Personal Statement

1. Long-term career goal: My long-term career goal is to serve as an independent investigator in translational imaging research. With the increasing capabilities of noninvasive imaging, translational research at the intersection of clinical needs and engineering innovations is now needed more than ever. Trained in clinical medicine, I am particularly interested in the underlying pathology and pathophysiology of human diseases. Meanwhile, I have a longstanding interest in engineering and believe technology should become an integral piece of modern medicine. Cardiovascular diseases are associated with an enormous social and economic burden. Imaging allows me to approach the pathophysiology of cardiovascular diseases from a unique perspective that fits perfectly with my personal interest in technological advances.

2. Translational Research Scholars Program (TRSP): My previous research training was focused on quantitative MRI of atherosclerosis. The University of Washington (UW) Vascular Imaging Lab provides a multidisciplinary environment, where I get to work and communicate with MR physicists, computer scientists, and biostatisticians on a daily basis. Through the many projects I have finished and professional conferences I attended in the past years, I have accumulated a broad knowledge in vascular medicine, vascular pathology, MR physics and epidemiology, and acquired a spectrum of research and scientific skills. I value a broad range of knowledge and a multidisciplinary know-now, which are critically needed in translational research.

To pursue an academic career, it is essential to formulate independent study plans, manage resources, interact within interdisciplinary fields, and bring together key research into presentations, publications, and follow-on programs. However, grant application is challenging for early stage investigators, who usually face very limited resources to fully develop their own proposals. According to the National Institutes of Health (NIH), the average age of researchers who won their first major research grant (R01 or equivalent) has increased to >40 in recent years. In such a competitive environment, the TRSP program will greatly boost my first NIH grant application. The program provides pilot research funding, supervised grant development, and feedback from mentors and peers with broad backgrounds, all of which are essential components to develop a competitive proposal as an early stage investigator. My goal is to collect preliminary data with the pilot research funding, fully develop the study designs/methods/analyses, build necessary collaborations within the UW community, and eventually come up with a high-quality R01 application by the end of the TRSP program.

In the 1-year pilot study, I would like to evaluate the performance of a simultaneous vessel wall T1/T2 mapping technique against the conventional multi-contrast MRI in terms of image quality and quantitative measurements on plaque burden and lipid content. This will be studied in 6 healthy volunteers and 10 patients with asymptomatic carotid plaque. Successful completion of the study will provide the scientific premise for a federally funded study to validate novel imaging markers of plaque composition based on quantitative T1/T2 mapping and to evaluate their sensitivity in detecting plaque lipid depletion during lipid-lowering therapy. Despite the great success of MRI in noninvasive characterization of carotid plaque composition, existing techniques are cumbersome to use when quantitative measures are needed. Therefore, the proposed studies will address an important research question with potential to expand and proliferate.

3. Translational research goals in the next five years: My goal in the next few years is to build a research program that focuses on development and translation of novel quantitative MRI methods for monitoring therapeutic response in an objective, effective, and time-efficient manner. Rapid progress in MR sequence design, image reconstruction, and image analysis present new opportunities for devising accurate, reproducible, and automatic MR measures of human diseases. However, physicians and pharmaceutical companies are lack of knowledge of technological potentials and limitations while engineers are not familiar with clinical needs and requirements concerning surrogate biomarkers. I am well positioned to overcome such barriers with my multidisciplinary background in clinical medicine, quantitative image analysis, and biostatistics. Because of my extensive experience with atherosclerosis research, I plan to start with projects exploring simultaneous vessel wall T1/T2 mapping in assessing in vivo effects of lipid-lowering and/or anti-inflammatory drugs. Research can be expanded to include other diseases in future projects (e.g. changes in hemodynamic condition under prostacyclin receptor agonists in pulmonary arterial hypertension).

Collectively, my unique background has been dedicated to defining an interdisciplinary path in the field of cardiovascular MR. The TRSP program will provide me with a protected opportunity in a critical stage of my career to oversee all research activities of a multidisciplinary team for a panoramic view of translational imaging research, to achieve scientific findings that will open up new avenues for future research and grant application, and to expand my skills in grantsmanship. These outcomes will promote my scientific career and allow me to perform high-quality translational research as an independent investigator in the long run.

Research Plan

A. Specific Aims: Atherosclerosis is a highly prevalent, progressive condition.[1-3] Myocardial infarction and ischemic stroke are the most devastating complications of atherosclerotic cardiovascular disease, which are the leading causes of death and disability in the US.[1] Although atherosclerotic plaques typically become flow-limiting as they progress, human autopsy studies have revealed that the majority of acute cardiovascular events are the consequence of intraluminal thrombosis triggered by atherosclerotic plaque rupture rather than chronic occlusion.[4-7] Atherosclerotic plaques prone to rupture are terms "high-risk" or "vulnerable" plaques, which demonstrate distinct differences in tissue composition from stable plaques in histopathological studies.[7,8] Consequently, tremendous efforts have been dedicated to develop noninvasive imaging methods for in vivo characterization of plaque composition as they pave the way to personalized risk assessment and treatment.[9]

