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| **BIOGRAPHICAL SKETCH**  Provide the following information for the Senior/key personnel and other significant contributors.  Follow this format for each person. **DO NOT EXCEED FIVE PAGES.** | | | | |
| NAME: Temel, Ryan E | | | | |
| eRA COMMONS USER NAME (credential, e.g., agency login): rtemel | | | | |
| POSITION TITLE: | Associate Professor  Saha Cardiovascular Research Center  Department of Physiology  University of Kentucky | | | |
| 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  MM/YYYY | FIELD OF STUDY |
| Allegheny College, Meadville, PA | | B.S. | 05/1995 | Chemistry |
| SUNY at Stony Brook, Stony Brook, NY | | Ph.D. | 08/2001 | Biochemistry & Molecular Biology |
| Wake Forest University School of Medicine, Winston-Salem, NC | | Postdoc | 07/2006 | Pathology/Lipid Sciences |

1. **Personal Statement**

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| I have been studying cholesterol and lipoprotein metabolism, atherosclerosis, and cardiovascular disease (CVD) for over 20 years. My lab is determining the effects of biliary cholesterol secretion on hepatic lipid and lipoprotein metabolism and atherosclerosis development. Using LDL receptor deficient mice with liver specific knockdown of ABCG8 and/or hepatic NPC1L1 overexpression, we have found that dramatic reductions in biliary cholesterol are associated with significantly decreased atherosclerosis development. This exciting and unanticipated result is counter to the concept that biliary cholesterol secretion is necessary for the anti-atherosclerotic effects of RCT. In addition to mice, nonhuman primates (NHPs) have been used for much of our research over the last decade. To discover new mechanisms and therapeutics that alter lipid metabolism and reduce the risk of coronary heart disease (CHD), we have treated monkeys with statins, nuclear receptors agonists, antisense oligonucleotides, and nanotherapeutics. We are currently conducting a study to determine whether antagonism of miR-33a/b in NHPs will regress/stabilize atherosclerosis in both the cardio- and cerebro-vasculature. In addition, we have recently started a project to identify anti-miR compounds for effective and safe inhibition of miR-128-1 and miR-22 and assess their therapeutic potential to treat non-alcoholic steatohepatitis (NASH) in highly relevant NHP models.   1. **Positions and Honors** | | | | | |
| Professional Appointments | | | | | |
| 2006-2008 | Instructor, Department of Pathology, Section on Lipid Sciences, Wake Forest University School of Medicine, Winston-Salem, NC | | | | |
| 2008-2013 | Assistant Professor, Department of Pathology, Section on Lipid Sciences, Wake Forest University School of Medicine, Winston-Salem, NC | | | | |
| 2013-2015 | Assistant Professor, Saha Cardiovascular Research Center, Department of Pharmacology and Nutritional Sciences, University of Kentucky, Lexington, KY | | | | |
| 2015-2018 | Associate Professor, Saha Cardiovascular Research Center, Department of Pharmacology and Nutritional Sciences, University of Kentucky, Lexington, KY | | | | |
| 2018-Present | Associate Professor, Saha Cardiovascular Research Center, Department of Physiology, University of Kentucky, Lexington, KY | | | | |
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| Professional Membership and Honors | | | | | |
| 2003-Present | American Society of Biochemistry and Molecular Biology | | | | |
| 2005-Present | American Heart Association, Council on Arteriosclerosis, Thrombosis and Vascular Biology (ATVB) | | | | |
|  | * ATVB Leadership Committee | | | 2013-2015 | |
|  | * ATVB Early Career Committee | | | 2008-2014 | |
|  | * + Chair | | | 2010-2012 | |
|  | * + Immediate Past Chair | | | 2012-2014 | |
|  | * ATVB Scientific Sessions Programming Committee | | | 2010 & 2011 | |
|  | * AHA Scientific Sessions Programming Committee | | | 2014-2017 | |
|  |  | | | | |
| 2018 | Alzheimer’s Association International Society to Advance Alzheimer’s Research and Treatment (ISTAART) | | | | |
| 1991-1995 | Presidential Scholarship, Allegheny College | | | | |
| 1991-1993 | Doane Distinguished Scholar, Allegheny College | | | | |
| 1991-1995 | Alden Scholar, Allegheny College | | | | |
| 1994 | Junior Chemistry Student of the Year, Allegheny College | | | | |
| 1995 | Phi Beta Kappa National Honor Society, Allegheny College | | | | |
| 2003 & 2006 | New Investigator Travel Award for ATVB Scientific Sessions | | | | |
| 2004 | Outstanding Poster Award for Gordon Research Conference on Lipoprotein Metabolism | | | | |
| 2013-2014 | American Heart Association Lipids Basic Science 2 Peer Review Study Group | | | | |
| 2014-2015 | American Heart Association Lipids Basic Science 1 Peer Review Study Group | | | | |
| 2015, October & 2016, February | NIH INMP Study Section, Temporary Member | | | | |
| 2016 October -Present | NIH INMP Study Section, Standing Member | | | | |

