Boston Claude D. Pepper Older Americans Independence Center
For Function Promoting Therapies

Annual Progress Report, May 2019

BOSTON PEPPER CENTER

A. SPECIFIC AIMS

In its third year of funding, Boston OAIC's integrated translational research and training programs supported 3 research education career (REC) awards, 3 development projects, and 3 pilot and exploratory science (PES) projects, and several external projects linked by their thematic focus on FPTs. The LAC will continue to direct the OAIC Program, organize monthly meetings of its Executive Committee, provide administrative support to all OAIC projects, and oversight to its resource cores. The LAC will continue to organize a weekly conference for OAIC members and trainees, and a Visiting Speaker program. During year 03, the OAIC issued a request for application for the next round of REC and PESC awardees. There were 17 applicants, with 5 chosen for funding (2 REC, 3 PESC), see **Table 1**. The LAC will continue to nurture collaborations with the Glenn Center for Aging and the Roybal Center. The REC will continue its mentorship and training of the currently funded REC candidates and foster their career advancement and transition to independent R series funding. Two of our REC awardees (Drs. Sinha and Lustgarten) will conclude their training periods this year. Dr. Lustgarten has won a K01 Award to support his ongoing work, and Dr. Sinha received a Beeson Award. The PESC continues its mentorship and training of the currently funded PESC candidates. Progress by the 1st round of awardees is shown in **Table 2**. In January 2018, a second call for applications was published, with an application due date of March 1. Seventeen applications were received and reviewed by the Boston Pepper Center steering committee, and new awardees were notified in May 2018. Early progress of the 2nd round of awardees is indicated in **Table 3**. The FAC will continue to solicit new projects and provide consultative services to the Pepper Community.

Specific aims of Boston OAIC are to:

1. Foster the growth of a collaborative, inter-disciplinary, cross-institutional community of translational scientists to facilitate FPT research across the entire spectrum of translational science, including:
    a. Mechanism elucidation, target identification and preclinical proof-of-concept studies of FPT candidates
    b. Development of biomarkers of efficacy of FPTs
    c. Development and validation of novel functional outcome measures for use in efficacy trials of FPTs
    d. Investigation of the epidemiology of functional limitations and disability in older Americans, and
    e. Randomized trials of FPTs
2. Maintain an interdisciplinary **Research Education Component (REC)** to find the most talented early career scientists and train them using a combination of didactic education and mentored research training
3. Maintain appropriate **Resource Core Facilities** to support inter-disciplinary research programs
4. Promote interdisciplinary collaborations and integration of OAIC teams and programs (**PROMOTE**)
5. Facilitate the commercialization of OAIC's inventions

Boston OAIC's research program is founded on a platform of four cores:

1. Leadership and Administrative Core (LAC)
2. Research Education Core (REC)
3. Resource Cores (RC) and Developmental Projects (DP)
4. Pilot and Exploratory Studies Core (PESC)

These specific aims have not changed.

List of new projects in Year 03 (REC, PESC and Developmental, Table 1):

Table 1. Year 02 PESC, REC and DP-Supported Research Projects

Candidate	Award type	Project
Ron Neppl, PhD	PESC	**Loss of a lncRNA exacerbates aging associated functional decline of skeletal muscle**. The project is based on a novel gene identified in a screen of lncRNAs whose expression is dysregulated in an established mouse model of skeletal muscle hypertrophy. Gm14635, now referred to as Kratos appears necessary for the maintenance of muscle mass and myogenic expression of transcription factors, and decreases with advancing age, thus suggesting that dysregulation of Kratos may be involved in aging related sarcopenia.
Lien Quach, MD, PhD, MPH	REC	**Physical function: the roles of social engagement and cognitive impairment**. The project is to examine the protective effect of rich social engagement on MCI at the baseline and physical function after 4 years of follow-up using the archive data from Boston

		Rehabilitative Impairment Study of the Elderly Boston (Boston RISE).
Shivani Sahni, PhD	PESC	**Mediterranean diet, related antioxidants and frailty**. The study proposes that higher intake of antioxidants from a Mediterranean style diet will be associated with reduced risk of frailty and slower progression of frailty over 16 years and this association will be partly mediated by specific markers of oxidative stress. We will address this work via two aims using up to 1,746 participants from a well-characterized cohort, the Framingham Offspring Study.
Rajan Singh, PhD	PESC	**Mechanistic basis of differential regulation of polyamine pathway by testosterone in the prostate and androgen-responsive skeletal muscle**. The study proposes that ornithine decarboxylase (ODC1) plays an essential role in the biosynthesis of polyamines in the prostate and in mediating the selective trophic effects of testosterone in this tissue.
Kieran Reid, PhD	REC	**Translating exercise into the community to preserve independence among older adults with motoric cognitive risk syndrome.** The study will examine and characterize the effects of translating LIFE physical activity intervention into a community setting while specifically targeting older adults with motoric cognitive risk syndrome and at increased risk for developing dementia.
Marcia Testa, MPH, PhD	Developmental Project	**Clinical outcome assessments for therapeutic interventions in older individuals.** This project goals are to develop, apply and evaluate clinical utility of "measures, tools, and endpoints that assess a minimum list of impacts that matter most to patients (e.g., patient-reported outcomes, PROs) and are likely to demonstrate change relating to disease burden, treatment burden and physical function. Specific applications to conditions and diseases of older individuals that impact the quality of life, functioning and feelings of older individuals within the context therapeutic interventions and programs.

Table 2. Summary of 2017 PESC and REC awardee progress report

Awardee	REC/PESC	Number of publications	Grants and Awards
Dae Kim, MD HMS/ Hebrew SeniorLife	PESC	12 publications	R01 award R01 pending (4%) R21 pending (8%)
Brad Manor, PhD HMS/ Hebrew SeniorLife	PESC	10 publications	R01 award R21 pending (5%) Marcus Appelbaum award
Donato Rivas, PhD Tufts HNRCA	PESC	8 publications	K01 award Foundation grant
Ariela Orkaby, MD BWH/ HMS	REC	18 publications	GEMSSTAR award, BWH award
Indranil Sinha, MD BWH/ HMS	REC	4 publications	Beeson Award AFAR junior faculty award
Michael Lustgarten, PhD Tufts HNRCA	REC	7 publication	K01 award

Table 3. Summary of 2018 PESC and REC new awardee progress report

Awardee	REC/PESC	Number of publications	Grants and Awards
Lien Quach, MD, PhD, MPH GRECC VA	REC	5 publications	UTMB award DOD award
Kieran Reid, PhD	REC	10 publications	UG3/NIH award

Tufts HNRCA			Tufts award HNRCA award
Shivani Sahni, PhD HMS/ Hebrew SeniorLife	PESC	5 publications	R01 (Co-I) Foundation award
Rajan Singh, PhD HMS/ BWH	PESC		R01 pending R01 pending
Ron Neppl, PhD HMS/ BWH	PESC	1 publication	R01 submitted

B. PROGRESS IN YEAR 03

1. LEADERSHIP AND ADMINISTRATIVE CORE (LAC). The LAC is led by Director, Shalender Bhasin, and Associate Directors, Lewis Lipsitz, and Roger Fielding, and Scientific Director, Monty Montano. In year 02, the LAC accomplished the following activities.

- The LAC has organized monthly meetings of its Executive Committee.
- The LAC continues to provide administrative support including budget management, personnel management, and logistic support to all OAIC projects.
- The OAIC issued a request for application through its participating institutions, received 17 applications, and organized review of the applications and selected 3 pilot projects and 2 REC candidates for funding. LAC has provided administrative support for salary allocations of REC awardees.
- The LAC has organized a weekly conference for OAIC members and trainees, and a Visiting Speaker program. The visiting speakers during the past year since July 2017 have included Charles Brenner, Joseph Baur, David Sinclair, Barry Paw, Sierra Kent, Masayuki Yamamoto. The LAC organized a muscle and aging symposia on NAD, Aging and Physical Function.
- The LAC has established three resource cores, has provided oversight to the cores and has facilitated access of the OAIC investigators to the core services.

Collaborations with Other NIA-Funded Centers in Boston.

- The Boston OAIC established the framework for collaborations with investigators at the Boston Roybal Center, the Harvard Alzheimer's Disease Center, the Glenn Center for the Biology of Aging and others (**Table 4**). The Boston Roybal Center and the OAIC jointly funded a pilot project by Dr. Dae Kim. The Alzheimer Disease Center and the OAIC have submitted a joint application for an administrative supplement for a pilot project to determine the sensitivity and specificity of a fall detection device in patients with Alzheimer's Disease. Dr. David Sinclair at The Glenn Center and Dr. Shalender Bhasin at the OAIC are collaborating in a translational first-in-human trial of a sirtuin activator discovered in the Glenn Center.

List of collaborations with other OAICs across the nation (Table 4)

Table 4. OAIC-Wide Projects Led by Boston OAIC Investigators, and OAIC-Wide Projects in which Boston Investigators are Contributors

Collaborative Initiative (Funding)	Role of Boston OAIC Investigators	Other Collaborating OAICs and Investigators	Purpose
The STRIDE Study (NIA and PCORI)	Joint PI: Bhasin; Co-I: Basaria, Latham, Travison, Storer	Yale, UCLA, Maryland, Mount Sinai, Wake Forest, Pittsburgh; UTMB, Johns Hopkins, Michigan, Florida	This is the largest multi-center, randomized clinical effectiveness trial of a fall injury prevention strategy.
Exercise, cognition & function in CKD	PI: Weiner; Co-I: Fielding, Reid	Maryland (Seliger)	Effects of exercise training on physical function, mobility and cognition in CKD.
Sarcopenia II Initiative (FNIH)	Bhasin (Chair); Co-Is: Travison, Fielding, Kiel	Maryland (Magaziner, Orwig); Pittsburgh OAIC (Greenspan, Pereira);	An FNIH-funded Consortium to develop an evidence-based definition of sarcopenia.
Reliance agreements amongst IRBs	Bhasin (leader)	BWH and other OAIC institutions (Yale, UCLA, Maryland, Hopkins, Florida, UCSF, Pittsburgh, UTMB, Michigan)	Established reliance agreements among several OAIC institutions to cede to a Central IRB at BWH.
Muscle Mass and Strength Cut-Points for Sarcopenia (NIA)	Bhasin (PI); Co-Is: Fielding, Kiel, Travison	Maryland (Magaziner); Florida (Pahor, Mannini); Pittsburg (Newman, Greenspan); Hopkins (Xue, Brown)	To establish muscle mass and strength cutpoints to identify older adults at risk for mobility limitations.

Contribution to the Generation of Consensus Statements and Guidelines. Drs. Fielding, Travison, Bhasin, Kiel, and Marcantonio have contributed to or led the consensus guidelines on the design of clinical trials of FPTs for sarcopenia, delirium, and mobility limitation. Dr. Bhasin chaired the development of Endocrine Society's guideline for testosterone therapy. Drs. Travison and Bhasin lead a consortium to generate reference ranges for testosterone. Drs. Bhasin (Chair), Travison, Pencina, Fielding, and Kiel are members of the Sarcopenia Biomarkers Consortium.

Oversight of Human Subjects Research for OAIC-Funded REC and PESC Projects

In accordance with the guidance provided by the NIA's Program office, the LAC has established the following procedures for oversight of the human subject's research in projects funded by the OAIC. These procedures that were developed in complete conformity with NIA's guidance, are described briefly here.

A three-member committee, consisting of Shalender Bhasin (OAIC Director), Doug Kiel, and Roger Fielding will serve as the Safety Monitoring Committee for the OAIC. The OAIC's Scientific Director, Monty Montano, serves as the Committee's Chair. The SMC oversees data and safety monitoring in OAIC projects that supported primarily or solely through OAIC award funds, such as Pilot/Exploratory studies, Developmental Projects within a Resource Core (RC), or a study supported by the Research Education Component (REC). OAIC-funded studies do not typically include External Projects of a Resource Core, which are funded primarily by other sources and, therefore, subject to the data and safety monitoring policies of those sources.

Each OAIC-funded human intervention study must have an NIA-approved Data and Safety Monitoring Plan (DSMP) prior to its initiation. A DSMP should include elements specified by the NIA in its guidance document, including a brief study overview; potential risks and benefits to participants; study staff procedures for collection, assessment, and notification of adverse events (AEs), serious adverse events (SAEs), and unanticipated problems (UPs); protection against study risks; procedures for data and safety monitoring. The Data and safety monitoring information for all OAIC-funded human intervention studies should be submitted to the NIA program official for approval prior to initiation of the study.

The SMC may designate either a single Safety Officer or may serve as the DSMB for the project, depending on the level of the risk and the complexity of the project. In the event that one or more members of the SMC have a conflict, the LAC will appoint alternate members.

A summary of the current status of the various OAIC-funded projects is provided in Table 5 below. As some of the projects were funded only recently, they are in various stages of review.