Among clinical imaging modalities, MRI holds the best promise for characterizing vulnerable plaques as it offers superb soft tissue contrast and is highly plastic to specific needs in tissue characterization.[10,11] Previous work by our group as well as other groups has established the capability of high-resolution vessel wall MRI in differentiating plaque components in carotid arteries.[12-16] As different plaque components have different T1/T2 relaxation times, a multi-sequence protocol (multi-contrast MRI) including T1-weighted, T2-weighted, and time-of-flight sequences is typically used, in which each component displays a unique combination of hyper- or hypo-intense signals (relative signal intensities as compared to a reference tissue) on multi-contrast-weighted images.[13,15] MRI measures of carotid plaque composition serve as imaging biomarkers in individual risk assessment and surrogate endpoints in clinical trials, which showed promising results in preliminary studies.[17-24]

However, current methods based on a combination of T1-/T2-weighted sequences have a number of notable limitations: **1)** Qualitative nature: In T1-/T2-weighted imaging, tissue T1/T2 relaxation properties are encoded in arbitrary signal intensity values. Thus, plaque components are identified by comparing to the signal intensity of a reference tissue (e.g. adjacent muscle), which is qualitative (hyper-, iso-, or hypo-intensity), subjective, and strongly influenced by imaging parameters and coil sensitivity; **2)** Errors from image misregistration: In multi-contrast MRI, several sequences need to be coregistered to classify plaque components, but misregistration between separate sequences is inevitable; **3)** Long scan duration: The use of multiple separate sequences results in prolonged acquisition time and increased susceptibility to motion artifacts. These limitations are particularly problematic for quantitative measurements,[25-28] which are needed for noninvasively monitoring plaque progression and/or therapeutic response.

Our long-term goal is to improve the prognosis of patients with atherosclerotic cardiovascular disease. In this application, we aim to investigate the feasibility and value of simultaneous vessel wall T1/T2 mapping for quantitative characterization of carotid plaque. Quantitative T1/T2 mapping of carotid plaque will eliminate the need for signal intensity normalization. Furthermore, a technique that allows simultaneous T1/T2 mapping will provide naturally coregistered images and avoid potential errors from image misregistration. Thus, we hypothesize that simultaneous T1/T2 mapping of carotid plaque will substantially improve the reproducibility of tissue characterization by carotid MRI, which is particularly helpful for longitudinal and/or multi-center studies.

Aim 1: Validate with histology a 3D high-resolution MRI sequence that performs simultaneous vessel wall T1/T2 mapping in quantifying carotid plaque components. We recently developed a new technique that allows simultaneous T1/T2 mapping of bilateral carotid arteries with large longitudinal coverage (12 cm) and 3D isotropic spatial resolution (0.8 mm) in a single 8-minute scan. For validation, carotid endarterectomy patients will be scanned prior to surgery. Using histology as the reference standard, we will test the hypothesis that plaque characterization by simultaneous T1/T2 mapping shows a higher correlation with histology than that by conventional multi-contrast MRI. **Aim 2:** Test the hypothesis that simultaneous vessel wall T1/T2 mapping improves test-retest reproducibility of carotid plaque tissue characterization compared to conventional multi-contrast MRI. We will perform repeated MRIs on patients with carotid atherosclerosis and compare test-retest reproducibility metrics between simultaneous T1/T2 mapping and multi-contrast MRI in quantifying carotid plaque composition. **Aim 3:** Test the hypothesis that simultaneous T1/T2 mapping of carotid plaque detects plaque lipid depletion within 6 months of statin therapy initiation in patients with hypercholesterolemia. We will perform repeated MRIs on patients with newly diagnosed hypercholesterolemia at baseline (prior to statin therapy) and every 3 months thereafter (post-treatment) till one year. Plaque lipid depletion will be measured as serial changes in percent lipid core volume and modeled against time using linear mixed models.

B. Significance: *Scientific implications*: Simultaneous vessel wall T1/T2 mapping overcomes the intrinsic limitations of current methods (i.e. using relative signal intensity information and multiple separate scans). As such, the proposed method is expected to provide improved accuracy and reproducibility in characterizing

carotid plaque composition over currently available methods. Given the large measurement variability of current methods which often overshadows biological signals,[25-28] the new method can be a powerful tool to facilitate serial imaging studies and multicenter efforts that are critically needed to expand our understanding of vulnerable plaques and effective therapies. *Clinical implications*: With devastating complications such as myocardial infarction and ischemic stroke, the role of prevention cannot be overemphasized in the clinical management of atherosclerosis. Identification of high-risk patients presents a time window for prevention with lifestyle changes and/or medical therapies. As imaging allows physicians to monitor individual response to therapies, preventive strategies can be tailored on an individual basis. As such, the proposed work has potential to promote precision medicine in atherosclerotic cardiovascular disease.

C. Innovation: *Technique*: A fast 3D high-resolution vessel wall T1/T2 mapping approach to carotid plaque characterization will be established and validated. This is highly innovative because it offers multiple advantages over current methods in vessel wall MRI. On the other hand, conventional T1 and T2 mapping techniques cannot be easily used for vessel wall MRI due to challenges with vessel wall visualization. Notably, a few recent studies including our own work have explored either T1 or T2 mapping of carotid vessel wall.[29-32] However, the proposed technique will be the first in the field to allow simultaneous T1/T2 mapping, avoiding separate scans and potential errors from image misregistration. *Study design*: Aim 1&2 will be the first head-to-head comparison between vessel wall T1/T2 mapping and conventional multi-contrast MRI in terms of diagnostic performance and test-retest reproducibility. Such data will be helpful for understanding the strengths and limitations of MRI techniques that we are using, with implications for planning future serial or multicenter studies. *Study design*: Aim 3 will determine the time course of plaque lipid depletion in the first year of statin therapy initiation. Changes in plaque lipid content have not been detectable in <6 months previously. Sensitive surrogate endpoints that are able to inform about drug efficacy early will be extremely valuable in clinical trials.

