis. ***Circulation*** 2005 Mar 22;111(11):1431-8.

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/pubmed/?term=John+P.+Cooke

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

1R01HL148338 (Cooke) 7/15/20 – 3/31/24
NIH/NHLBI $440,172/year (direct)
Reversal of Heart Failure: Role of Vascular Recovery. Using scRNAseq and lineage tracing, we will define the role of mesenchyme-to-endothelial transition in restoring cardiac microvasculature, reducing fibrosis, and improving ventricular function, in an animal model, and in patients, with non-ischemic cardiac failure

1R01HL133254 (Cooke) 04/01/2018 – 03/31/2022
NIH/NHLBI
Role of S-nitrosylation in Transdifferentiation
The goal of this proposal is to understand the epigenetic mechanisms and changes in chromatin conformation by which one cell transforms into a different cell lineage (transdifferentiation).

RP150611 (Cooke) 12/1/2020 – 11/30/2025
Cancer Prevention Institute of Texas $800,000/year (direct)
The CPRIT Core for RNA Therapeutics and Research is directed towards generating RNA constructs, such as chimeric antigen receptors, for the cancer biology and clinical trials community.

1R01HL149303-01 (Abe) 07/15/2019 – 06/30/2023
NIH/NHLBI
Pathological flow-induced endothelial damage and plaque erosion

The goal of the study is to investigate signaling events triggered by pathological blood flow that lead to the damage of vascular endothelium and erosion of atherosclerotic plaque.

1R01HL145170-01A1 (Chen) 07/01/2019 – 06/30/2024
NIH/NHLBI
Long non-coding RNA-mediated chromatin remodeling in angiogenesis
The goal of the study is to investigate RNA mediated chromatin remodeling in endothelial cells.

1R01GM125632 (Chen) 7/1/2018-4/30/2022
NIH/NHLBI
Computational epigenetics modeling of cell identity genes
The goal of this proposal to develop model-based algorithms to define histone modification feature for individual genes, develop computational epigenetic methods for discovery of novel cell identity determinants and apply these methods to define EC identity genes.

R01HL132155 (Fang) 04/01/2016 – 01/31/2021
NIH/NHLBI
AIBP Mediates a Novel Interplay between Cholesterol Metabolism and Lymphangiogenesis
The goal of this proposal is to test the hypothesis that AIBP, by accelerating cholesterol efflux, regulates caveolae/lipid raft abundance, VEGFR3 signaling and lymphangiogenesis.

1 R61 HL146775-01 (Tierney) 03/20/2020 – 03/31/2025
NIH/NHLBI
RE-NERGIZE FONTAN – RandomizEd Exercise INtERvention DesiGned to MaximIZE Fitness in Pediatric FONTAN Patients
Role: Co-Investigator
The goal is to assess the effects of an exercise intervention in Fontan patients on endothelial function

Chair Fund 01/01/2015 – Present
HMRI
Joseph C. “Rusty” Walter and Carole Walter Looke Presidential Distinguished Chair in Cardiovascular Research

<u>Completed Research Support</u>

1UM1 HL113456-01 Yang, PI 04/01/12 - 03/30/**17**

NIH. Cell Characterization and Imaging for Regenerative Therapies in Ischemic Diseases. This UM1 funds our work in the NHLBI Cardiovascular Cell Therapy Research Network (CCTRN) in which we will use novel cell characterization methods (mass cytometry) and imaging (MEMRI) to elucidate the mechanisms by which adult stem cell therapy improves function in ischemic tissues in patients with CAD and PAD.