Table 5. Status of Human Subjects Research in the PESC and REC-Supported Research Projects

Candidate	Award type	IRB approval	Reviewed by the SMC	Safety Monitor or DSMB established
Year 2017 awardees				
Dae Kim, MD	PESC	Approved	Yes	Safety Monitor designated
Brad Manor, PhD	PESC	Approved	Yes	Safety Monitor designated
Donato Rivas, PhD	PESC	Approved	Yes	Two Safety Monitors designated
Ariela Orkaby, MD	REC	Approved	Yes	Not required since secondary data analysis
Indranil Sinha, MD	REC	No human subjects	Yes	Not required since no human subjects
Michael Lustgarten, PhD	REC	Approved	Yes	Safety Monitor designated
Year 2018 awardees				
Lien Quach, MD, PhD, MPH	PESC	Approved	Yes	Not required since secondary data analysis
Kieran Reid, PhD	PESC	Approved	Yes	DSMP established
Shivani Sahni, PhD	REC	Approved	Yes	Not required since secondary data analysis
Rajan Singh, PhD	REC	No human subjects	Yes	Not required since no human subjects

Ron Neppl, PhD	REC	No human subjects	Yes	Not required since no human subjects

Table 6. List of major new accomplishments by Senior Pepper investigators	
Awards / Honors/ Grants	
Lew Lipsitz, MD	Kent Award, new R01
Shalender Bhasin, MD	Appointed to NIA Council; Hooton Foundation Legacy Award; 2 R01s, R13
Monty Montano, PhD	Appointed to ACTG HIV and Aging Working Group
Amy Wagers, PhD	2 R01s, DP1, R13; Recipient of NIH Director's Pioneer Award
Ravi Jasuja, PhD	SBIR grant
Tom Travison, PhD	Promoted to Associate Professor
Roger Fielding, PhD	Appointed Associate Director of the Jean Mayer USDA Human Nutrition Research Center on Aging
Douglas Kiel, MD	R13

Major Publications in 2018 in NEJM, JAMA journals, Lancet journals, Nature journals, Science, and Cell journals

1. Bhasin S, Seidman S. Testosterone Treatment of Depressive Disorders in Men: Too Much Smoke, Not Enough High-Quality Evidence. JAMA Psychiatry. 2018 Nov 14. doi: 10.1001/jamapsychiatry.2018.2661. [Epub ahead of print] PubMed PMID: 30428087.
2. Bischoff-Ferrari HA, Bhasin S, Manson JE. Preventing Fractures and Falls: A Limited Role for Calcium and Vitamin D Supplements? JAMA. 2018 Apr 17;319(15):1552-1553. doi: 10.1001/jama.2018.4023. PubMed PMID: 29677284.
3. Bhasin S, Ellenberg SS, Storer TW, Basaria S, Pahor M, Stephens-Shields AJ, Cauley JA, Ensrud KE, Farrar JT, Cella D, Matsumoto AM, Cunningham GR, Swerdloff RS, Wang C, Lewis CE, Molitch ME, Barrett-Connor E, Crandall JP, Hou X, Preston P, Cifelli D, Snyder PJ, Gill TM. Effect of testosterone replacement on measures of mobility in older men with mobility limitation and low testosterone concentrations: secondary analyses of the Testosterone Trials. Lancet Diabetes Endocrinol. 2018 11; 6(11):879-890. PMID: 30366567.
4. Bhasin S, Apovian CM, Travison TG, Pencina K, Moore LL, Huang G, Campbell WW, Li Z, Howland AS, Chen R, Knapp PE, Singer MR, Shah M, Secinaro K, Eder RV, Hally K, Schram H, Bearup R, Beleva YM, McCarthy AC, Woodbury E, McKinnon J, Fleck G, Storer TW, Basaria S. Effect of Protein Intake on Lean Body Mass in Functionally Limited Older Men: A Randomized Clinical Trial. JAMA Intern Med. 2018 Apr 01; 178(4):530-541. PMID: 29532075.
5. Kim DH, Afilalo J, Shi SM, Popma JJ, Khabbaz KR, Laham RJ, Grodstein F, Guibone K, Lux E, Lipsitz LA. Evaluation of Changes in Functional Status in the Year After Aortic Valve Replacement. JAMA Intern Med. 2019 Feb 04. PMID: 30715097.
6. Wachterman MW, O'Hare AM, Rahman OK, Lorenz KA, Marcantonio ER, Alicante GK,Kelley AS. One-Year Mortality After Dialysis Initiation Among Older Adults. JAMA Intern Med. 2019 Apr 22. doi: 10.1001/jamainternmed.2019.0125. [Epub ahead of print] PubMed PMID: 31009039.
7. Subramaniam B, Shankar P, Shaefi S, Mueller A, O'Gara B, Banner-Goodspeed V, Gallagher J, Gasangwa D, Patxot M, Packiasabapathy S, Mathur P, Eikermann M, Talmor D, Marcantonio ER. Effect of Intravenous Acetaminophen vs Placebo Combined With Propofol or Dexmedetomidine on Postoperative Delirium Among Older Patients Following Cardiac Surgery: The DEXACET Randomized Clinical Trial. JAMA. 2019 02 19; 321(7):686-696. PMID: 30778597.
8. Jones RN, Cizginer S, Pavlech L, Albuquerque A, Daiello LA, Dharmarajan K, Gleason LJ, Helfand B, Massimo L, Oh E, Okereke OI, Tabloski P, Rabin LA, Yue J, Marcantonio ER, Fong TG, Hshieh TT, Metzger ED, Erickson K, Schmitt EM, Inouye SK. Assessment of Instruments for Measurement of Delirium Severity: A Systematic Review. JAMA Intern Med. 2019 Feb 01; 179(2):231-239. PMID: 30556827.
9. Marcantonio ER. Delirium in Hospitalized Older Adults. N Engl J Med. 2018 01 04; 378(1):96-97. PMID: 29298149.
10. Morris JA, Kemp JP, Youlten SE, Laurent L, Logan JG, Chai RC, Vulpescu NA,Forgetta V, Kleinman A, Mohanty ST, Sergio CM, Quinn J, Nguyen-Yamamoto L, Luco AL, Vijay J, Simon MM, Pramatarova A, Medina-Gomez C, Trajanoska K, Ghirardello EJ, Butterfield NC, Curry KF, Leitch VD, Sparkes PC, Adoum AT, Mannan NS, Komla-Ebri DSK, Pollard AS, Dewhurst HF, Hassall TAD, Beltejar MG; 23andMe Research Team, Adams DJ, Vaillancourt SM, Kaptoge S, Baldock P, Cooper C, Reeve J, Ntzani EE, Evangelou E, Ohlsson C, Karasik D, Rivadeneira F, Kiel DP, Tobias JH, Gregson CL, Harvey NC, Grundberg E, Goltzman D, Adams DJ, Lelliott CJ, Hinds DA, Ackert-Bicknell CL, Hsu YH, Maurano MT, Croucher PI, Williams GR, Bassett JHD, Evans DM, Richards JB. Author Correction: An atlas of genetic influences on osteoporosis in humans and mice. Nat Genet. 2019 Apr 15. doi: 10.1038/s41588-019-0415-x. [Epub ahead of print] PubMed PMID: 30988516.

11. Morris JA, Kemp JP, Youlten SE, Laurent L, Logan JG, Chai RC, Vulpescu NA, Forgetta V, Kleinman A, Mohanty ST, Sergio CM, Quinn J, Nguyen-Yamamoto L, Luco AL, Vijay J, Simon MM, Pramatarova A, Medina-Gomez C, Trajanoska K, Ghirardello EJ, Butterfield NC, Curry KF, Leitch VD, Sparkes PC, Adoum AT, Mannan NS, Komla-Ebri DSK, Pollard AS, Dewhurst HF, Hassall TAD, Beltejar MG, Adams DJ, Vaillancourt SM, Kaptoge S, Baldock P, Cooper C, Reeve J, Ntzani EE, Evangelou E, Ohlsson C, Karasik D, Rivadeneira F, Kiel DP, Tobias JH, Gregson CL, Harvey NC, Grundberg E, Goltzman D, Adams DJ, Lelliott CJ, Hinds DA, Ackert-Bicknell CL, Hsu YH, Maurano MT, Croucher PI, Williams GR, Bassett JHD, Evans DM, Richards JB. An atlas of genetic influences on osteoporosis in humans and mice. Nat Genet. 2019 Feb; 51(2):258-266. PMID: 30598549.
12. Samelson EJ, Broe KE, Xu H, Yang L, Boyd S, Biver E, Szulc P, Adachi J, Amin S, Atkinson E, Berger C, Burt L, Chapurlat R, Chevalley T, Ferrari S, Goltzman D, Hanley DA, Hannan MT, Khosla S, Liu CT, Lorentzon M, Mellstrom D, Merle B, Nethander M, Rizzoli R, Sornay-Rendu E, Van Rietbergen B, Sundh D, Wong AKO, Ohlsson C, Demissie S, Kiel DP, Bouxsein ML. Cortical and trabecular bone microarchitecture as an independent predictor of incident fracture risk in older women and men in the Bone Microarchitecture International Consortium (BoMIC): a prospective study. Lancet Diabetes Endocrinol. 2019 Jan; 7(1):34-43.PMID: 30503163.
13. Berry SD, Rothbaum RR, Kiel DP, Lee Y, Mitchell SL. Association of Clinical Outcomes With Surgical Repair of Hip Fracture vs Nonsurgical Management in Nursing Home Residents With Advanced Dementia. JAMA Intern Med. 2018 Jun 01; 178(6):774-780. PMID: 29801122.
14. Lu AT, Xue L, Salfati EL, Chen BH, Ferrucci L, Levy D, Joehanes R, Murabito JM, Kiel DP, Tsai PC, Yet I, Bell JT, Mangino M, Tanaka T, McRae AF, Marioni RE, Visscher PM, Wray NR, Deary IJ, Levine ME, Quach A, Assimes T, Tsao PS, Absher D, Stewart JD, Li Y, Reiner AP, Hou L, Baccarelli AA, Whitsel EA, Aviv A, Cardona A, Day FR, Wareham NJ, Perry JRB, Ong KK, Raj K, Lunetta KL, Horvath S. GWAS of epigenetic aging rates in blood reveals a critical role for TERT. Nat Commun. 2018 01 26; 9(1):387. PMID: 29374233.
15. Jiang X, O'Reilly PF, Aschard H, Hsu YH, Richards JB, Dupuis J, Ingelsson E, Karasik D, Pilz S, Berry D, Kestenbaum B, Zheng J, Luan J, Sofianopoulou E, Streeten EA, Albanes D, Lutsey PL, Yao L, Tang W, Econs MJ, Wallaschofski H, Völzke H, Zhou A, Power C, McCarthy MI, Michos ED, Boerwinkle E, Weinstein SJ, Freedman ND, Huang WY, Van Schoor NM, van der Velde N, Groot LCPGM, Enneman A, Cupples LA, Booth SL, Vasan RS, Liu CT, Zhou Y, Ripatti S, Ohlsson C, Vandenput L, Lorentzon M, Eriksson JG, Shea MK, Houston DK, Kritchevsky SB, Liu Y, Lohman KK, Ferrucci L, Peacock M, Gieger C, Beekman M, Slagboom E, Deelen J, Heemst DV, Kleber ME, März W, de Boer IH, Wood AC, Rotter JI, Rich SS, Robinson-Cohen C, den Heijer M, Jarvelin MR, Cavadino A, Joshi PK, Wilson JF, Hayward C, Lind L, Michaëlsson K, Trompet S, Zillikens MC, Uitterlinden AG, Rivadeneira F, Broer L, Zgaga L, Campbell H, Theodoratou E, Farrington SM, Timofeeva M, Dunlop MG, Valdes AM, Tikkanen E, Lehtimäki T, Lyytikäinen LP, Kähönen M, Raitakari OT, Mikkilä V, Ikram MA, Sattar N, Jukema JW, Wareham NJ, Langenberg C, Forouhi NG, Gundersen TE, Khaw KT, Butterworth AS, Danesh J, Spector T, Wang TJ, Hyppönen E, Kraft P, Kiel DP. Genome-wide association study in 79,366 European-ancestry individuals informs the genetic architecture of 25-hydroxyvitamin D levels. Nat Commun. 2018 01 17; 9(1):260. PMID: 29343764.
16. Bhasin S, Apovian CM, Travison TG, Pencina K, Moore LL, Huang G, Campbell WW, Li Z, Howland AS, Chen R, Knapp PE, Singer MR, Shah M, Secinaro K, Eder RV, Hally K, Schram H, Bearup R, Beleva YM, McCarthy AC, Woodbury E, McKinnon J, Fleck G, Storer TW, Basaria S. Effect of Protein Intake on Lean Body Mass in Functionally Limited Older Men: A Randomized Clinical Trial. JAMA Intern Med. 2018 Apr 01; 178(4):530-541. PMID: 29532075.
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19. Goldstein JM, Wagers AJ. What's in a (Sub)strain? Stem Cell Reports. 2018 Aug 14; 11(2):303-305. PMID: 30110622.
20. Bar-Nur O, Gerli MFM, Di Stefano B, Almada AE, Galvin A, Coffey A, Huebner AJ, Feige P, Verheul C, Cheung P, Payzin-Dogru D, Paisant S, Anselmo A, Sadreyev RI, Ott HC, Tajbakhsh S, Rudnicki MA, Wagers AJ, Hochedlinger K. Direct Reprogramming of Mouse Fibroblasts into Functional Skeletal Muscle Progenitors. Stem Cell Reports. 2018 May 08; 10(5):1505-1521. PMID: 29742392.

Boston Pepper Center External Advisory Board

The EAB annual meeting was in November of 2018 and was focused on new REC and PESC awardees, as well as a Developmental Project awardee. All awardees presented their projects. There was broad enthusiasm among the advisory board members that the Boston OAIC is a highly productive multi-institutional center composed of talented established as

well as early career scientists, who are engaged in high quality aging research. The EAB will meet in May (15-16) for a comprehensive review of the Pepper Cores and progress. Based on NIA feedback, we have added a new member to our board: Laura Neidernhofer, PhD. Brief descriptions of the board are as follows:

- **Marco Pahor, MD.** Dr. Pahor is the director of the University of Florida Institute on Aging, and the founding chairman of the department of aging and geriatric research in the UF College of Medicine. Dr. Pahor is an internationally recognized expert on population-based studies, clinical trials and multidisciplinary translational research in the fields of aging and disability. Dr. Pahor is the director of the UF Claude D. Pepper Older Americans Independence Center.

- **Tom Gill, MD.** Dr. Gill is Professor of Medicine, Epidemiology, and Investigative Medicine and the Humana Foundation Professor of Geriatric Medicine at Yale University. Dr. Gill is a leading authority on the epidemiology and prevention of disability among older persons and is the recipient of numerous awards. Dr. Gill holds several leadership positions at Yale, including Director of the Program on Aging and Claude D. Pepper Older Americans Independence Center.