D. Approach: Study approach has been outlines under each aim in **A. Specific Aims**. All study procedures will be HIPAA-compliant and receive approval from the University of Washington Human Subjects Committee. *Participants*: We plan to recruit three groups of patients: 1) patients scheduled for carotid endarterectomy (Aim 1-validation); 2) patients with carotid plaque identified from the ultrasound laboratories (Aim 2-reproducibility); 3) patients with newly diagnosed hypercholesterolemia who will initiate statin therapy for primary prevention (Aim 3-longitudinal cohort study). *Simultaneous vessel wall T1/T2 mapping*: Based on our recently published T1 mapping technique,[32] the new sequence (iGOAL-SNAP) introduces variable-duration T2 preparation to allow simultaneous T1/T2 mapping. Phantoms studies showed promising results (Figure). *Histopathological processing and analysis*: Carotid endarterectomy specimens will be collected during surgery and immediately transferred, processed and analyzed consistently with previous publications by our group.[12-14] *Scan procedures*: Subjects will be scanned on a 3T scanner (Ingenia CX, Philips Healthcare) with an 8-channel carotid coil. Aim 1 will scan subjects on the day prior to scheduled surgery. Aim 2 will scan subjects twice within one week. Aim 3 will scan subjects before statin therapy initiation and every 3 months thereafter till one year.

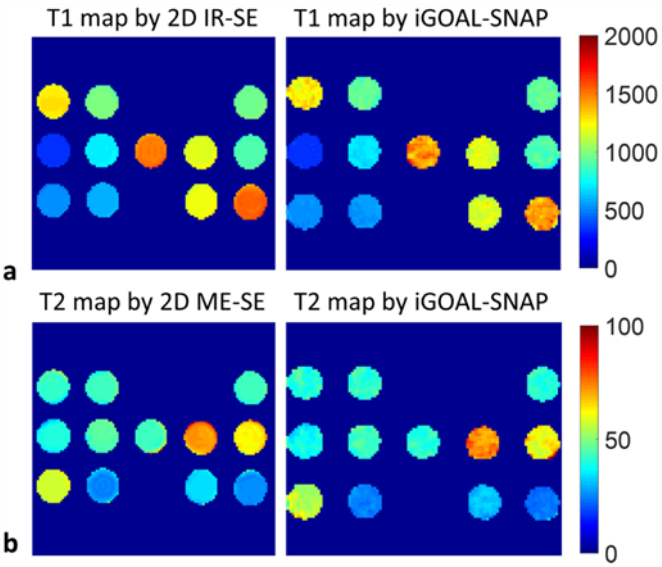

Figure. Phantom scans comparing T1/T2 mapping by iGOAL-SNAP (spatial resolution: 0.8 mm 3D isotropic) to standard 2D sequences (spatial resolution: 1.6x1.6x5 mm^3) including IR-SE for T1 mapping **(a)** and ME-SE for T2 mapping **(b)**. Overall the T1/T2 maps of phantoms are similar between iGOAL-SNAP and the reference methods (linear regression lines: R^2=0.99 for both). Due to smaller voxel size and reduced scan time, iGOAL-SNAP has lower SNR, which caused signal inhomogeneity in certain phantoms. But its performance in the range of clinically relevant T1 (<1000 ms; relevant to intraplaque hemorrhage) and T2 (<60 ms; relevant to lipid core) values appear to be satisfactory.

D. Translational Impact: Successful achievement of these aims will establish a fast, objective, accurate, and reproducible imaging method to noninvasively identify high-risk patients and monitor individual response to therapies. These properties are highly desirable in the clinical setting and will facilitate the translation of MR plaque imaging from research into clinical practice. Furthermore, a clinical viable approach to therapeutic response can be adopted in clinical trials to assess the efficacy of new lipid-modifying agents or regimens.

References

1. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, de Ferranti SD, Floyd J, Fornage M, Gillespie C, Isasi CR, Jiménez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Mackey RH, Matsushita K, Mozaffarian D, Mussolino ME, Nasir K, Neumar RW, Palaniappan L, Pandey DK, Thiagarajan RR, Reeves MJ, Ritchey M, Rodriguez CJ, Roth GA, Rosamond WD, Sasson C, Towfighi A, Tsao CW, Turner MB, Virani SS, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS, Muntner P. Heart Disease and Stroke Statistics—2017 Update: A Report From the American Heart Association. *Circulation*. 2017;135:e146-e603.

2. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2015;385:117-171.