1. **Contribution to Science**

*Use of nonhuman primates to study targets and therapies for metabolic and cardiovascular disease*

Over the last decade, our lab has used NHP models to bridge the translational gap between mice and humans. Although admittedly not the perfect model for studying metabolic and cardiovascular disease, NHPs do have the advantage of their genome and physiology being closest to that of humans. For instance, NHPs and humans but not mice develop atherosclerosis in the coronary and intracranial arteries. Because of the financial and ethical issues surrounding their use, NHPs are employed by my lab for studies with high translational potential or focus on specific factors or pathways that are primate-specific. In addition, our lab has been proactive in distributing rare and expensive NHPs samples to labs around the country. Because of the very limited number of academic investigators using NHPs, my lab has created a unique niche within the metabolic and cardiovascular research community. Our experience and expertise with NHPs and access to unique NHP samples has resulted in collaborations with some of the top researchers in our field resulting in 13 peer-reviewed publications, many of which are in high-impact journals.

1. Inhibition of miR-33a/b in non-human primates raises plasma HDL and lowers VLDL triglycerides. Rayner KJ, Esau CC, Hussain FN, McDaniel AL, Marshall SM, van Gils JM, Ray TD, Sheedy FJ, Goedeke L, Liu X, Khatsenko OG, Kaimal V, Lees CJ, Fernandez-Hernando C, Fisher EA, **Temel RE\***, Moore KJ. Nature. 2011;478:404-7. PMCID: PMC3235584 **(\* equal contribution to study)**
2. Monocyte tissue factor-dependent activation of coagulation in hypercholesterolemic mice and monkeys is inhibited by simvastatin. Owens AP 3rd, Passam FH, Antoniak S, Marshall SM, McDaniel AL, Rudel L, Williams JC, Hubbard BK, Dutton JA, Wang J, Tobias PS, Curtiss LK, Daugherty A, Kirchhofer D, Luyendyk JP, Moriarty PM, Nagarajan S, Furie BC, Furie B, Johns DG, **Temel RE**, Mackman N. J Clin Invest. 2012;122:558-68.
3. The LXR-Idol Axis Differentially Regulates Plasma LDL Levels in Primates and Mice. Hong C, Marshall SM, McDaniel AL, Graham M, Layne JD, Cai L, Scotti E, Boyadjian R, Kim J, Chamberlain BT, Tangirala RK, Jung ME, Fong L, Lee R, Young SG, **Temel RE\***, Tontonoz. Cell Metab. 2014;20:910-918. **(\* co-corresponding author)**
4. Efficacy and safety assessment of a TRAF6-targeted nanoimmunotherapy in atherosclerotic mice and non-human primates. Lameijer M, Binderup T, van Leent MMT, Senders ML, Fay F, Malkus J, Sanchez-Gaytan BL, Teunissen AJP, Karakatsanis N, Robson P, Zhou X, Ye Y, Wojtkiewicz G, Tang J, Seijkens TTP, Kroon J, Stroes ESG, Kjaer A, Ochando J, Reiner T, Pérez-Medina C, Calcagno C, Fischer EA, Zhang B, **Temel RE**, Swirski FK, Nahrendorf M, Fayad ZA, Lutgens E, Mulder WJM, Duivenvoorden R. Nature Biomedical Engineering. 2018; 279–292.