- **Stephen Kritchevsky, PhD.** Dr. Kritchevsky is an epidemiologist whose primary research interests are in the areas of nutrition, body composition, chronic disease and age-related declines in physical function. Dr. Kritchevsky has extensive leadership experience of complex research enterprises. He is the Co-Director of the Wake Forest Claude D. Pepper Older Americans Independence Center.

- **Laura Niederhofer, PhD.** Laura is the Director of the newly founded Institute on the Biology of Aging and Metabolism (iBAM) at the University of Minnesota Medical School. Drs. Niedernhofer is internationally recognized expert in the molecular and cellular basis of aging. Dr. Niedernhofer's expertise is in cellular senescence and the role of DNA repair during aging and drug discovery of senescent cell targeted compounds, i.e., senolytics.

2. RESEARCH AND EDUCATION CORE (REC)

The REC is led by Lewis A. Lipsitz (Director), Amy J. Wagers, (Assoc. Director), Edward R. Marcantonio (Assoc. Director). The overall goal of the Research Education Component (REC) of the Boston OAIC is to train future independent research scientists who have the knowledge and the skill to translate fundamental mechanisms of disease and disability into novel interventions that can improve the health, physical function, and well-being of people as they age. The REC achieves this by selecting the most promising early career scientists from clinical and basic science disciplines and providing them with both collective and individual educational activities, research experiences, mentoring, and career guidance that will enable them to acquire future career development or research awards and ultimately become leaders in translational research devoted to the discovery of function promoting therapies (FPTs).

During this funding period, the REC has continued the training of our initial three early career investigators who have all been quite successful, as described in their individual progress reports below. We also identified two new trainees through a competitive application and review process. After a Harvard-wide solicitation and pre-screening process, we received and reviewed 17 full applications, then decided which ones had the highest merit and were best suited for REC Awards. These were then vetted and approved by our external advisory committee last fall. Funding began early this year.

All trainees are on target and making important progress in their science and careers. All have completed the required coursework in the responsible conduct of research and are meeting the explicit goals and milestones laid out in the Individual Development Plans (IDPs) each developed with his/her mentor at the beginning of the training period. They are also attending various courses offered by Harvard Catalyst (our CTSA) or other programs that are relevant to their career development goals. **As a group, they have published 45 manuscripts and received 11 grants during their time as OAIC junior investigators.**

As noted last year, our REC trainees established a new junior investigator collaborative group through the Pepper Center, entitled **Aging Researchers in Early Stages (ARIES)**. This group which now includes nearly 20 members is co-led by Dr. Orkaby, together with Dr. Kei Ouchi and Dr. Tammy Hshieh, and its mission is to bring together early stage investigators in Boston to promote cross-disciplinary clinical and translational research focused on the application of aging principles to improve clinical outcomes. The group meets once every 1-2 months to provide peer mentoring and collaborative support, including review of each other's' specific aims and grants. Since the start of this group, 4 K awards and one R03 have been funded to participants. Finally, each of the trainees has presented or been scheduled to present his/her research at the monthly Boston OAIC seminar series.

List of projects: Summary of Each Individual REC Awardee's Progress.

Indranil Sinha, MD (*Mentor*: Amy Wagers, PhD)

***Trainee Profile*:** Dr. Sinha is a Plastic Surgeon and Assistant Professor at Brigham and Women's Hospital (BWH). He became an Affiliated Faculty member of the Harvard Stem Cell Institute in 2017. Dr. Sinha's research laboratory focuses on skeletal muscle regeneration, uncovering new strategies for accelerating healing and improving function after injury and in the context of aging and chronic disease.

***Scientific Progress*:** Dr. Sinha's work suggests that aging-related deficits in skeletal muscle regeneration after injury may be associated with a loss of skeletal muscle hypoxia signaling. Specifically, protein levels of aryl hydrocarbon nuclear receptor translocator (ARNT), which is a critical regulator of hypoxia signaling, severely declines with aging. Genetically modified mice in which there is skeletal muscle specific loss of ARNT exhibit decreased skeletal muscle regeneration, whereas activation of this pathway with a pharmacologic agent, ML228, promotes regeneration. He continues to evaluate the mechanism underlying hypoxia signaling and muscle regeneration. This past year he received a prestigious Beeson Award based on the preliminary data generated from the REC award.

***Publications*:** Selected papers submitted, in press or published since July 1, 2017

1. Sinha I, Sakthivel D, Olenchock BA, Kruse CR, Williams J, Varon DE, Smith JD, Madenci AL, Nuutila K, Wagers AJ. Prolyl Hydroxylase Domain-2 Inhibition Improves Skeletal Muscle Regeneration in a Male Murine Model of Obesity. *Front Endocrinol.* 2017 8:153-159.
2. Roh D, Panayi A, Orgill DP, Bhasin S, Sinha I. Implications of Aging in Plastic Surgery. *Plast Reconstr Surg Glob Open* 2019 7:e2085.
3. Guadagnin E; Bagchi D; Sinha I, Neppl R. Nuclear localized Akt limits skeletal muscle derived fibrotic signaling. *Biochem Biophys Res Comm* 2019 508:838-843.
4. Panayi AC, Orkaby A, Sakthivel D, Neppl R, Endo Y, Roh D, Javedan H, Varon D, Orgill DP, Bhasin S, Sinha I. Impact of Frailty on Outcomes in Surgical Patients: A Systematic Review and Meta-analysis. *Am J Surg* (*Accepted*).

Presentations:

1. Skeletal muscle VEGF activity decreases with aging and impairs skeletal muscle regeneration. Presented at Claude D. Pepper Annual Conference, 2018. Washington, DC. *(Poster)*
2. Aging-Associated Loss of ARNT Signaling Impairs Skeletal Muscle Regeneration. Presented at Gerontological Society of America, 2018. Boston, MA. (*Poster*)
3. Impact of Frailty on Outcomes in Surgical Patients: A Systematic Review and Meta-analysis. Presented at Gerontological Society of America, 2018. Boston, MA. (*Poster*)
4. Restoration of hypoxia signaling promotes skeletal muscle regeneration. Presented at International Conference of Sarcopenia and Frailty Research, 2019. Miami, FL. (*Oral Presentation*)

Awards: Brigham Research Institute Hypoxia Conference Research Award, 2019

***Grants received*:**

1. NIH 1K76 AG059996 (Sinha, PI) Title: Aging-associated dysregulation of the hypoxia pathway limits skeletal muscle regeneration. Duration: 07/01/2018 – 06/30/2023
   Mentors: Wagers, Bhasin
2. AFAR Junior Faculty Award (Sinha, PI) Title: Aging-associated dysregulation of the hypoxia pathway limits skeletal muscle regeneration. Duration: 09/01/2018 – 08/31/2020. Declined due to overlap with K76 Award)

Inventions reported, and patents issued: since July 1, 2017

1. Li B, Udeh K, Sinha I. 2019. Promoting hypoxia signaling for skeletal muscle repair. *Under review.*

Pepper Center Core Usage:
Dr. Sinha is using the Preclinical Discovery Core for NMR imaging, grip strength testing, and endurance measurements in aging, exercised and gene-modified mice. Pilot studies have been completed, and additional analyses are planned for the future.

Michael Lustgarten, PhD (Mentor: Dr. Roger Fielding)

***Trainee Profile*:** Dr. Lustgarten received a PhD in Physiology in 2009 from the University of Texas-Health Science Center at San Antonio, and subsequently completed postdoctoral fellowships at University of Texas and Tufts University. He is currently appointed as a Scientist II in the Nutrition, Exercise Science and Physiology Laboratory at the Jean Mayer Human Nutrition Research Center on Aging at Tufts University. His particular focus is on the role of the gut microbiome and the serum metabolome on lean mass and physical function in older adults. In addition to receiving support from the OAIC REC, Dr. Lustgarten has also received a K01 from the National Institute on Aging, and his support therefore moved to the PESC last year.

***Scientific progress*:** During the period from July 2016 to present, Dr. Lustgarten enrolled 29 subjects into his OAIC REC funded study, including 18 high functioning (HF) and 11 low functioning (LF) older adults. These 2 groups were significantly different in terms of body composition and physical function. HF had an increased whole body percent lean mass but a decreased percent fat mass, and better physical function, including higher values for the short physical performance battery (SPPB), 400-meter gait speed, and the leg press one repetition maximum (1 RM). In addition, the two groups were well-matched for age, BMI, percent lean and fat mass. Differences observed at the baseline visit when comparing HF with LF older adults were also identified at a 1-month follow-up visit, including a more favorable body composition and better physical functioning in HF, when compared with LF.

Gut microbiome compositional (and functional, *data not shown*) differences between HF and LF older adults were then evaluated at a baseline visit, and at the 1-month follow visit, to examine the stability and reproducibility of the microbiome over time. Bacteria that were significantly different when comparing HF with LF older adults at both the baseline and 1-months visits included family-level *24_7* and *Prevotellaceae*, genus-level *Prevotella* and *Barnesiella*, and species-level *Barnesiella intestinihominis*. These data complete AIM1 of the K01 project. Training that Dr. Lustgarten received in microbiome compositional and functional analysis during Years 1 and 2 of his K01 project were of great benefit in allowing him to analyze these data for his K01 study.

To evaluate AIM2 from his funded K01 award, fecal samples were transplanted from 6 HF (3 males, 3 females) and 6 LF (3 males, 3 females) older adult humans into young, sex-matched germ-free mice. One month after transplantation, fecal samples from mice colonized with human stool samples were collected (for microbiome analysis), and measurements of body composition and physical function were performed. First, bacteria that were significantly different when comparing the larger human group including family-level *24_7* and *Prevotellaceae*, genus-level *Prevotella* and *Barnesiella*, and species-level *Barnesiella intestinihominis* were also significantly different when comparing the human fecal donors, and when comparing HF- with LF-colonized mice.

Additionally, mice colonized with fecal samples from HF-functioning older adults had increased grip strength when compared with mice colonized with fecal samples from LF-functioning older adults, evidence that suggests a causative role for *S24_7* and *Prevotellaceae*, genus-level *Prevotella* and *Barnesiella*, and species-level *Barnesiella intestinihominis* on the maintenance of muscle strength. Interestingly, *S24_7* were decreased in the larger human HF group at baseline and at the 1-month follow up visit, but were increased in HF fecal donors and in their recipient mice. Accordingly, *S24_7* may not be involved in the maintenance of muscle strength, as changes in microbiome composition in the same direction between all groups were expected. Body composition and treadmill endurance capacity were not different when comparing HF- with LF-colonized mice, evidence that argues against a role for the gut microbiome on these outcomes in older adults. These data are currently *in review* (*Aging Cell*, submitted 2/2019). In sum, AIMS 1 and 2 of the K01 project have been completed.

Additional measurements to be performed for Dr. Lustgarten's K01 project include quantification of serum levels of zonulin, and fecal levels of intestinal alkaline phosphatase (IAP). These proteins are involved in mechanisms related to intestinal permeability. Zonulin levels are expected to be increased, whereas IAP is expected to be decreased in LF, when compared with HF older adults and in their respectively colonized mice. Findings from Dr. Lustgarten's K01 study are allowing for elucidation of the emerging gut-muscle axis in older adults.

***Publications*:** Papers submitted, in press or published since July 1, 2016:

1. Fielding , R.A., Reeves, A.R. , Jasuja, R., Liu, C. , Barrett, B.B. , Lustgarten, M.S. Muscle strength is increased in mice that are colonized with microbiota from high-functioning older adults. *Submitted, in review*, Aging Cell, 2/2019.
2. Jazani NH, Savoj J, Lustgarten M, Lau WL, Vaziri ND. Impact of Gut Dysbiosis on Neurohormonal Pathways in Chronic Kidney Disease. Diseases. 2019 Feb 13;7(1). PMID: 30781823.
3. Lustgarten, M.S. and Fielding, R.A. Metabolites related to renal function, carbamylation, and immune activation are associated with muscle composition in older adults. Exp Gerontol. 2017 Dec 15;100:1-10. doi: 10.1016/j.exger.2017.10.003. Epub 2017 Oct 10. PMID: 29030163.
4. Grosicki G.J., Fielding R.A., Lustgarten M.S. Gut Microbiota Contribute to Age-Related Changes in Skeletal Muscle Size, Composition, and Function: Biological Basis for a Gut-Muscle Axis. Calcif Tissue Int. 2017 Oct 20. doi: 10.1007/s00223-017-0345-5. [Epub ahead of print] Review. PMID: 29058056.
5. Lustgarten M.S., Fielding R.A. Metabolites Associated With Circulating Interleukin-6 in Older Adults. J Gerontol A Biol Sci Med Sci. 2017 Sep 1;72(9):1277-1283. doi: 10.1093/gerona/glw039. PMID: 26975982.
6. Lustgarten M.S. Classifying Aging As a Disease: The Role of Microbes. Front Genet. 2016 Dec 1;7:212. eCollection 2016. PMID:27990156

Grants received:

Mentored Research Scientist Development Award (K01), National Institute on Aging, *Title:* "Role of the gut microbiome

and the serum metabolome on lean mass and physical function in older adults." Project Duration: 2016-20

Pepper Center Core Usage: Dr. Lustgarten used the Core to measure body composition, grip strength, and treadmill endurance capacity in mice colonized with fecal samples from either high or low-functioning older adults.

Ariela Orkaby, MD, MPH (Mentor: Dr. Jane Driver).