3. Fernandez-Friera L, Penalvo JL, Fernandez-Ortiz A, Ibanez B, Lopez-Melgar B, Laclaustra M, Oliva B, Mocoroa A, Mendiguren J, Martinez DVV, Garcia L, Molina J, Sanchez-Gonzalez J, Guzman G, Alonso-Farto JC, Guallar E, Civeira F, Sillesen H, Pocock S, Ordovas JM, Sanz G, Jimenez-Borreguero LJ, Fuster V. Prevalence, Vascular Distribution, and Multiterritorial Extent of Subclinical Atherosclerosis in a Middle-Aged Cohort: The PESA (Progression of Early Subclinical Atherosclerosis) Study. *Circulation*. 2015;131:2104-2113.

4. Falk E, Shah PK, Fuster V. Coronary Plaque Disruption. *Circulation*. 1995;92:657-671.

5. Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons from sudden coronary death - A comprehensive morphological classification scheme for atherosclerotic lesions. *Arterioscler Thromb Vasc Biol*. 2000;20:1262-1275.

6. Spagnoli LG, Mauriello A, Sangiorgi G, Fratoni S, Bonanno E, Schwartz RS, Piepgras DG, Pistolese R, Ippoliti A, Holmes DR. Extracranial thrombotically active carotid plaque as a risk factor for ischemic stroke. *JAMA*. 2004;292:1845-1852.

7. Redgrave J, Lovett JK, Gallagher PJ, Rothwell PM. Histological assessment of 526 symptomatic carotid plaques in relation to the nature and timing of ischemic symptoms - The Oxford plaque study. *Circulation*. 2006;113:2320-2328.

8. Narula J, Nakano M, Virmani R, Kolodgie FD, Petersen R, Newcomb R, Malik S, Fuster V, Finn AV. Histopathologic characteristics of atherosclerotic coronary disease and implications of the findings for the invasive and noninvasive detection of vulnerable plaques. *J Am Coll Cardiol*. 2013;61:1041-1051.

9. Fleg JL, Stone GW, Fayad ZA, Granada JF, Hatsukami TS, Kolodgie FD, Ohayon J, Pettigrew R, Sabatine MS, Tearney GJ, Waxman S, Domanski MJ, Srinivas PR, Narula J. Detection of High-Risk Atherosclerotic Plaque: Report of the NHLBI Working Group on Current Status and Future Directions. *JACC: Cardiovascular Imaging*. 2012;5:941-955.

10. Yuan C, Mitsumori LM, Beach KW, Maravilla KR. Carotid atherosclerotic plaque: Noninvasive MR characterization and identification of vulnerable lesions. *Radiology*. 2001;221:285-299.

11. Kerwin WS, Hatsukami T, Yuan C, Zhao XQ. MRI of carotid atherosclerosis. *AJR Am J Roentgenol*. 2013;200:W304-W313.

12. Cai JM, Hatsukami TS, Ferguson MS, Small R, Polissar NL, Yuan C. Classification of human carotid atherosclerotic lesions with in vivo multicontrast magnetic resonance imaging. *Circulation*. 2002;106:1368-1373.

13. Saam T, Ferguson MS, Yarnykh VL, Takaya N, Xu D, Polissar NL, Hatsukami TS, Yuan C. Quantitative evaluation of carotid plaque composition by in vivo MRI. *Arterioscler Thromb Vasc Biol*. 2005;25:234-239.

14. Cai JM, Hatsukami TS, Ferguson MS, Kerwin WS, Saam T, Chu BC, Takaya N, Polissar NL, Yuan C. In vivo quantitative measurement of intact fibrous cap and lipid-rich necrotic core size in atherosclerotic carotid plaque: comparison of high-resolution, contrast-enhanced magnetic resonance imaging and histology. *Circulation*. 2005;112:3437-3444.

15. Trivedi RA, U-King-Im J, Graves MJ, Horsley J, Goddard M, Kirkpatrick PJ, Gillard JH. Multi-sequence in vivo MRI can quantify fibrous cap and lipid core components in human carotid atherosclerotic plaques. *Eur J Vasc Endovasc Surg*. 2004;28:207-213.

16. Wasserman BA, Smith WI, Trout HH, Cannon RO, Balaban RS, Arai AE. Carotid artery atherosclerosis: in vivo morphologic characterization with gadolinium-enhanced double-oblique MR imaging--Initial results. *Radiology*. 2002;223:566-573.

17. Gupta A, Baradaran H, Schweitzer AD, Kamel H, Pandya A, Delgado D, Dunning A, Mushlin AI, Sanelli PC. Carotid Plaque MRI and Stroke Risk: A Systematic Review and Meta-analysis. *Stroke*. 2013;44:3071-3077.