*Effects of miR-33 antagonism on HDL metabolism and atherosclerosis regression*

The two members of the microRNA-33 (miR-33) family miR-33a and miR-33b coordinately regulate lipid metabolism with their host genes sterol regulatory element binding transcription factor 2 (SREBF2) and SREBF1. Notably, miR-33a/b induce mRNA degradation and/or translational repression of genes involved in cholesterol efflux and fatty acid oxidation. A major target of miR-33a/b is the ATP binding cassette transporter A1 (ABCA1), a protein essential for cholesterol efflux from foam cells and the formation of HDL. In mice, which encode only miR-33a, we showed that an antisense oligonucleotide targeting miR-33 (anti-miR-33) increased hepatic and macrophage ABCA1, HDL cholesterol, and atherosclerosis regression (1). However the translational value of the studies in mice was limited by the lack of miR-33b, which is expressed in humans and NHPs. To test the effects of inhibiting both miR-33a and b, we treated NHPs with anti-miR-33 and found that hepatic ABCA1 and HDL were elevated and VLDL triglyceride was decreased (2). We are currently working to determine the effects of anti-miR-33 on atherosclerosis regression or stabilization in NHPs. The results from our project will greatly aid in assessing miR-33 antagonism as a potential clinical treatment for CHD.

1. Antagonism of miR-33 in mice promotes reverse cholesterol transport and regression of atherosclerosis. Rayner KJ, Sheedy FJ, Esau CC, Hussain FN, **Temel RE**, Parathath S, van Gils JM, Rayner AJ, Chang AN, Suarez Y, Fernandez-Hernando C, Fisher EA, Moore KJ. J Clin Invest. 2011;121:2921-31
2. Inhibition of miR-33a/b in non-human primates raises plasma HDL and lowers VLDL triglycerides. Rayner KJ, Esau CC, Hussain FN, McDaniel AL, Marshall SM, van Gils JM, Ray TD, Sheedy FJ, Goedeke L, Liu X, Khatsenko OG, Kaimal V, Lees CJ, Fernandez-Hernando C, Fisher EA, **Temel RE\***, Moore KJ. Nature. 2011;478:404-7 **(\* equal contribution to study)**
3. miRNA targeting of oxysterol-binding protein-like 6 regulates cholesterol trafficking and efflux. Ouimet M, Hennessy EJ, van Solingen C, Koelwyn GJ, Hussein MA, Ramkhelawon B, Rayner KJ, **Temel RE**, Perisic L, Hedin U, Maegdefessel L, Garabedian MJ, Holdt LM, Teupser D, Moore KJ. Arterioscler Thromb Vasc Biol. 2016 May;36(5):942-51

*Determination of the molecular mechanisms of transintestinal cholesterol excretion*

A way to reduce LDL cholesterol, the primary risk factor for coronary heart disease (CHD), is to increase cholesterol excretion from the body. The majority of fecal cholesterol is derived from bile. However, there is mounting evidence that the liver may create lipoproteins that can traffic excess cholesterol to the intestine. Through a process known as transintestinal cholesterol excretion (TICE), lipoprotein-associated cholesterol is internalized by the enterocytes and is secreted into the lumen of the small intestine. Our lab studies TICE using the Niemann-Pick C1-like 1 hepatic transgenic (L1Tg) mouse. While working as a post-doctoral scholar in Dr. Larry Rudel’s lab and collaborating with Dr. Liqing Yu, we found that L1Tg mice had an 80-90% decrease in biliary cholesterol but had normal cholesterol absorption and fecal cholesterol excretion (1). Dr. Mark Brown and I subsequently reported that L1Tg mice had normal macrophage-to-feces reverse cholesterol transport (2) thus indicating that TICE was stimulated in this mouse model. We have also shown that apoB-containing lipoproteins may feed cholesterol into the TICE pathway since reducing hepatic VLDL secretion decreased fecal cholesterol excretion in L1Tg mice (3). Although most of the molecular pathways contributing to TICE are undefined, we recently reported that flavin monooxygenase 3 (FMO3), a central regulator of cholesterol balance, was dramatically reduced in L1Tg mice (4). We believe our ongoing studies on TICE could lead to TICE-stimulating therapies that could be used to reduce the risk of CHD.