***Trainee Profile*:** Dr. Orkaby is a Geriatrician with advanced training in preventive cardiology and epidemiology. She completed her internal medicine residency at Boston Medical Center in 2013 and a clinical geriatrics fellowship at the Harvard Combined program in 2014. She then pursued a research fellowship in preventive cardiology at the VA Boston, during which she earned an MPH from the Harvard School of Public Health. In July 2016 she joined the Brigham & Women's Hospital (BWH) Division of Aging as Instructor in Medicine, and the Geriatric Research, Education and Clinical Center (GRECC) at VA Boston as an advanced research fellow.

***Scientific progress*:** Dr. Orkaby's project builds on her prior work to examine the hypothesis that aspirin use is inversely associated with frailty and self-reported functional limitation. As a secondary aim she is exploring the role of aspirin in mediating the relationship between frailty and inflammatory biomarkers such as CRP, IL-6, and TNF- α to elucidate putative biologic mechanisms of frailty. This project will provide the preliminary data needed to design a multi-center prospective trial to test the efficacy of anti-inflammatory medications in preventing frailty and functional limitation.

***Publications*:** Papers submitted, in press or published since July 1, 2017

1. **Orkaby AR**, Hshieh TT, Gaziano JM, Djousse L, Driver JA. Comparison of Two Frailty Indices in the Physicians' Health Study. *Arch Gerontol Geriatr* 2017 Jul;71:21-27. PMID: 28242579 PMCID: PMC5618108
2. **Orkaby AR,** Cho K, Cormack J, Gagnon DR, Driver JA. Metformin vs. Sulfonylurea Use and Risk of Dementia in US Veterans ≥65 Years with Diabetes. *Neurology.* 2017 Oct 31;89(18): 1877-1885. PMID: 28954880 PMCID: PMC5664297
3. **Orkaby AR**, Gaziano JM, Djousse L, Driver JA. Statins for Primary Prevention of Cardiovascular Events and Mortality in Older Men. *J Am Geriatr Soc.* 2017 Nov;65(11): 2362-2368. PMID: 28892121 PMCID: PMC5681374
4. **Orkaby AR**, Forman DE. Physical Activity and CVD Prevention in Older Adults: an Expert's Perspective*. Expert Rev Cardiovasc Ther.* 2018 Jan;16(1):1-10. PMID: 29129219
5. **Orkaby AR**, Onuma O, Qazi S, Gaziano JM, Driver JD. Preventing cardiovascular disease in older adults: One size does not fit all. *Cleve Clin J Med.* 2018 January;85(1):55-64. PMID: 29328899
6. **Orkaby AR**. Backwards and Forwards. *J Gen Intern Med.* 2018 Feb;33(2):233-234. PMID: 29192389 PMCID: PMC5789097
7. **Orkaby AR,** Rich MW. Cardiovascular Screening and Primary Prevention in Older Adults. *Clin Geriatr Med.* 2018 Feb;34(1):81-93. PMID: 29129219
8. **Orkaby AR**, Schwartz AW. Toenails as the "Hemoglobin A1c" of Functional Independence – Beyond the Polished Wingtips. *JAMA Intern Med*. 2018 May 1;178(5):598-599.. PMID: 29630696
9. Patel YR, Kurgansky K, Imran TF, **Orkaby AR**, Cho K, Gagnon D, Ho Y, Gaziano JM, Djousse L, Joseph J. Prognostic significance of baseline serum sodium in heart failure with preserved ejection fraction. J Am Heart Assoc. 2018 Jun 13;7(12). pii: e007529.
10. **Orkaby AR**, Lunetta KL, Sun FJ, Driver JA, Benjamin EJ, Hamburg N, Mitchell GF, Vasan RS, Murabito JM. Cross-Sectional Association of Frailty and Arterial Stiffness in Community-Dwelling Older Adults: The Framingham Heart Study. J Gerontol A Biol Sci Med Sci. 2019 Feb 15;74(3):373-379. doi: 10.1093/gerona/gly134. PMID: 29917058
11. Patel YR, Robbins JR, Kurgansky KE, Imran TF, **Orkaby AR**, McLean RR, Ho YL, Cho K, Gaziano JM, Djousse L, Gagnon D, Joseph J. Development and Validation of a Heart Failure with Preserved Ejection Fraction Cohort using Electronic Medical Records. BMC Cardiovascular Disorders. (2018)18:128. PMID: 29954337 PMCID: PMC6022342
12. McCaw ZR*, **Orkaby AR***, Wei LJ, Kim DH, Rich MW. Applying Evidence-Based Medicine to Shared Decision Making: Value of Restricted Mean Survival Time. Am J Med. 2019 Jan;132(1):13-15. doi: 10.1016/j.amjmed.2018.07.026. Epub 2018 Aug 1. PMID: 30076822
13. **Orkaby AR**, Rich MW, Sun R, Lux E, Wei LJ, Kim DH. Pravastatin for Primary Prevention in Older Adults: Restricted Mean Survival Time Analysis. J Am Geriatr Soc. 2018 Oct;66(10):1987-1991. PMID: 30251369
14. **Orkaby AR**, Nussbaum L, Ho YL, Gagnon D, Quach L, Ward R, Quaden R, Yaksic E, Harrington K, Paik JM, Kim DH, Wilson PW, Gaziano JM, Djousse L, Cho K, Driver JA. The Burden of Frailty among US Veterans and its Association with Mortality, 2002-2012. J Gerontol A Biol Sci Med Sci. 2018 Oct 11. [Epub ahead of print] PMID: 30307533
15. Panayi AC, **Orkaby AR**, Sakthivel D, Endo Y, Varon D, Roh D, Orgill DP, Neppl RL, Javedan H, Bhasin S, Sinha I. Efficacy of the Modified Frailty Index on Assessing Surgical Patients: A Systematic Review and Meta-analysis. Am J Surg. 2018 Nov 27. pii: S0002-9610(18)31242-X. PMID: 30509455

16. Bean JF, **Orkaby AR**, Driver JA. Geriatric Rehabilitation shouldn't be an Oxymoron: A path forward. Archives of Physical Medicine and Rehabilitation. 2019 Feb 05. pii: S0003-9993(19)30084-X. PMID: 30735624
17. Goyal P, Alpert C, **Orkaby AR**. Time to Get Going on Involving FITs in Clinical Trials. J Am Coll Cardiol. 2018 Dec 4;72(22):2802-2805. PMID: 30497566
18. Yaksic E, Lecky V, Sharnprapai S, Tungkhar T, Cho K, Driver, JA, **Orkaby AR**. Defining Frailty in Research Abstracts: A Systematic Review and Recommendations for Standardization. Journal of Frailty & Aging. 2019; In Press.

***Awards*:**
1. Young Investigator Travel Award to attend the ACC/AGS/NIA U13 Conference on Polypharmacy in Older Adults, Washington, DC, February 2017.
2. Finalist (3rd place), Jay D. Coffman Early Career Investigator Award, American Heart Association Annual Meeting, Anaheim, CA November 2017.
3. Junior Investigator Travel Award to attend the ACC/AGS/NIA U13 Conference on Polypharmacy in Older Adults, Washington, DC, October 2018.

***Grants received or submitted*:** Grants received or submitted since July 1 2017.
ACTIVE AWARDS
1. VA Career Development Award (Orkaby, PI) Title: Statins for primary prevention of cardiovascular disease and frailty. Duration: 1/2019 – 12/2023
   -currently being resubmitted. Dr. Lipsitz wrote a letter of support, will provide career mentorship
   - oral abstract of findings presented at the 2018 American Heart Association annual meeting and poster presentation at 2019 Gerontological Society of America annual meeting. 2 manuscripts to be submitted in the next 2-4 months (awaiting data check)
2. NIA – GEMSSTAR (R03) (Orkaby, PI) Title: Frailty, statins and cardiovascular disease burden in older adults. Duration: 8/2018 – 7/2020
   -Council meets at the end of Feb, Dr. Bhasin wrote a letter of support, will provide career mentorship
3. BWH Faculty Career Development Award/Eleanor and Miles Shore Career Development Award (Orkaby, PI) Title: Association between non-steroidal anti-inflammatory drug use, frailty and function in older men. Duration: 7/2018-6/2019
   -Builds off current Pepper CDA work

Pepper Center Core Usage: since July 1, 2017
Biostatistics and Analytical Core: Dr. Orkaby is working very actively with Tom Travison on analysis and has used a portion of REC awarded funds to pay for analyst time.
Preclinical Discovery Core: Dr. Orkaby is planning to begin use of this Core in 2-4 months.

New Awardees:

Lien Quach, PhD, MPH, MD (Mentor: Jonathan F. Bean, MD, MPH, MS**)**

Trainee Profile: Dr. Quach is a gerontologist with a strong interest in the interface of social factors and cognitive and physical functions. She obtained her PhD degree in gerontology from the University of Massachusetts Boston in December 2016, a Master of Public Health degree at Brown University and a MD degree from Hanoi Medical School. After graduation from the PhD program, she began working as a Research Scientist at the Geriatric Research, Education and Clinical Center (GRECC) and the Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC), VA Boston Healthcare System. She has received grants from the Boston Pepper Center and the Center for Large Data Research and Data Sharing in Rehabilitation (CLDR) at the University of Texas Medical Branch. She has previously published 23 peer-reviewed journal articles. Her work resulted in important articles on depression, cognitive functions, social behaviors and falls.

Scientific Progress: Dr. Quach's research examines the role of social engagement in mild cognitive impairment, physical functions and falls among older adults. The project is in the final stage of getting IRB approval. Under separate IRB approval, she has obtained preliminary data, which resulted in the publications listed below. Additionally, she has undertaken training in Network Science and is preparing a CDA grant application, which she intends to submit in June 2019.

Presentations
1. A poster was presented at the GSA 2018 in Boston from Nov 14-18, 2018: **L. T. Quach**, R. Ward, S. Leveille, K. Cho, D. Gagnon, J. F. Bean. The Role of Mild Cognitive Impairment and Social Engagement in Predicting Falls among Primary Care Patients.

2. An oral presentation was delivered at the GSA 2018 in the symposium on how to use archived data from Boston RISE: Amy Pienta, Rachel Ward, **Quach L**. Accessing and Utilizing Archived Boston RISE Data
3. A poster was presented at AMRC in Dallas, TX from Sep 28-Oct3, 2018: **Quach L,** Rycroft S, Leritz E, Burr JA, Gagnon D, Bean JF.The Role of Personal Activities and Mild Cognitive Impairment in Predicting Falls Among Older Adults. American Congress of Rehabilitation Medicine in Dallas, TX, Sep 20-Oct3, 2018

Publications since June 2018 to present

Peer-Reviewed Scholarship in print:

1. Quach L, Ward RE, Pedersen MM, Leveille SG, Grande L, Gagnon DR, Bean JF. The Association between Social Engagement, Mild Cognitive Impairment and Falls among Older Primary Care Patients. Arch Phys Med Rehabil. 2019 Feb 27. pii: S0003- 993(19)30112-1. doi: 10.1016/j.apmr.2019.01.020. [Epub ahead of print]
2. Ward RE, Quach L, Sarah A. Welch, Suzanne G. Leveille, Elizabeth Leritz, Jonathan F. Bean, Interrelated neuromuscular and clinical risk factors that contribute to falls. J Gerontol A Biol Sci Med Sci (in press)
3. Steere HK, Quach L, Laura Grande, Jonathan F. Bean. Evaluating the influence of social engagement on cognitive impairment and mobility outcomes within the Boston RISE cohort study. American Journal of Physical Medicine & Rehabilitation. 2019 Mar 8, [Epub ahead of print]
4. Rycroft SS, Quach L, Ward RE, Pedersen MM, Grande L, Bean JF. The Relationship between Cognitive Impairment and Upper Extremity Function in Older Primary Care Patients. J Gerontol A Biol Sci Med Sci. 2018 Oct 25. doi: 10.1093/gerona/gly246. [Epub ahead of print]
5. Orkaby AR, Nussbaum L, Ho YL, Gagnon D, Quach L, Ward R, Quaden R, Yaksic E, Harrington K, Paik JM, Kim DH, Wilson PW, Gaziano JM, Djousse L, Cho K, Driver JA. The Burden of Frailty among US Veterans and its Association with Mortality, 2002-2012. J Gerontol A Biol Sci Med Sci. 2018.
6. *Reviews/chapters:*
7. Nguyen US, Quach L, Tran TV: Social Stress and Aging. Encyclopedia of Gerontology and Population Aging (in press).

Grants received

The University of Texas Medical Branch at Galveston (5P2CHD065702-09)
Title: THE ASSOCIATION BETWEEN SOCIAL ENGAGEMENT, MILD COGNITIVE IMPAIRMENT AND FALLS."
Duration: July 2018-August 2019
Role: PI
Ministry of Defense: PR180271
Title: Military Veterans with Eating Disorders: Prevalence, Incidence, Patterns of Comorbidity and Cost of Care
Duration: Sep 2019-2024
Role: Co-I

Kieran F. Reid, PhD, MPH (Mentor: Dr. Roger Fielding)

***Trainee Profile*:** Dr. Kieran F. Reid is a Scientist II at the Nutrition, Exercise Physiology and Sarcopenia Laboratory at the Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University. He is also an Assistant Professor at the Friedman School of Nutrition Science and Policy, Tufts University. In addition to his initial undergraduate training in Exercise Physiology, Dr. Reid also possesses an MPH degree from Tufts School of Medicine. Dr. Reid completed his PhD in Clinical Research from Trinity College Dublin in 2014. His research focuses on the implementation of physical activity interventions to maintain the physical and cognitive independence of vulnerable older adults in community-based settings.

***Scientific progress*:** Since July 2018, Dr. Reid successfully initiated a new community-based randomized controlled trial of physical activity among older adults with motoric cognitive risk syndrome (MCR). This study is being conducted within the existing infrastructure of a senior center in Somerville, MA. Study recruitment began in January 2019 and, to-date, 8 older adults with MCR have been randomized to either 24-weeks of physical activity or healthy aging education. This project builds on Dr. Reid's recent ENGAGE pilot study and will provide further preliminary data to design a larger study to unequivocally demonstrate the real-world effectiveness of physical activity for preserving independence among at-risk older adults in community settings.