18. Takaya N, Yuan C, Chu BC, Saam T, Underhill H, Cai JM, Tran N, Polissar NL, Isaac C, Ferguson MS, Garden GA, Cramer SC, Maravilla KR, Hashimoto B, Hatsukami TS. Association between carotid plaque characteristics and subsequent ischemic cerebrovascular events: a prospective assessment with MRI - initial results. *Stroke*. 2006;37:818-823.
19. Saam T, Hetterich H, Hoffmann V, Yuan C, Dichgans M, Poppert H, Koeppel T, Hoffmann U, Reiser MF, Bamberg F. Meta-analysis and systematic review of the predictive value of carotid plaque hemorrhage on cerebrovascular events by magnetic resonance imaging. *J Am Coll Cardiol*. 2013;62:1081-1091.
20. Sun J, Zhao XQ, Balu N, Neradilek MB, Isquith DA, Yamada K, Canton G, Crouse JR, Anderson TJ, Huston JR, O'Brien K, Hippe DS, Polissar NL, Yuan C, Hatsukami TS. Carotid Plaque Lipid Content and Fibrous Cap Status Predict Systemic CV Outcomes: The MRI Substudy in AIM-HIGH. *JACC Cardiovasc Imaging*. 2017;10:241-249.
21. Corti R, Fuster V, Fayad ZA, Worthley SG, Helft G, Smith D, Weinberger J, Wentzel J, Mizsei G, Mercuri M, Badimon JJ. Lipid lowering by simvastatin induces regression of human atherosclerotic lesions: two years' follow-up by high-resolution noninvasive magnetic resonance imaging. *Circulation*. 2002;106:2884-2887.
22. Underhill HR, Yuan C, Zhao XQ, Kraiss LW, Parker DL, Saam T, Chu B, Takaya N, Liu F, Polissar NL, Neradilek B, Raichlen JS, Cain VA, Waterton JC, Hamar W, Hatsukami TS. Effect of rosuvastatin therapy on carotid plaque morphology and composition in moderately hypercholesterolemic patients: a high-resolution magnetic resonance imaging trial. *Am Heart J*. 2008;155:581-584.
23. Zhao XQ, Dong L, Hatsukami T, Phan BA, Chu B, Moore A, Lane T, Neradilek MB, Polissar N, Monick D, Lee C, Underhill H, Yuan C. MR imaging of carotid plaque composition during lipid-lowering therapy: a prospective assessment of effect and time course. *J Am Coll Cardiol Img*. 2011;4:977-986.
24. Sun J, Balu N, Hippe DS, Xue Y, Dong L, Zhao X, Li F, Xu D, Hatsukami TS, Yuan C. Subclinical carotid atherosclerosis: short-term natural history of lipid-rich necrotic core--a multicenter study with MR imaging. *Radiology*. 2013;268:61-68.
25. Wasserman BA, Astor BC, Sharrett AR, Swingen C, Catellier D. MRI measurements of carotid plaque in the atherosclerosis risk in communities (ARIC) study: methods, reliability and descriptive statistics. *J Magn Reson Imaging*. 2010;31:406-415.
26. Li F, Yarnykh VL, Hatsukami TS, Chu B, Balu N, Wang J, Underhill HR, Zhao X, Smith R, Yuan C. Scan-rescan reproducibility of carotid atherosclerotic plaque morphology and tissue composition measurements using multicontrast MRI at 3T. *J Magn Reson Imaging*. 2010;31:168-176.
27. Sun J, Zhao XQ, Balu N, Hippe DS, Hatsukami TS, Isquith DA, Yamada K, Neradilek MB, Canton G, Xue Y, Fleg JL, Desvigne-Nickens P, Klimas MT, Padley RJ, Vassileva MT, Wyman BT, Yuan C. Carotid magnetic resonance imaging for monitoring atherosclerotic plaque progression: a multicenter reproducibility study. *Int J Cardiovasc Imaging*. 2015;31:95-103.
28. Touze E, Toussaint JF, Coste J, Schmitt E, Bonneville F, Vandermarcq P, Gauvrit JY, Douvrin F, Meder JF, Mas JL, Oppenheim C. Reproducibility of high-resolution MRI for the identification and the quantification of carotid atherosclerotic plaque components: consequences for prognosis studies and therapeutic trials. *Stroke*. 2007;38:1812-1819.
29. Biasiolli L, Lindsay AC, Chai JT, Choudhury RP, Robson MD. In-vivo quantitative T2 mapping of carotid arteries in atherosclerotic patients: segmentation and T2 measurement of plaque components. *J Cardiovasc Magn Reson*. 2013;15:69.
30. Coolen BF, Poot DH, Liem MI, Smits LP, Gao S, Kotek G, Klein S, Nederveen AJ. Three-dimensional quantitative T1 and T2 mapping of the carotid artery: Sequence design and in vivo feasibility. *Magn Reson Med*. 2016;75:1008-1017.
31. Yuan J, Graves MJ, Patterson AJ, Priest AN, Ruetten PPR, Usman A, Gillard JH. The development and optimisation of 3D black-blood R2* mapping of the carotid artery wall. *Magn Reson Imaging*. 2017.
32. Qi H, Sun J, Qiao H, Chen S, Zhou Z, Pan X, Wang Y, Zhao X, Li R, Yuan C, Chen H. Carotid Intraplaque Hemorrhage Imaging with Quantitative Vessel Wall T1 Mapping: Technical Development and Initial Experience. *Radiology*. 2017.(Accepted)

Applicant Name (Last, First, Middle):Sun, Jie

ITHS Institute of Translational Health Sciences
Accelerating Research. Improving Health.