1. Hepatic Niemann-Pick C1-like 1 regulates biliary cholesterol concentration and is a target of ezetimibe. **Temel RE**, Tang W, Ma Y, Rudel LL, Willingham MC, Ioannou YA, Davies JP, Nilsson LM, Yu L. J Clin Invest. 2007;117:1968-78
2. Biliary sterol secretion is not required for macrophage reverse cholesterol transport. **Temel RE**, Sawyer JK, Yu L, Lord C, Degirolamo C, McDaniel A, Marshall S, Wang N, Shah R, Rudel LL, Brown JM. Cell Metab. 2010;12:96-102
3. Reduction of VLDL secretion decreases cholesterol excretion in Niemann-Pick C1-like 1 hepatic transgenic mice. Marshall SM, Kelley KL, Davis MA, Wilson MD, McDaniel AL, Lee RG, Crooke RM, Graham MJ, Rudel LL, Brown JM, **Temel RE**. PLoS One. 2014;9:e84418
4. The TMAO-Generating Enzyme Flavin Monooxygenase 3 Is a Central Regulator of Cholesterol Balance. Warrier M, Shih DM, Burrows AC, Ferguson D, Gromovsky AD, Brown AL, Marshall S, McDaniel A, Schugar RC, Wang Z, Sacks J, Rong X, Vallim TA, Chou J, Ivanova PT, Myers DS, Brown HA, Lee RG, Crooke RM, Graham MJ, Liu X, Parini P, Tontonoz P, Lusis AJ, Hazen SL, **Temel RE**, Brown JM. Cell Rep. 2015;10:326-338.

**Complete List of Published Work in My Bibliography:**

[**http://www.ncbi.nlm.nih.gov/sites/myncbi/ryan.temel.1/bibliograpahy/40455165/public/?sort=date&direction=ascending**](http://www.ncbi.nlm.nih.gov/sites/myncbi/ryan.temel.1/bibliograpahy/40455165/public/?sort=date&direction=ascending)

1. **Research Support**

Current

Title: *Therapeutic targeting of metabolic microRNAs as a new treatment paradigm for NASH*

Principal Investigator: Sakari Kauppinen

Co-Investigator: Ryan E. Temel

Agency: Novo Nordisk Foundation

Grant No.: 33438

Period: 1/1/2019– 12/31/2024

Major Goal of Research: Identify antimiR compounds for effective and safe inhibition of miR-128-1

and miR-22 and assess their therapeutic potential to treat NASH in highly relevant mouse and non-human

primate NASH models.

Title: *Targeting microRNA-33 to reduce intracranial atherosclerosis and other neurovascular hallmarks of vascular cognitive impairment and dementia*

Principal Investigator: Ryan E. Temel

Agency: NIH, NINDS

Grant No.: R21NS111979

Period: 04/01/2019 – 03/31/2021

Major Goal of Research: Determine whether miR-33 antagonism reduces intracranial atherosclerosis and other neurovascular pathologies associated with vascular cognitive impairment and dementia

Title: *TRAF6 nanoimmunotherapy to resolve plaque inflammation*

Principal Investigator: Willem Mulder

Co-Investigator: Ryan E. Temel

Agency: NIH, NHLBI

Grant No.: R01 HL144072

Period: 7/1/2018– 06/30/2022

Major Goal of Research: Induce plaque regression in a nonhuman primate atherosclerosis model by TRAF6i-HDL.

Title: *Contributions of Hepatic and Intestinal Pathways to Cholesterol Excretion*

Principal Investigator: Gregory Graf

Co-Investigator: Ryan E. Temel

Agency: NIH, NIDDK

Grant No.: R01DK113625

Period: 09/13/17 – 07/31/22

Major Goal of Research: Determine how transintestinal cholesterol elimination (TICE) is regulated by biliary cholesterol output, plasma lipoprotein donors, and an enterohepatic signaling axis involving bile acids.

Previous

Title: *A novel mechanism for ART-associated dyslipidemia and atherosclerosis*

Principal Investigator:Changcheng Zhou

Co-Investigator: Ryan Temel

Agency: NIH, NHLBI

Grant No.: R01HL123358

Period**:** 08/01/15 - 05/31/19

Major Goal of Research: Determine whether antiviral therapy for HIV increases dyslipidemia and atherosclerosis by stimulating PXR.

Title: *Effects of Anti-miR-33 on Atherosclerosis Regression and RCT in Nonhuman Primates*

Principal Investigator:Ryan E. Temel

Agency: NIH, NHLBI

Grant No.: R01HL111932

Period**:** 02/01/13 – 11/30/17 (No cost extension until 11/30/18)

Major Goal of Research: Determine the impact of miR-33a/b antagonism on atherosclerosis regression and reverse cholesterol transport using a nonhuman primate model.