***Publications*:** Papers submitted, in press or published since July 1, 2018:

1. Reid KF, Laussen J, Bhatia K, Englund D, Kirn DR, Price LL, Manini T, Liu C, Kowaleski C, Fielding RA. Translating the Lifestyle Interventions and Independence for Elders Clinical Trial to Older Adults in a Real-World Community-Based Setting. J Gerontol A Biol Sci Med Sci. 2018 Jul 16. [Epub]
2. Englund DA, Price LL, Grosicki GJ, Iwai M, Kashiwa M, Liu C, Reid KF, Fielding RA. Progressive resistance training improves torque capacity and strength in mobility-limited older adults. J Gerontol A Biol Sci Med Sci. 2018 Aug 27. [Epub]

3. Wanigatunga AA, Manini TM, Cook DR, Katula J, Fielding RA, Kramer AF, Verghese J, Rapp SR, Sink KM, King AC, Buford TW, Anton S, Nadkarni N, Jennings JM, Reid KF, Espeland MA, Gill TM, Pahor M, Nocera JR. Community-Based Activity and Sedentary Patterns Are Associated With Cognitive Performance in Mobility-Limited Older Adults. Front Aging Neurosci. 2018 Nov 15;10:341.
4. von Berens Å, Fielding RA, Gustafsson T, Kirn D, Laussen J, Nydahl M, Reid KF, Travison TG, Zhu H, Cederholm T, Koochek A. Effect of exercise and nutritional supplementation on health-related quality of life and mood in older adults: the VIVE2 randomized controlled trial. BMC Geriatr. 2018 Nov 21;18(1):286.
5. Groessl EJ, Kaplan RM, Rejeski WJ, Katula JA, Glynn NW, King AC, Anton SD, Walkup M, Lu CJ, Reid KF, Spring B, Pahor M. Physical Activity and Performance Impact Long-term Quality of Life in Older Adults at Risk for Major Mobility Disability. Am J Prev Med. 2019 Jan;56(1):141-146.
6. Grosicki G, Englund DA, Price LL, Iwai M, Kashiwa M, Reid KF, Fielding RA. Lower-extremity torque capacity and physical function in mobility-limited older adults. The journal of nutrition, health & aging, Accepted, Feb 2019.
7. Harkey MS, Price LL, Reid KF, Lo GH, Liu S, Lapane KL, McAlindon TE, Driban JB. Objective Physical Function Reference Values Across Sex, Age, Radiographic Knee Osteoarthritis Severity, and Body Mass Index: Data from the Osteoarthritis Initiative. Submitted to Osteoarthritis and Cartilage. Feb 2019.
8. Chang AH, Lee J, Song J, Price LL, Lee A, Reid KF, Fielding RA, Driban J, Harvey W, Wang C. Association between Pre-Intervention Physical Activity Level and Treatment Response to Exercise Therapy in Persons with Knee Osteoarthritis – An Exploratory Study. ACR Open Rheumatology Accepted, Feb 2019.
9. Reid KF, Banurru RR, Wang C, Mori DL, Niles BL. The Effects of Tai Chi Mind-Body Approach on the Mechanisms of Gulf War Illness: an Umbrella Review. Integrative Medicine Research. Submitted, Mar 2019.
10. Zytnick D, Folta S, Reid KF, Tybor D, Gayathri K, Chomitz V. Wearable activity monitor use is associated with national physical activity guidelines and walking among older adults. Preventive Medicine. Submitted Mar 2019.

***Grants received or submitted*:** Grants received or submitted since July 1 2018 (including those that were submitted but not funded.
UG3 NIH HEAL Initiative: Back Pain Consortium ((Reid, Co-I). Title: Progressive Exercise Training as a Multi-System Therapeutic Approach to Treating Chronic Low Back Pain: Examination of Underlying and Sex-Specific Mechanisms and Moderators. 10/01/2019 – 09/30/2024

Tufts University One Healthy Aging Pilot Program (Reid, PI). Title: Assessment of Frailty, Functional Performance, Nutritional Risk and Health Status of Older Adults in the Low Resource Setting of Jimma Town, Southwest Ethiopia. 05/1/2019 – 04/30/2020

HNRCA Pilot Study Program (Reid, PI). Title: ENhancing independence using Group-based community interventions for healthy AGing in Elders: The ENGAGE for Brain Health Pilot Study (ENGAGE-B). 6/1/19 – 5/31/2020

Pepper Center Core Usage: since July 1, 2018
Dr. Reid received study design guidance from Dr. Tom Travison from the Biostatistics and Analytical Core. Dr. Reid is also utilizing the Function Assessment Core for the provision of standardized protocols to measure mobility and cognition outcomes.

3. PILOT EXPLORATORY STUDIES CORE (PESC)

The PESC is led by Director Monty Montano, PhD and Co-Director (Douglas Kiel, MD). Within the context of the OAIC's overall mission, the Pilot and Exploratory Studies Core (PESC) aims to provide catalytic support – seed funding, core support, and mentorship – for innovative pilot research projects that generate data on the mechanisms of FPT action to facilitate more definitive mechanistic studies, feasibility data to guide efficacy trials, hypothesis generating or proof-of-concept exploratory studies and retrospective analysis of existing epidemiologic data that inform FPT interventions. The PESC is cross-institutional collaborative effort that plays a key role in the Boston OAIC. Bi-monthly meetings of the PESC leadership are scheduled to review progress, discuss core activities, review grant proposals and solicit feedback. PESC trainees also attend a regular pepper seminar series and invited speakers hosted by Pepper faculty.

During this initial funding period, the Pilot Exploratory Studies Core of the Boston OAIC supported three outstanding early career investigators that were identified through a competitive application and review process. All three trainees, Drs. Brad Manor, Dae Hyun Kim and Donato Rivas were identified during the preparation of our Pepper renewal grant application study. All of the trainees are on target and making significant progress in their projects. As a group, they have **published 16 manuscripts**. In addition to their projects, the trainees are also participating in the monthly Boston OAIC seminar series. This forum provides valuable opportunities for constructive feedback from our faculty and sparks collaborations among our Center's investigators.

In January 2018, a second call for applications was published, with an application due date of March 1. Seventeen applications were received and reviewed by the Boston Pepper Center steering committee, and new awardees will be notified by May 1, 2018.

Over the past year, the Pilot Exploratory Studies Core of the Boston OAIC selected three outstanding early career investigators that were identified through a competitive application and review process. All three trainees, Drs. Ron Neppl, Shivani Sahni, Rajan Singh were identified through a request for applications that was widely disseminated across the collaborating institutions. The original RFA generated 16 applicants. Applications were reviewed initially for their responsiveness to the OAIC theme and appropriateness to the program. Some applications were triaged based on initial review and the remaining 12 were reviewed by multiple reviewers who submitted formal summaries to the OAIC leadership team. Dr. Montano and Kiel then conducted an NIH study section type of meeting to rank the final applicants. The top three applications were awarded. All of the trainees presented their projects to the External Advisory Board and were approved to begin their projects. Drs Montano and Kiel will meet with each of them in the coming months to ensure they are meeting their milestones and in addition to their projects, the trainees will also be participating in the monthly Boston OAIC seminar series. This forum provides valuable opportunities for constructive feedback from our faculty and sparks collaborations among our Center's investigators. Our REC trainees also have established a new junior investigator collaborative group through the Pepper Center, entitled **Aging Researchers in Early Stages (ARIES)**. This 6-member group is co-led by Dr. Orkaby, together with Dr. Kei Ouchi and Dr. Tammy Hshieh, and its mission is to bring together early stage investigators in Boston to promote cross-disciplinary clinical and translational research focused on the application of aging principles to improve clinical outcomes. The group meets once every 1-2 months to provide peer mentoring and collaborative support, including review of each other's' specific aims and grants. Finally, each of the trainees has presented or been scheduled to present his/her research at the monthly Boston OAIC seminar series. The PESC awardees will also participate in this unique experience

Newly awarded PESC candidates are listed below.

- Ron Neppl, PhD: Loss of a lncRNA exacerbates aging associated functional decline of skeletal muscle. The project is based on a novel gene identified in a screen of lncRNAs whose expression is dysregulated in an established mouse model of skeletal muscle hypertrophy. Gm14635, now referred to as Kratos appears necessary for the maintenance of muscle mass and myogenic expression of transcription factors, and decreases with advancing age, thus suggesting that dysregulation of Kratos may be involved in aging related sarcopenia
- Shivani Sahni, PhD: Mediterranean diet, related antioxidants and frailty. The study proposes that higher intake of antioxidants from a Mediterranean style diet will be associated with reduced risk of frailty and slower progression of frailty over 16 years and this association will be partly mediated by specific markers of oxidative stress. We will address this work via two aims using up to 1,746 participants from a well-characterized cohort, the Framingham Offspring Study.
- Rajan Singh, PhD: Mechanistic basis of differential regulation of polyamine pathway by testosterone in the prostate and androgen-responsive skeletal muscle. The study proposes that ornithine decarboxylase (ODC1) plays an essential role in the biosynthesis of polyamines in the prostate and in mediating the selective trophic effects of testosterone in this tissue.

1st year PESC candidates and their progress are listed below.

- Donato Rivas, PhD: The potential for microRNAs to serve as predictors of anabolic response of skeletal muscle in aged humans.
- Dae Hyun Kim, MD: Home-based exercise intervention to improve functional status after trans-catheter aortic valve replacement.
- Brad Manor PhD: Optimization of non-invasive brain stimulation for improving physical function in older adults.

Donato Rivas, PhD

Research Project: Circulating microRNA as novel predictors of skeletal muscle anabolic response in aged humans.
***Trainee Profile*:** PhD. in Biomedical Science (Bioenergetics) from the Royal Melbourne Institute of Technology, Australia. Dr. Rivas' interests are in the role of substrates on cellular signaling pathways controlling skeletal muscle metabolism and growth; and how nutrition, aging and exercise contribute to alterations in skeletal muscle energy homeostasis.

Scientific Progress: Dr. Rivas is on target and making significant progress in his project, as indicated by his publications below.

Publications:

1. Rivas, D.A., N.P. Rice, Y. Ezzyat, D.J. McDonald, B.E. Cooper, R.A. Fielding. The S1P analog FTY720 reverses obesity but not age-induced anabolic resistance to muscle contraction. *Am. J. Physiol. Cell Physiol.* In 2nd Review.
2. Lessard S.J., T.L. MacDonald, P. Pathak, M.S. Han, V.G. Coffey, J. Edge, D.A. Rivas, M.F. Hirshman, R.J. Davis, L.J. Goodyear. JNK regulates muscle remodeling via myostatin/SMAD inhibition. *Nature Commun.* 2018 Aug 2;9(1):3030. doi: 10.1038/s41467-018-05439-3. PMCID: PMC6072737
3. Margolis L.M., L. Ceglia, D.A. Rivas, B. Dawson-Hughes, R.A. Fielding. Pilot Study Examining the Influence of Potassium Bicarbonate Supplementation on Nitrogen Balance and Whole-Body Ammonia and Urea Turnover Following Short-Term Energy Restriction in Older Men. *Nutrients.* 2018 May 16;10(5). pii: E624. doi: 10.3390/nu10050624. PMCID: PMC5986503

Grants received or submitted

K01 award (K01AG047247): *Role of microRNAs on age and contraction-induced skeletal muscle growth*. This project will provide novel insights into the role of microRNA in the attenuation of aging skeletal muscle to changes in gene expression after anabolic stimulation.

R01 (RAG065469A): *Contributions of circulating exosomal microRNA to adipose-muscle crosstalk in skeletal muscle atrophy.* This proposal is to determine if age-associated changes in miRNA expression from adipose tissue accelerates sarcopenia by altering skeletal muscle anabolic gene expression through exosome-based cell-to-cell communication.

Dae Kim, MD, MPH, ScD

Research Project (REC or PESC): Home-based exercise in patients undergoing TAVR.
Trainee Profile: Dr. Kim received his MD from the Yonsei University College of Medicine before attending John Hopkins School of Public Health to receive his M.P.H. in Epidemiology. He then performed his residency at Thomas Jefferson University Hospital in Internal Medicine, as well as a Fellowship at the Beth Israel Deaconess Medical Center in Geriatric Medicine. Most Recently, Dr. Kim has received a Sc.D. from Harvard School of Public Health. Dr. Kim's research interests are in improving clinical and functional outcomes of aging populations through judicious use of drugs and interventions.
***Scientific Progress*:** Dr. Kim is on target and making significant progress in his project, as indicated by his publications below.

***Publications*:**

1. Kim DH, Glynn RJ, Avorn J, Lipsitz LA, Rockwood K, Pawar A, Schneeweiss S. Validation of a Claims-Based Frailty Index Against Physical Performance and Adverse Health Outcomes in the Health and Retirement Study. J Gerontol A Biol Sci Med Sci. 2018. doi: https://doi.org/10.1093/gerona/gly197. [Epub ahead of print] PMID: 30165612; PMCID: in process

2. Kim DH, Afilalo J, Shi SM, Popma JJ, Khabbaz KR, Laham RJ, Grodstein F, Guibone K, Lux E, Lipsitz LA. Evaluation of Changes in Functional Status in the Year Following Aortic Valve Replacement. JAMA Intern Med. 2019; 179: 383-391. doi:10.1001/jamainternmed.2018.6738. PMID: 30715097; PMCID: in process

3. Shi SM, Sung M, Afilalo J, Lipsitz LA, Kim CA, Popma JJ, Khabbaz KR, Laham RJ, Guibone K, Lee J, Marcantonio ER, Kim DH. Delirium Incidence and Functional Outcomes After Transcatheter and Surgical Aortic Valve Replacement. J Am Geriatr Soc. 2019 Mar 18. PMID: 30882905. PMC in process.