DETAILED BUDGET

FROM 03/01/18 THROUGH 02/28/19

List PERSONNEL *(* Applicant Organization Only*)*
Enter Dollar Amounts Requested (omit cents) for Salary Requested and Fringe Benefits

Use Cal, Acad, or Summer to Enter Months Devoted to Project

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTAL
Jie Sun	PI	-	-	-	79,560	0	0	0
Chun Yuan	Mentor	-	-	-	253,044	0	0	0
Kristi Pimentel	Research Coordinator	0.60	-	-	66,057	3,303	1,073	4,376
SUBTOTALS →						3,303	1,073	4,376

CONSULTANT COSTS Research participants payments	800
EQUIPMENT *(Itemize)*	
SUPPLIES *(Itemize by category)*	
TRAVEL	
OTHER EXPENSES (Itemize by category) MRI scan time	4,800

CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	
SUBTOTAL DIRECT COSTS FOR BUDGET PERIOD		**$** 9,976
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATION COSTS	
TOTAL DIRECT COSTS FOR BUDGET PERIOD		$ 9,976
TOTAL INDIRECT COSTS FOR BUDGET PERIOD		$ 0
TOTAL COSTS FOR BUDGET PERIOD		**$ 9,976**

BUDGET JUSTIFICATION

PERSONNEL

Jie Sun, MD, Principle Investigator (1.2 calendar months effort [10% FTE]), is an Acting Instructor of Radiology at the University of Washington. He has eight years of research experience in cardiovascular MR. Dr. Sun will be responsible for the overall activities of this proposal, including: 1) application for institutional review board (IRB) approval; 2) implementation of MRI sequences; 3) study design and execution; 4) image analysis; 5) statistical analysis; 6) preparation of abstract(s) and manuscript(s) reporting study findings. No funds requested for Dr. Sun's effort. Fringe benefits are calculated at a rate of 24.9%.

Chun Yuan, PhD, Mentor, is a Professor in the Departments of Radiology and Bioengineering, and Co-Director of the Vascular Imaging Lab. Dr. Yuan has a Ph.D. in Biomedical Physics with expertise in MR imaging physics and software design, especially in the area of atherosclerosis imaging. He will serve as Primary Mentor for Dr. Sun on this project and provide ongoing guidance and support. Fringe benefits are calculated at a rate of 24.9%.

Kristi Pimentel, Research Coordinator (0.6 calendar months effort [5% FTE]). Ms. Pimentel will be responsible for: 1) obtaining IRB approval and cooperative clinics agreements; 2) recruiting and consenting eligible patients for participation in this study. Fringe benefits are calculated at a rate of 32.5%.

CONSULTANT COSTS

Subject Payment: IRB approved, to reimburse subjects for expense of travel, time off from work and study participation. ($50 per subject x 16 subjects = $800)

OTHER EXPENSES

MRI scan time: User fee of MR scanners. ($300 per subject [30 minutes] x 16 subjects = $4,800)

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: Sun, Jie

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

POSITION TITLE: Acting Instructor of Radiology

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Peking Union Medical College, Tsinghua University, Beijing, China	M.D.	07/2009	Medicine
University of Washington, Seattle, WA	Post-doctoral	06/2015	Radiology

A. Personal Statement

My previous research training has been focused on: 1) development and validation of MRI techniques for in vivo characterization of atherosclerotic plaques; and 2) applying novel imaging methods to understand key aspects of plaque progression and identify therapeutic opportunities. I believe medical imaging should be keen to derive quantitative imaging biomarkers that allow physicians to understand disease processes at new levels, thereby fundamentally increasing the effectiveness of radiology – a future I am dedicated to pursuing. This application builds logically on my previous training. Study procedures and hypotheses are based on my previous work. I have played a leading role in these related projects either by managing the project or by instructing junior fellows/graduate students.

B. Positions and Honors

Positions and Employment

2009-2015 Senior Fellow, Department of Radiology, University of Washington, Seattle, WA
2015- Acting Instructor, Department of Radiology, University of Washington, Seattle, WA

Other Experience and Professional Memberships

2010- Member, American Heart Association
2011- Member, International Society of Magnetic Resonance in Medicine
2012- Journals Reviewer for BioMed Research International, European Radiology, International Journal of Cardiovascular Imaging, Journal of Cardiovascular Magnetic Resonance, Journal of Magnetic Resonance Imaging, Neuroradiology
2012- Conference Reviewer for the American Heart Association Scientific Sessions

Honors

2003 Third-prize in the 19th College Student Physics Competition
Beijing Physics Society, Beijing, China
2003-2007 Annual scholarship (Top 20%) for excellent academic performance
Peking Union Medical College, Tsinghua University, Beijing, China
2007 AAA Student Award (for excellence in curriculum, character, and sports; 1st of 36 candidates)
Peking Union Medical College, Tsinghua University, Beijing, China
2008 First-class scholarship (Top 10%) for excellent academic performance
Peking Union Medical College, Tsinghua University, Beijing, China
2012 Imaging Sciences Research Day Trainee Award