Grants received or submitted related to your project:

- Dr. Kim received his R01 grant entitled "Epidemiology and Risk of Antipsychotic Use in Hospitalized Elderly with Delirium" (NIA 1R01AG056368-01A1). This study aims to evaluate the utilization and comparative safety of antipsychotics and other psychoactive drugs in older hospitalized patients undergoing major surgery.
- He has a pending R01 grant entitled "Prospective Monitoring of Newly Approved Cardiovascular Drugs in Older Adults with Frailty" (NIA 1R01AG062713-01, percentile 4). This study aims to establish a prospective monitoring program for newly approved cardiovascular drugs for older adults with frailty in routine healthcare databases and identify predictors of benefit from the new drugs.
- He also has a pending R21 grant entitled "Restricted Mean Survival Time to Interpret Clinical Trials for Treatment Decision-Making in Older Adults" (NIA 1R21AG060227-01A1, percentile 8). This study aims to evaluate the usefulness of restricted mean survival time as an alternative to hazard ratios to summarize treatment effect for intuitive interpretation and treatment decision-making.

Bradley Manor, PhD

Research Project: Optimization of non-invasive brain stimulation for improving physical function in older adults.
Trainee profile: Dr. Manor received his B.S in Kinesiology as well as his M.S in Biomechanics from the University of Toledo. He later attended Louisiana State University where he received a PhD in Biomechanics. Dr. Manor also performed a post-doctoral fellowship at the Beth Israel Deaconess Medical Center with a focus on Gerontology. Dr. Manor is trained in the neural control and rehabilitation of human movement and conducts research aimed at alleviating the burden of balance decline and falls in older adults.
Scientific Progress: Dr. Manor is on target and making significant progress in his project, as indicated by his publications below.

Publications:

1. Jor'dan AJ, Manor B, Iloputaife I, Habtemarian D, Bean JF, Sorond FA, Lipsitz LA. Diminished locomotor control is associated with reduced neurovascular coupling in older adults. Journal of Gerontology Series A: Biological Sciences and Medical Sciences. 2019. Epub ahead of print. doi: 10.1093/gerona/glz006.
2. Manor B, Zhou J, Harrison R, Lo OY, Travison TG, Hausdorff JM, Pascual-Leone A, Lipsitz LA. Transcranial direct current stimulation may improve cognitive-motor function in functionally limited older adults. Neurorehabil Neural Repair. 2018 Sep;32(9):788-798. PMCID: PMC6143414.
3. Zhou J, Lo OY, Lipsitz LA, Zhang J, Fang J, Manor B. Transcranial direct current stimulation enhances foot sole somatosensation when standing in older adults. Exp Brain Res. 2018 Mar;236(3):795-802. PMCID: PMC5828881.
4. Manor B, Yu W, Zhu H, Harrison R, Lo OY, Lipsitz L, Travison T, Pascual-Leone A, Zhou J. Smartphone app-based assessment of gait during normal and dual-task walking: demonstration of validity and reliability. JMIR Mhealth Uhealth. 2018 Jan 30;6(1):e36. PMCID: PMC5811655.
5. Dagan M, Herman T, Harrison R, Zhou J, Giladi N, Ruffini G, Manor B, Hausdorff JM. Multitarget transcranial direct current stimulation for freezing of gait in Parkinson's disease. Mov Disord. 2018 Apr;33(4):642-646. PMCID: 5964604.
6. Lo OY, Halko MA, Zhou J, Harrison R, Lipsitz LA, Manor B. Gait speed and gait variability are associated with different functional brain networks. Front Aging Neurosci. 2017 Nov 29;9:390. PMCID: PMC5715372.
7. Gow BJ, Hausdorff JM, Manor B, Lipsitz LA, Macklin EA, Bonato P, Novak V, Peng CK, Ahn AC, Wayne PM. Can Tai Chi training impact fractal stride time dynamics, an index of gait health, in older adults? Cross-sectional and randomized trial studies. PLoS One. 2017 Oct 11;12(10):e0186212. PMCID: PMC5636131.
8. Wayne PM, Gagnon MM, Macklin EA, Travison TG, Manor B, Lachman M, Thomas CP, Lipsitz LA. The Mind Body-Wellness in Supportive Housing (Mi-WiSH) study: design and rationale of a cluster randomized controlled trial of Tai Chi in senior housing. Contemp Clin Trials. 2017 Sep;60:96-104. PMCID: PMC5639896.
9. Zhou J, Habtemariam D, Iloputaife I, Lipsitz LA, Manor B. The complexity of standing postural sway associates with future falls in community-dwelling older adults: the MOBILIZE Boston Study. Sci Rep. 2017 Jun 7;7(1):2924. PMCID: PMC5462759.
10. Jor'dan AJ, Poole VN, Iloputaife I, Milberg W, Manor B, Esterman M, Lipsitz LA. Executive network activation is linked to walking speed in older adults: functional MRI and TCD ultrasound evidence from the MOBILIZE Boston Study. J Gerontol A Biol Sci Med Sci. 2017 Nov 9;72(12):1669-1675. PMCID: PMC5861979.

Grants received or submitted related to your project

- Marcus Applebaum Pilot Award (PI = Manor; 05/01/17 – 04/30/18): *Home-based measurement of dual task balance in older adults receiving noninvasive brain stimulation***.** The overall goal of this pilot grant was to inform a randomized controlled trial to establish the effects of a multi-session transcranial direct current stimulation (tDCS) intervention on dual tasking and falls in older adults with high risk of falling, as defined by a recent history of recurrent falls. This goal was accomplished by implementing a validated smartphone-based home assessment of dual task balance to an ongoing study (funded by a Boston OAIC Pilot Award) examining the effects of tDCS on balance in older adults with a recent history of recurrent falls.
- K01AG044543 (PI = Manor; 2015-18): *Modulating brain activity to preserve gait in older adults.* This career development award combined walking assessments, functional brain imaging and noninvasive brain stimulation techniques to demonstrate that in healthy older adults, performing a cognitive task interferes with the control of walking by diminishing the brain's responsiveness to walking-related sensory feedback.
- R01 AG059089-01A1 (PI = Manor; 10/1/2019-9/30/2024): *Personalized brain activity modulation to improve balance and cognition in elderly fallers*. The goals of this project are to conduct a randomized, sham-controlled, double-blinded trial with immediate, 3- and 6-month follow-ups in older adults with previous falls to compare the effects of a personalized multisession transcranial direct current stimulation (tDCS) intervention, as compared to sham, on the dual task costs to standing and walking, as well as other physical and cognitive outcomes that are on the causal pathway to falls and are important to everyday function.

- R21 AG064575-01 (PI = Manor; Pending: SRG Outcome: Impact Score = 23; 5th percentile). *Optimizing transcranial direct current stimulation (tDCS) to improve dual task gait and balance in older adults*. The overarching goal of this project is to examine the immediate after-effects of personalized high-resolution tDCS, conventional low-resolution tDCS, and sham stimulation, on dual task standing and walking in older adults with poor baseline dual task walking performance.
- Alzheimer's disease and its related Dementias (AD/ADRD)-focused Administrative supplement to the Boston Claude D. Pepper Older Americans Independence Center (OAIC) (P30-AG031679-08) (PI = Manor; Pending). *Noninvasive brain stimulation to improve cognition and mobility in mild Alzheimer's disease.* The goal of this pilot study is to test the feasibility and effects of a multi-session transcranial direct current stimulation (tDCS) intervention on dual task gait and balance in older adults with mild Alzheimer's disease. This goal will be accomplished by expanding upon a study supported by a Boston OAIC Pilot Grant awarded to Dr. Manor.

2nd year PESC candidates and their progress are listed below.

- Ronald L Neppl, PhD: *Research Project:* Loss of lncRNA exacerbates aging associated function decline of skeletal muscle
- Rajan Singh, PhD: Mechanistic basis of differential regulation of polyamine pathway by testosterone in the prostate and androgen-responsive skeletal muscle
- Shivani Sahni, PhD: Mediterranean diet, related antioxidants and frailty.

Ronald L Neppl, PhD

Research Project: Loss of lncRNA exacerbates aging associated function decline of skeletal muscle
Trainee Profile: Dr. Neppl received his PhD in Biophysics from the University of Virginia and completed postdoctoral fellowships at Boston Children's Hospital and Boston University School of Medicine where he focused on skeletal and cardiac muscle physiology and the molecular regulation of gene expression. Dr. Neppl's research interests include the molecular regulation of muscle metabolism, growth, and regeneration, and how these processes become dysregulated during aging.
Scientific Progress: Dr. Neppl is on target and making significant progress on his project.
Publications:

1. Guadagnin E, Bagchi D, Sinha I, Neppl RL. (2018) Nuclear localized Akt limits skeletal muscle derived fibrotic signaling. Biochem Biophys Res Commun. Dec 7. pii: S0006-291X(18)32640-8. doi: 10.1016/j.bbrc.2018.11.202. [Epub ahead of print]

Grants submitted:
NIH R01 AG061208-02: *The role of lncRNA Chronos in aging associated muscle atrophy.* This study utilizes multiple novel mouse knockout lines to determine the physiological and molecular roles of the lncRNA Chronos, and its novel interaction partners, in the regulation of gene expression and muscle metabolism as a function of age

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Rajan Singh, PhD

Research Project: Mechanistic basis of differential regulation of polyamine pathway by testosterone in the prostate and androgen-responsive skeletal muscle

Trainee profile: Dr. Singh received his B.S in Chemistry from Kolkata University and his M.S in Biochemistry from Jadavpur University. He attended Indian Institute of Chemical Biology (IICB) where he received a PhD in Molecular Biology. Dr. Singh did his post-doctoral fellowship at UCLA School of Medicine in specific areas of cardiovascular/androgen biology as well as specific role of arginine/polyamine biosynthetic pathways related to cell fate determination in breast cancer cells. Dr. Singh subsequently joined Division of Endocrinology at Charles R Drew University of Medicine and Science where he focused on identifying the molecular targets of testosterone responsible for its action on fat and muscle mass and identified follistatin as a direct down-stream target of androgen action. Dr. Singh holds joint appointments at UCLA School of Medicine (Associate Professor, in-residence) and Research Scientist at Brigham and Women's Hospital.

Scientific Progress: To generate a conditional knock-out (KO) and a constitutive KO of the *Odc1* gene, Dr. Singh has successfully generated chimeric G0 mice by microinjection of validated ES cell clones into blastocysts and transferred the injected blastocysts into pseudopregnant females. The final heterozygous mice are being generated by IVF fertilization using sperm of a G0 chimeric mouse and C57BL/6 N Tac oocytes. The G1 mice will be available by the middle of this

year to assess the effects of testosterone withdrawal and replacement in conditional prostate-specific and muscle-specific genetic disruption of Odc1 using Odc1 $^{flox/flox}$/ Pbsn ^{CreEsr1} mice. We expect to complete the proposed experiments in time.

Publications: Awaiting the completion of the proposed experiments after successfully generating the G1 mice.

Grants received or submitted:

Grant Submitted on March11th, 2019: Revised R01 (***RO1 AG061747-A1***) application entitled "*Mechanisms of differential regulation of prostate and skeletal muscle by testosterone".*
The overall objective is to elucidate the mechanisms by which testosterone differentially regulates the polyamine pathway in the prostate and the androgen-responsive skeletal muscle and assess the therapeutic selectivity and safety of a combination of testosterone plus an ornithine decarboxylase 1 inhibitor. The proposed studies in this grant application will advance our understanding of the mechanisms of tissue selectivity of testosterone's effects on the prostate vs. muscle and provide novel information about the potential role of the alternate pathway for putrescine synthesis through agmatine in regulation of skeletal muscle growth by testosterone.
Role: Co-investigator

Grant Submitted on March 5th 2019: Revised RO1 (RHL146520A) application entitled *"Novel roles of follistatin in enhancing brown Adipogenesis and protection against the development of atherosclerosis".*
This overall goal of this project is to test the effect of follistatin (Fst)-induced adipose browning on regulation of lipid and cholesterol metabolism that contribute to the development of dyslipidemia and atherosclerosis using both *in-vivo* and *in-vitro* approaches and identify key molecular targets involved in mitigating dyslipidemia and development of atherosclerosis.
Role: Principal Investigator

Shivani Sahni, PhD

Research Project (PESC): Mediterranean diet, related antioxidants and frailty.
***Trainee Profile*:** PhD. in Nutritional Epidemiology from the Friedman School of Nutrition Science and Policy, Tufts University, Boston, MA. Dr. Sahni's interests are in the role of nutrition and diet on age-related osteoporosis, sarcopenia and frailty.
Scientific Progress: Dr. Sahni has received the IRB approval and established the DMDA with Framingham Heart Study. She has acquired multiple datasets on diet, frailty components and covariates. She is currently working on analysis of Aim 1 of her grant.

Publications:

1. Hruby A, Sahni S, Bolster D, Jacques PF. Protein intake and functional integrity in aging: The Framingham Heart Study Offspring. The Journals of Gerontology: Series A 2018 September 24. doi:10.1093/gerona/gly201. PMID: 30247514.
2. Hannan MT, Weycker D, McLean RR, Sahni S, Bornheimer R, Barron R, Travison R, Kiel D. Predictors of imminent risk of non-vertebral fracture in older, high-risk women: The Framingham Osteoporosis Study. Journal of Bone and Mineral Research Open, 2018 December 3. doi: 10.1002/jbm4.10129.
3. Mangano KM, Noel SE, Sahni S, Tucker KL. Dairy Intakes are associated with Bone Mineral Density among adults with sufficient Vitamin D status: Results from the Boston Puerto Rican Osteoporosis Study. Journal of Nutrition, 2019 Jan 2. doi: 10.1093/jn/nxy234. PMID: 30601986.
4. Darling, AL, Manders R, Sahni S, Zhu H, Hewitt CE, Prince R, Millward DJ, Lanham-New SA. Dietary protein and bone health across the life-course: an updated systematic review and meta-analysis over 40 years. Osteoporosis International, 2019 March 21, doi: 10.1007/s00198-019-04933-8. PMID: 30903209.
5. Bailey RL, Chocano P, Daly R, Sahni S, Weaver C, Welch A. Guidelines for Observational Research to Assess the Relationship of Nutrition and Bone: An International Working Group Summary. Advances in Nutrition, 2019 Mar 30. pii: nmy111. doi: 10.1093/advances/nmy111. PMID: 30926984.