Department of Radiology, University of Washington, Seattle, WA

2012 Melvin Judkins Young Clinical Investigator Award Finalist
American Heart Association

2014 Early Career Investigator Travel Award
American Heart Association

2016 Editor's Recognition Award for Special Distinction in Reviewing
Journal of Magnetic Resonance Imaging

2017 Mentored Clinical and Population Research Award (Career Development Award)
American Heart Association

C. Contribution to Science

1. MRI of carotid intraplaque hemorrhage

Atherosclerotic lesions generated in animal models lack certain high-risk features of human atherosclerotic plaques, which represents a major gap between basic research and clinical practice. My research harnesses in vivo high-resolution vessel wall MRI for studying the pathogenesis and natural history of high-risk plaque in humans. I and my colleagues were the first to discover that the development of intraplaque hemorrhage altered the trajectory of plaque progression, suggesting that intraplaque hemorrhage is able to fundamentally alter the biology of atherosclerosis (cover article in *JACC: Cardiovascular Imaging*). I further proposed that hemodynamic changes from acute decrease in diastolic blood pressure may comprise microvascular integrity and cause intraplaque hemorrhage (cover article in *ATVB*). Recently, I have been leading our efforts on quantitative characterization of IPH signals on MRI as this may provide novel information regarding the severity and activity of intraplaque hemorrhage.

a. Sun J, Underhill HR, Hippe DS, Xue Y, Yuan C, Hatsukami TS. (**2012**). Sustained acceleration in carotid atherosclerotic plaque progression with intraplaque hemorrhage: a long-term time course study. **J Am Coll Cardiol Img**, 5:798-804. (cover article; selected for the Editor's page) PMCID: PMC3422506

b. Sun J, Canton G, Balu N, Hippe DS, Xu D, Liu J, Hatsukami TS, Yuan C. (**2016**). Blood pressure is a major modifiable risk factor implicated in pathogenesis of intraplaque hemorrhage: an in vivo magnetic resonance imaging study. **Arterioscler Thromb Vasc Biol**, 36:743-749. (cover article) PMCID: PMC4808377

c. Wang X, Sun J*, Zhao X, Hippe DS, Hatsukami TS, Liu J, Li R, Canton G, Song Y, Yuan C, for the CARE-II study investigators. (**2017**). Ipsilateral plaques display higher T1 signals than contralateral plaques in recently symptomatic patients with bilateral carotid intraplaque hemorrhage. **Atherosclerosis**, 257:78-85. (*co-first author) PMCID: PMC5325786

d. Qi H, Sun J, Qiao H, Chen S, Zhou Z, Pan X, Wang Y, Zhao X, Li R, Yuan C, Chen H. (**2017**). Carotid intraplaque hemorrhage imaging with quantitative vessel wall T1 mapping: technical development and initial experience. **Radiology**. (Accepted)

2. MRI-based surrogate markers of cardiovascular risk

There is a longstanding quest to find novel measures of carotid atherosclerosis as effective surrogate markers of cardiovascular risk in clinical practice. Imaging measures of specific biological targets can also be utilized as efficacy endpoints in clinical trials to get early signals regarding drug effectiveness or enrich our knowledge regarding specific mechanisms of drugs. In the past years, I served as a lead researcher in multiple government- or industry-funded pharmaceutical trials and epidemiological studies. We standardized carotid MRI protocols for multicenter studies and established measurement reproducibility of carotid MRI. These methods have been used in several multicenter studies and led to novel insights into cardiovascular risk in patients treated with current standard of care. I and my colleagues described rapid changes in lipid-rich necrotic core with and without intraplaque hemorrhage and hypothesized that intraplaque hemorrhage may be accountable for a substantial portion of residual cardiovascular risk in the poststatin era. Lp(a) was found to be associated with high-risk plaque on MRI in the AIM-HIGH MRI substudy. We further demonstrated that carotid plaque lipid content and fibrous cap status as detected by MRI predicted cardiovascular events that occurred during the AIM-HIGH trial.

a. Sun J, Balu N, Hippe DS, Xue Y, Dong L, Zhao X, Li F, Xu D, Hatsukami TS, Yuan C. (**2013**). Subclinical carotid atherosclerosis: short-term natural history of lipid-rich necrotic core – a multicenter study with MR imaging. **Radiology**, 268:61-68. PMCID: PMC4059194

b. Zhao XQ, Hatsukami TS**,** Hippe DS**,** Sun J, Balu N, Isquith DA, Crouse JR, Anderson T, Huston J, Polissar N, O'Brien K, Yuan, C. (**2014**). Clinical factors associated with high-risk carotid plaque features as assessed by magnetic resonance imaging in patients with established vascular disease (from the AIM-HIGH study). **Am J Cardiol**, 114:1412-1419. PMCID: PMC4195846

c. Sun J*, Zhao XQ, Balu N, Hippe DS, Hatsukami TS, Isquith DA, Yamada K, Neradilek MB, Canton G, Xue Y, Fleg JL, Desvigne-Nickens P, Klimas MT, Padley RJ, Vassileva MT, Wyman BT, Yuan, C. (**2015**). Carotid magnetic resonance imaging for monitoring atherosclerotic plaque progression: a multicenter reproducibility study. **Int J Cardiovasc Imaging**, 31:95-103. (*corresponding author) PMCID: PMC4297722

d. Sun J, Zhao XQ, Balu N, Neradilek MB, Isquith DA, Yamada K, Canton G, Crouse JR 3rd, Anderson TJ, Huston J 3rd, O'Brien KD, Hippe DS, Polissar NL, Yuan C, Hatsukami TS. (**2017**). Carotid plaque lipid content and fibrous cap status predict systemic cardiovascular outcomes: the MRI substudy in AIM-HIGH. **J Am Coll Cardiol Img**, 10:241-249. PMCID: PMC5347460