Grants received or submitted related to your project:

- *Dairy food intake, related nutrients and frailty* funded by the National Dairy Council. The goal of this project is to determine the role of dairy foods intake (defined as intake of milk, yogurt, cheese and a combination of milk+yogurt+cheese, low-fat dairy and high-fat dairy) on the risk of frailty over time, and whether dairy specific nutrients such as dietary protein, calcium and vitamin D represent an important part of the biologic pathway involving dairy foods intake and frailty.
- *Novel phenotypes for musculoskeletal aging* submitted to the NIA/NIH (R01) (PI: Dr. Douglas P. Kiel). The goal of this project is to measure total muscle mass via D_3-creatine dilution method and determine its association with

genetic and non-genetic risk factors, as well as the relation with falls, injurious falls and fractures in a large, community-based cohorts of older adults, the Framingham Heart Study and the Osteoporotic Fractures in Men.

4. RESOURCE CORES

Function Assessment Core (FAC)

The FAC is led by Roger A. Fielding, PhD and Co-Director Thomas Storer, PhD. The FAC is jointly located at Tufts USDA Human Nutrition Research Center on Aging (HNRCA), and BWH, which allows greater participation of BWH aging researchers, and facilitates access to the resources of BWH and Harvard Medical School along with Tufts. The FAC seeks to provide direct measurement and consultative services, as well as assist with proposal development for clinical studies supported by, or associated with, the theme of the OAIC that require measures of musculoskeletal impairments, physical function, and/or disability. All Core services employ standardized equipment and operating protocols for the assessment of muscle performance and functional limitations in human studies and maintain extensive quality control procedures including: personnel training and certification; equipment maintenance; and instrument quality control. The FAC is a truly inter-institutional collaborative tool that plays an integral role in the Boston OAIC. Monthly meetings of the FAC leadership are held to discuss core activities, review requests for utilization of FAC services, to assess progress of developmental projects and other initiatives. Availability of FAC services are being promoted promoted through several mechanisms including the BU-Tufts OAIC websites, announcements at OAIC seminars and meetings, and outreach to colleagues at our respective institutions. Recent publications and support for OAIC pilot and REC activities is listed below. The specific aims of the FAC have not changed since the initial grant submission and include:

Aim 1: We will provide an organized infrastructure for FAC-supported procedures and activities across Tufts' Human Nutrition Research Center on Aging, and Brigham and Women's Hospital Laboratory of Exercise Physiology and Physical Function and serve as focal point for interdisciplinary collaboration by OAIC investigators in the development, evaluation, and application of new and existing tools and instruments to assess musculoskeletal impairments, physical function, and disability in older adults to evaluate the efficacy of function promoting therapies.

Aim 2: We will provide direct measurement and consultative services, as well as assist with proposal development for clinical studies supported by, or associated with, the theme of the OAIC that require measures of musculoskeletal impairments, physical function, and/or disability. All Core services will use standardized equipment and operating protocols for the assessment of muscle performance and functional limitations in human studies and will maintain extensive quality control procedures including: personnel training and certification; equipment maintenance; and quality control.

Aim 3: We will develop novel and innovative approaches to assess musculoskeletal impairments, physical function, and disability in older adults. The FAC will also support innovative developmental projects that seek to develop or further validate innovative approaches to assess musculoskeletal impairments, physical function, and disability in older adults.

List of projects that include or engage use of Core services.

Pepper Center-supported projects:

1. Donato Rivas, PhD: The potential for microRNAs to serve as predictors of anabolic response of skeletal muscle in aged humans.
2. Dae Hyun Kim, MD: Home-based exercise intervention to improve functional status after trans-catheter aortic valve replacement.
3. Brad Manor PhD: Optimization of non-invasive brain stimulation for improving physical function in older adults.
4. Michael Lustgarten, PhD: The effect of prebiotic supplementation on lean mass and physical function in older adults.
5. Ariela Orkaby, MD, MPH: Is aspirin use associated with frailty and functional limitation in older men?
6. Kieran Reid, PhD: Translating exercise into the community to preserve independence among older adults with motoric cognitive risk syndrome.
7. Lien Quach, PhD, MD: Physical Function: The roles of social engagement and cognitive impairment.
8. Shivani Shah, PhD: Mediterranean diet, related antioxidants and frailty.
9. Marsha A. Testa, MPH, PhD: The impact of NMN treatment on self-reported function and well being in older men with functional limitations.

External Projects:

R01AI108541 **Montano (PI)**
Biomarkers For Muscle Function And Aging In Chronic HIV Infection
Source: NIAID

This study will test a model wherein HIV associated chronic inflammation promote an imbalance in muscle tissue remodeling resulting in an accelerated muscle fibrosis. We expect that skeletal muscle fibrosis would help to explain the observed disproportionate decline in muscle function, a phenomenon that is similar to what is observed in human aging.

R21AG055415 **Montano (PI)**
Role of ART in Novel HIV-Associated Myopathy
Source: NIA
This study will characterize whether a novel muscle myopathy associated with HIV infection is influenced by antiretroviral (ART) therapy regimen, specifically efavirenz (EFV). This R21 proposal is in response to PAR-15-282 (HIV and Aging) and NOT-15-137 (NIH Research Priorities), which set a high priority for studies on “HIV-associated comorbidities and premature aging associated with long-term HIV disease and antiretroviral therapy”.

R01AG025037 **Lipsitz (PI)**
Health Outcomes of Tai Chi in Subsidized Senior Housing
Source: NIA
This study will determine whether Tai Chi is an effective and practical intervention to improve overall function and lower health care costs in an expensive, vulnerable population of seniors that is more representative of many US communities than those previously studied. If the results are favorable, our study will also provide the necessary training and protocol manuals to replicate Tai Chi programs in senior housing facilities across the nation to help prevent, better manage, and overcome frailty among seniors.

R01AG041785 **Lipsitz (PI)**
CEREBROVASCULAR MECHANISMS OF SLOW GAIT AND FALLS
Source: NIA
This study explores alterations in cerebral blood flow as a pathological mechanism of falls, develops cutting-edge magnetic resonance imaging techniques to detect early microstructural markers of brain damage that can predict falls, and identifies a compensatory mechanism that protects some people from the effects of this damage on falls - all in a large representative elderly cohort of the MOBILIZE Boston Study. The study will provide new information necessary for the early diagnosis and ultimate prevention of cerebrovascular causes of falls and mobility impairments in elderly people.

RO1AG048326 **Bhasin S (PI)**
Randomized Trial of a Multi-factorial Fall Injury Prevention Strategy
Source: NIA-PCORI
This is an RCT of a risk-factor based, multi-factorial fall injury prevention strategy.

8050-51000-091-01S / USDA/ARS **Fielding (PI)**
Nutrition, Sarcopenia, Physical Function, and Skeletal Muscle Capacity during Aging
Source: USDA-ARS
This grant supports the core functions of the Nutrition, Exercise Physiology and Sarcopenia Laboratory and its mission is to conduct research into how exercise and diet can influence age-related loss of skeletal muscle mass and function (sarcopenia). Projects include both human and animal studies, ranging from the molecular level to population-based observational and intervention studies.

U01 AG050499 **Pahor (PI)**
The ENRGISE Study, Reduction of Inflammation in Seniors
Source: NIA
The primary goals of the ENRGISE Pilot Study are to assess the effects of the interventions on several inflammatory markers, walking speed, physical function and strength.

1R01NR014502 **Bhasin S (PI)**
A Selective Androgen Receptor Modulator for Symptoms of Androgen Deficiency in Prostate Cancer
Source: NINR
Specific Aims: To conduct a randomized trial of a prostate sparing SARM in men with prostate cancer experiencing symptoms of androgen deficiency
Overlap: None

R01 AG051728 **Sahni (PI)**
Novel Factors for Muscle Mass and Strength in Adults
Source: NIA
The major goals of this project are to examine the association of antioxidant intake, vascular function and mitochondrial function with age-related loss of muscle mass, quality, strength and gait speed using data from the Framingham Offspring Study (FOS) and Cardiovascular Health Study (CHS).

UO1 AG051421 **Bhasin (PI)**
Muscle Mass and Strength Cut-points in Persons at Risk of Mobility Disability
Source: NIA
The goals of this project are to establish evidence-based cut-points for muscle mass and strength to define sarcopenia as a biomarker to identify older adults at risk for physical disability.

RO1 AG060639 **Bhasin (PI)**
Improving Quality of Life of Prostate Cancer Survivors with Androgen Deficiency
Source: NIA
The goal of this project is to conduct a double-blind, placebo-controlled, parallel-group, randomized trial to determine whether testosterone replacement is safe and efficacious in improving sexual and physical function in men with androgen deficiency, who have undergone radical prostatectomy for pT2,N0,M0, Gleason score ≤6 disease and are at very low risk of disease recurrence.

R21AR074138 **Dawson-Hughes (PI)**
Effect of a ghrelin receptor agonist on muscle and bone
Source: NIAMS
The major goal of this project is to determine the effect of a ghrelin receptor agonist on bone remodeling, lean tissue mass, and muscle function in adults with low bone and muscle mass.

R01DK115562 **Shlipak and Coca (PI)**
Impact of Exercise on Kidney Function and Injury Among Elders in the LIFE Trial
Source: NIDDK
The goal of this project is to measure the impact of structured physical activity (SPA) intervention compared with a health education (HE) intervention on reducing kidney function decline.

R01AG055443 **Ceglia (PI)**
Impact of protein and alkali supplementation on skeletal muscle in older adults
Source: NIA
The goal of this project is to determine whether an alkaline salt supplement (potassium bicarbonate) can enhance the beneficial impact of a high protein diet on muscle performance and mass.

Manuscripts published, in press or in preparation by users

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PRECLINICAL DISCOVERY CORE (PDC)

The PDC is led by Ravi Jasuja, PhD. Dr. Jasuja is a Principal Investigator in the Muscle and Aging Research Unit at the Brigham and Women's Hospital and a faculty at Harvard Medical School. In the first year, the PDC finalized a series of service request form that are placed online on the Boston OAIC website (www.bostonpeppercenter.org). In the past several months, Dr. Jasuja has worked closely with LASC staff and the PIs in the Pepper OAIC funded studies to implement the online access to the core facilities and corresponding requisition forms. A total of 8 OAIC projects (previously funded through Pepper Center and currently supported) are utilizing the Scientific consultation and PDC resources. The investigators at UTHSCA and at Mount Sinai Pepper centers sought consulting advice from Dr. Jasuja, scientific review of translational research applications and support for NIH grant submissions. The PDC core has been instrumental in supporting submission of several grants, on which 4 projects have successfully obtained funding in this year (DOD, NIH, Beeson grant award).

The Preclinical Discovery Core provides the infrastructure for these services by accomplishing the following specific aims:

1. Provide a focal point for interdisciplinary collaboration by Boston OAIC investigators in the application of existing and new tools to assess muscle impairments, metabolic alterations and physical function.
2. Provide standardized, state-of-the-art methods and instruments to assess body composition (lean body mass, whole body and regional fat mass, skeletal muscle mass, functional microscopy of the muscle) in animal models of aging and to quantitate response to FPTs.
3. Provide standardized equipment and operating protocols for the assessment of muscle performance and physical function in preclinical models of aging.
4. Develop novel non-invasive imaging modalities for longitudinal proof-of-concept and mechanistic studies of muscle loss and regeneration in the preclinical studies of FPT.
5. Provide OCT/paraffin embedded muscle tissue histology and histomorphometry for animal models.
6. Implement rigorous quality control by personnel training and certification in standardized procedures for assessment of muscle performance and physical function, and by maintaining equipment calibration.

Brief Description of services available through the core:

1. Longitudinal Assessment of Body Composition by NMR and MicroCT Scanner. Body composition of mice and determined by small animal NMR (EchoMRI 900; echoMRI, TX) calibrated and certified for non-invasive monitoring of small experimental animals.

2. Measures of Muscle Performance and Physical Function

a. Grip strength. Grip strength serves as a global measure of muscle strength,and will be assessed by a computer-integrated grip meter (Columbus Instruments) using standardized laboratory protocols. Animals grasp a bar linked to a computer-integrated force transducer with their front limbs and are then drawn away from the bar. Peak force is recorded as the outcome measure.

b. Ex-vivo Muscle Mechanics. Muscle mechanics measurements are performed on an Intact Muscle Test System (1205A 10N force, Aurora Scientific, Inc., Ontario, Canada)). Maximal tetanic forces in EDL and SOL muscles are determined using 80 HZ-1500 ms and 120 HZ-500 ms supramaximal electrical pulses, following the standardized protocols. The quantifiable outcomes include contraction and half-relaxation times, force-velocity relationships and the maximum velocity of unloaded shortening extrapolated from the force-velocity curves

c. Aerobic capacity. The Oxymax System is linked to an enclosed treadmill for monitoring metabolic performance under exercise. The laboratory also houses a multi-lane motorized treadmill (Columbus Instruments) for determining exercise capacity (running speed, time, distance, work and power) and conducting exercise training studies.

d. Physical Activity. The metabolic chambers are equipped with photocells that are aligned to the X-, Y- and Z-axes to quantify habitual physical activity in the horizontal (ambulation) and vertical (rearing) planes.