3. Dynamic contrast-enhanced MRI for imaging the cardiovascular system

Atherosclerosis is recognized as an inflammatory disease rather than a bland lipid storage disorder. Dynamic contrast-enhanced MRI provides an appealing approach to probing inflammation in the cardiovascular system as it is free of ionizing radiation and uses routine contrast media. Over the years, I and my colleagues successfully implemented dynamic contrast-enhanced MRI protocols at multiple centers involving different vendor platforms, which facilitated multicenter collaborative studies using this technique. The technique was tested in patient populations and compared with ^{18F}-fluorodeoxyglucose positron emission tomography. These work extended our understanding of the molecular information and clinical implications of physiological measurements from dynamic contrast-enhanced MRI.

a. Sun J, Song Y, Chen H, Kerwin WS, Hippe DS, Dong L, Chen M, Zhou C, Hatsukami TS, Yuan C. (**2013**). Adventitial perfusion and intraplaque hemorrhage: a dynamic contrast-enhanced MRI study in the carotid artery. **Stroke**, 44:1031-1036. PMCID: PMC4059194

b. Wang J, Liu H, Sun J, Xue H, Xie L, Yu S, Liang C, Han X, Guan Z, Wei L, Yuan C, Zhao X, Chen H. (**2014**). Varying correlation between ^{18F}-fluorodeoxyglucose positron emission tomography and dynamic contrast-enhanced MRI in carotid atherosclerosis: implications for plaque inflammation. **Stroke**, 45:1842-1845.

c. Chen H, Sun J, Kerwin WS, Balu N, Neradilek MB, Hippe DS, Isquith D, Xue Y, Yamada K, Peck S, Yuan C, O'Brien K, Zhao XQ. (**2014**). Scan-rescan reproducibility of quantitative assessment of inflammatory carotid atherosclerotic plaque using dynamic contrast-enhanced 3T CMR in a multi-center study. **J Cardiovasc Magn Reson**, 16:51. PMCID: PMC4237824

d. Wang J, Chen H, Sun J*, Hippe DS, Zhang H, Yu S, Cai J, Xie L, Cui B, Yuan C, Zhao X, Yuan W, Liu H. (**2017**). Dynamic contrast-enhanced MR imaging of carotid vasa vasorum in relation to coronary and cerebrovascular events. **Atherosclerosis**, 263:420-426. (*co-first author)

4. Improving the usability and efficiency of vessel wall MRI

Vessel wall MRI is currently only accessible at academic imaging centers with many years of experience in cardiovascular MR research. One major barrier to its widespread use in clinical settings relates to the sophisticated image analysis process. Another hurdle is long scan times associated with 2D multicontrast acquisition. One of my research focuses has been on developing and validating 3D imaging protocols and automated analytic algorithms.

a. Chiu B, Sun J, Zhao X, Wang J, Balu N, Yuan C, Kerwin WS. (**2011**). Fast plaque burden assessment of the femoral artery using 3D black-blood MRI and automated segmentation. **Med Phys**, 38:5370-5384. PMCID: PMC3189974

b. Liu W, Balu N, Sun J, Zhao X, Chen H, Yuan C, Zhao H, Xu J, Wang G, Kerwin WS. (**2012**). Segmentation of carotid plaque using multicontrast 3D gradient echo MRI. **J Magn Reson Imaging**, 35:812-819. PMCID: PMC3298637

c. Yoneyama T, Sun J*, Hippe DS, Balu N, Xu D, Kerwin WS, Hatsukami TS, Yuan, C. (**2016**). In vivo semi-automatic segmentation of multicontrast cardiovascular magnetic resonance for prospective cohort studies on plaque tissue composition: initial experience. **Int J Cardiovasc Imaging**, 32:73-81. (*co-first and corresponding author) PMCID: PMC4707978

d. Shu H, Sun J*, Hatsukami TS, Balu N, Hippe DS, Liu H, Kohler TR, Zhu W, Yuan C. (**2017**). Simultaneous non-contrast angiography and intraplaque hemorrhage (SNAP) imaging: comparison with contrast-enhanced MR angiography for measuring carotid stenosis. **J Magn Reson Imaging**, 46:1045-1052. (*corresponding author) PMCID: PMC5545168

Complete List of Published Work in Google Scholar:
https://scholar.google.com/citations?user=6K8lRv0AAAAJ&hl=en

D. Research Support

Ongoing Research Support

ISSBRIL0369 D5130L00114 Zhao (PI) 01/28/2015 – 10/31/2017
AstraZeneca
MRI Reproducibility of Lower Extremity PAD
The goal of this project is to conduct a reproducibility study using 3D-MRI and DCE techniques to establish variance of plaque and thrombus burden, atherosclerotic lesion characteristics and vessel wall neovascularization and inflammatory status.
Role: Co-Investigator

17MCPRP33671077 Sun (PI) 07/01/2017 – 06/30/2019
American Heart Association
Quantitative vessel wall T1 mapping for noninvasive characterization of carotid intraplaque hemorrhage
The goal of this project is to develop and validate a 3D vessel wall T1 mapping technique and to build an integrated biomarker from plaque T1 maps that estimates total methemoglobin deposition within atherosclerotic plaques.
Role: Principal Investigator