3. Metabolic Outcomes Assessment

3a. Energy Expenditure and Basal Metabolic Rate. Energy expenditure and basal metabolic rate in mice and rats are determined using a computer-integrated Oxymax Open Circuit Calorimeter System (Columbus Instruments) linked to collection chambers to quantify VO_2, VCO_2, respiratory exchange ratio, and basal metabolic rate over 24 hours. The oxygen and carbon dioxide analyzers are calibrated prior to every experiment using a standardized laboratory protocol. The system accommodates 8 mice or 4 rats per experiment.

3b. Core Body Temperature. Core body temperatures of mice and rats is measured by using an infrared high-performance non-contact Raynger MX4 thermometer (Raytek Portable Products). In longitudinal experiments, core body temperature can also be measured by using implantable microchips containing temperature transponders (IPTT-100) and a hand-held reader (Bio-Medic Data Systems, Delaware).

Small Animal Resource Core Utilization

A total of 8 OAIC projects (previously funded through Pepper Center and currently supported) are utilizing the Scientific consultation and PDC resources. The investigators at UTHSCA and at Mount Sinai Pepper centers sought consulting advise from Dr. Jasuja, scientific review of translational research applications and support for NIH grant submissions. The PDC core has been instrumental in supporting submission of several grants, on which 4 projects have successfully obtained funding in this year (DOD, NIH, Beeson grant award).

List of projects that include or engage use of PDC services (Table 7).

PI	Title	Services Provided
Sinha, I	Increased cyclooxygenase-2 activity mediates aging-associated decrease in skeletal muscle regeneration.	**Continued support to the Beeson Award.** Physical function, Exercise capacity Neuromuscular coordination, Spontaneous activity, NMR imaging
Garza, A	Role of Striatin in Age-associated Functional Limitations	Scientific consultation, NMR imaging, Physical Function and exercise capacity
Lustgarten, M	Role of Striatin in Age-associated Functional Limitations	**Continued support to the NIH funded grant**. Scientific consultation, NMR imaging, Physical Function and exercise capacity
Giatsidis, G	Skeletal muscle regeneration after Volumetric Muscle Loss injury	**Continued support to the DOD funded grant.** Scientific consultation, NMR imaging, Physical Function and exercise capacity
Christou, H	Preclinical models of Pulmonary Hypertension and the effect of a novel intervention	**Continued support to the NIH funding (R21).** Scientific consultation, NMR imaging, Physical Function and exercise capacity
Neppl, R	Loss of lncRNA exacerbates aging associated function decline of skeletal muscle	**Continued support to the revised submission of (R01)** Scientific consultation, NMR imaging, Physical Function and exercise capacity
Singh, R	Mechanisms of prostate sparing, muscle anabolic effects of combined administration of ornithine decarboxylase inhibitor and testosterone	**Continued support to the revised submission of (R01)** Scientific consultation, Metabolic and physical function characterization
Romero, JA	Mineralocorticoid Receptor Activation and Physical Function in Aging: Role of Striatin	Scientific consultation, Metabolic and physical function characterization
Bastarrachea, RA	Engineering brown fat into skeletal muscle using UTMD Gene Therapy in baboons	
Lessard, S	Investigation of SNARK as a novel regulator of age-induced muscle atrophy	Scientific consultation, NMR imaging, Physical Function and exercise capacity

Guo, W	Mechanisms of Testosterone's Effects on Erythropoiesis: Guo	NMR imaging, Physical Function, and exercise capacity
Zawaki, AM	Defining how Thyroid hormone alters/impairs muscle regeneration in aging	Scientific consultation, Exercise capacity, NMR and Habitual activity monitoring and muscle histology

Procedures for Animal Care

All projects that are utilizing PDC services must receive an independent IACUC approval before they can initiate the use of core resources. Evidence of continuing IACUC review and approval is documented and the approved version of the IACUC protocol is kept in the core office.

Animals are housed at AAALAC accredited facilities of BWH. Routine veterinary care to animals is provided daily by veterinary technicians under the direction of one of the attending veterinarians. Animal use is additionally monitored by the Coordinator for Training and Compliance. The veterinary staff at each of the participating institutions has substantial experience in maintaining older mice.

Progress on innovative contributions

Ex-vivo Muscle Mechanics available in the PDC core is now being customized for sensitive measurements of muscle dynamics requested by OAIC funded investigators. Muscle mechanics measurements are performed on an Intact Muscle Test System (1205A 10N force, Aurora Scientific, Inc., Ontario, Canada)). Maximal tetanic forces in EDL and SOL muscles are determined using 80 HZ-1500 ms and 120 HZ-500 ms supramaximal electrical pulses, following the standardized protocols. The quantifiable outcomes include contraction and half-relaxation times, force-velocity relationships and the maximum velocity of unloaded shortening extrapolated from the force-velocity curves. This setup allows for an extensible framework for integration of force transducers for small measurements up to 0.5N with a resolution of 0.3mN.

BIOSTATISTICAL DESIGN AND ANALYSIS CORE CORE (BDAC)

The BDAC is led by Tom Travison, PhD. Dr. Travison is Associate Professor at Harvard Medical School and is the Director of Biostatistics and Data Science at the Marcus Institute for Aging Research at Hebrew SeniorLife. The overall goals of the BDAC are (1) to provide resource and environmental supports promoting best statistical and data management practices to strengthen the quality of OAIC training and research activities; and (2) to facilitate the development of FPTs through the support and execution of research at all stages of the development process. The latter goal encompasses conduct of: (a) epidemiologic investigations in the endocrinology of aging and physical function; (b) translational research projects bridging the development of therapeutic agents and practices to clinical utility; and (c) randomized trials with the goal of demonstrating the safety and efficacy of FPTs in improving physical in aging.

The Specific Aims of the BDAC are as follows:

Specific Aim 1. To provide rigorous, secure and comprehensive biostatistical and data management support to OAIC projects. BDAC provides expertise and resource support for all aspects of project design, development, execution and publication.

Specific Aim 2. To conduct novel applied and methodologic research aligned with the OAIC initiatives, with emphasis on conduct of intervention trials and translational research in FPTs. BDAC maintains a program of independent and collaborative epidemiologic and translational research thematically related to and supportive of the OAIC mission.

Specific Aim 3. To insure rigorous training in research design and data analysis of clinical and quantitative scientists, with emphasis on the epidemiology and treatment of loss of physical function in aging. Through training, peer mentoring and promotion of collaborative investigation, the Core promotes the training and education of its members, OAIC scientists and OAIC trainees in rigorous design and analytic procedures.

NIA-Funded Projects Making Use of BDAC personnel and Resources.

Bhasin S, Reuben D, Gill T. *Randomized Trial of a Multifactorial Fall Injury Prevention Strategy.*

Basaria S. *Elucidating the Mechanisms of Insulin resistance in Men Undergoing Androgen Deprivation Therapy for Prostate Cancer*

Cawthon P, Bhasin S. *Muscle mass and strength cut-points in Persons at Risk of Mobility Disability*

Kramer D. *Frailty, Physical Activity, and Mobility in Patients With Cardiac Implantable Electrical Devices*

Kiel D. *Risk Factors for Age Related Bone Loss*

Lipsitz L, Wayne P. *Health Outcomes of Tai Chi in Subsidized Senior Housing*

Manor B. *Treatment of Cerebral Microvascular Disease with Noninvasive Brain Stimulation*

Orkaby A. *Aspirin use, frailty and functional decline in HRS.*

Reid K. *Tai Chi or traditional physical activity for preserving independence among older adults with motoric cognitive risk syndrome: a pragmatic community-based study*

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Strategic Plan
Over the next year, the BDAC will continue progress on its goals. Specifically it will: continue to support active projects, with emphasis on newly-funded PESC and REC core candidates and projects; conduct training workshops for young and mid-career investigators; support applications for new funding, with emphasis on early-career investigators; and, in cooperation with the HSL Interventional Studies and Aging Center (co-directors Mitchell S and Travison T) continue to develop and make available tools created in part through funding of its development project (see below).

Development Project
Specific Aims / Goals

PI: Travison TG

Building on recent improvements in relevant technologies, this project will be focused on the development of reusable web-based technologies for the production of replicable analytic results in the clinical research setting. Importantly, it will result in a reusable architecture that can be readily adapted for the monitoring and reporting of randomized and non-randomized research studies at the Boston OAIC as well as in new technologies that can be disseminated and shared within the OAIC consortium.

Development Project Aim 1. To develop a suite of web-based interactive data reporting and analysis tools consistent with the principles of reproducible research and suitable for deployment in a complex clinical trial.

Development Project Aim 2. To develop tools for automated adaptation of the analysis suite to new data structures, bringing the functionality developed in Aim 1 to new investigations in a resource-effective manner.
The developmental project has now completed its aims.

Publications related to the Developmental Project

This project is focused on the development and dissemination of software tools. The following are currently available and mature:

kableExtra (**Zhu H, Travison TG, Tsai T et al**.) https://CRAN.R-project.org/package=kableExtra. Invents a new syntax to customize the display of publication-quality complex tables in reproducible documents and HTML.

ezsummary (**Zhu H, Tsai T, Umyarov A, Travison TG**): https://CRAN.R-project.org/package=ezsummary
Simplifies the process of generating print-ready data summaries from data objects.

memoR (Zhu H, Tsai T, Travison TG): https://github.com/hebrewseniorlife/memor Template for document production for reproducible research. Facilitates user-friendly generation of publication-quality statistical analysis and scientific work product using the R programming system and linked technologies.

R2cluster (Zhu H, Travison TG): https://hebrewseniorlife.github.io/r2cluster/) App to automate remote computing requests when working with large biomedical datasets. Allows for automated passing of instructions to the remote device, and shared configuration of said instructions across multiple laboratory users

CURATOR (BDAC and HSL Biostats Teams) https://hebrewseniorlife.github.io/curator/ Toolset for dynamic data display and reproducible biomedical research We maintain a compendium of tools and tutorials for the conduct of reproducible statistical analysis in biomedical research, called curator (Customizable Reporting, Analysis and Templating For Reproducible Research)

Strategic plan related to Developmental Project

We plan to develop an R01 application intended to expand this methodologic work to other data types and settings, with specific focus on statistical learning and big data (e.g. intensely longitudinal data captured in physical activity studies.)

PLANS FOR THE COMING YEAR

LAC: The LAC will continue to direct the OAIC Program, organize monthly meetings of its Executive Committee, provide administrative support to all OAIC projects, and oversight to its resource cores. The LAC will continue to organize a weekly conference for OAIC members and trainees, and a Visiting Speaker program

During year 03, the OAIC issued a request for application for the next round of REC and PESC awardees. There were 17 applicants, with 5 chosen for funding (2 REC, 3 PESC). The LAC will continue to nurture collaborations with the Harvard Glenn Center for the Biology of Aging and the Boston Roybal Center.

REC: The REC will continue its mentorship and training of the currently funded REC candidates and foster their career advancement and transition to independent R series funding. Two of our REC awardees (Drs. Sinha and Lustgarten) concluded their training periods this year. Dr. Lustgarten has already won a K01 Award to support his ongoing work, and Dr. Sinha has received a promising score on a K76 Award that will hopefully start this summer. As noted above, we reviewed applications for subsequent awards after the application close date (March 1) and notified new awardees by April 1. As before, applications will be reviewed and ranked according to the NIH scoring convention by a committee of senior investigators with expertise in the applicants' fields of study. At the beginning of each trainee's funding period, the trainee and his/her mentor were asked to develop an Individual Development Plan with explicit goals and milestones for the training period. The IDP prompts them for 1) career and learning goals, 2) plans for training in the responsible conduct of research, 3) proposed coursework, 4) scientific meetings and conferences, 5) a professional development plan, 6) proposed papers and abstracts, and 7) proposed grant applications. They are asked to list the specific activities under each of these categories and target dates for completion. IDPs will be revisited every 6 months and the date that each activity is completed recorded. These plans were also reviewed by the REC Core leaders, Drs. Lipsitz, Wagers, and Marcantonio at one of their quarterly meetings. Any problems in meeting the trainee's goals are discussed with the trainee and mentor and a course correction or alternative plan is established. New trainees will also be scheduled to present their research at the monthly Boston OAIC seminar series, which provides valuable opportunities for constructive feedback from our faculty and sparks collaborations among our Center's investigators. In addition, over the next 3 months we will conduct evaluations of Drs. Orkaby, Sinha and Lustgarten, with input from their mentors, and ask these three current awardees to provide evaluations and feedback on their mentors and program as a whole. This input will be reviewed by the REC Core leaders and used to improve the program for future trainees.

PESC. The PESC continues its mentorship and training of the currently funded PESC candidates. In January 2018, a second call for applications was published, with an application due date of March 1. Seventeen applications were received and reviewed by the Boston Pepper Center steering committee, and new awardees were notified by May 1, 2018.

Resource Cores. During year 03, we conducted a comprehensive evaluation of our three resource cores, their utilization and quality of service.

FAC: We will continue to solicit new projects and provide consultative services to the Pepper Community and the extended community of aging researchers.

TRAINEE 2018-2019 PUBLICATIONS

REC

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NEW REC

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PESC

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37. Zhou J, Lo OY, Lipsitz LA, Zhang J, Fang J, Manor B. Transcranial direct current stimulation enhances foot sole somatosensation when standing in older adults. Exp Brain Res. 2018 Mar;236(3):795-802. PMCID: PMC5828881.
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New PESC

40. Guadagnin E, Bagchi D, Sinha I, Neppl RL. (2018) Nuclear localized Akt limits skeletal muscle derived fibrotic signaling. Biochem Biophys Res Commun. Dec 7. pii: S0006-291X(18)32640-8. doi: 10.1016/j.bbrc.2018.11.202. [Epub ahead of print]
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