Application Summary of : Fromen, Catherine

Cover Page

Proposal Data	
*Proposal ID:	18A00xxx
*Version ID:	V101
Faculty should provide their applicable Departmental Administrator with a budget and justification so that a record in UD's Grant Management System, People Soft (PS) may be initiated. Once completed use your PS number and version V101 above and click on the button to access that information.	
Cover Page	
*Employee ID:	
*Email:	CFROMEN@UDEL.EDU
*First Name:	Catherine
Middle Name Initial:	Ann
*Last Name:	Fromen
*Hire Date:	09/01/2017
*Proposal ID:	18A00xxx
*Proposal Title:	UDRF FROMEN 2018
*Proposal Title (Long):	Optimizing Nanoparticle Delivery to Lung Dendritic Cell Subsets for Development of New Pulmonary Therapeutics
Education	
*Department:	Chemical & Biomolecular Engr (03110)
*College:	Engineering (EG)
*Rank:	Assistant Professor (2C1001)
*Rank Date:	01/09/2017
*Degree:	PhD
*Year:	2014
Tenured Faculty Name *(for UDRF-SI)*:	
*Dept Admin Name:	McMullen,Tracy Ann
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*Dean Name:	Ogunnaike,Babatunde A
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*Discipline:	Chemical Engineering
*Honors:	1. Univ Michigan Outstanding Postdoctoral Fellow Award (August 2016) 2. Univ Michigan President's Postdoctoral Fellow (2014-2017) 3. Travel Award Recipient to attend National Academy of Science's Committee on Key Challenge Areas for Convergence and Health Workshop, Washington DC (September 2013) 4. NextProf Workshop Selected Participant, University of Michigan (September 2013) 5. Mentored Teaching Award, North Carolina State University (Spring 2013) 6. Shelby A. Miller Prize in Chemical Engineering Design, University of Rochester (2009) 7. Eisenberg Research Fellowship, University of Rochester (2008)
*Applicant's Relevant Publications:	1. Fromen, C.A., Kelley, W.J., Fish, M.B., Adili, R., Noble, J., Hoenerhoff, M.J., Holinstat, M., Eniola-Adefeso, O., Neutrophil-Particle Interactions in Blood Circulation Drive Particle Clearance and Alter Neutrophil Responses in Acute Inflammation. ACS Nano 11:11 (2017) 10797-10807. 2. Noble, J., Zimmerman, A., Fromen, C.A., Potent Immune Stimulation from Nanoparticle Carriers Relies on the Interplay of Adjuvant Surface Density and Adjuvant Mass Distribution. ACS Biomater Sci Eng 3:4 (2017) 560-571. 3. Fish, M.B., Fromen, C.A., Lopez-Cazares, G., Golinski, A.W., Scott, T.F., Adili, R., Holinstat, M., Eniola-Adefeso, O., Exploring Deformable Particles in Vascular-Targeted Drug Delivery: Softer is Only Sometimes Better. Biomaterials 124 (2017) 169-179. 4. Fromen, C.A., Fish, M.B., Zimmerman, A., Adili, R. Holinstat, M., Eniola-Adefeso, O., Evaluation of Receptor-Ligand Mechanisms of Dual-Targeted Particles to an Inflamed Endothelium. Bioeng Transl Med 1 (2016) 103–115. 5. Rahhal, T.B., Fromen, C.A., Wilson, E.M., Kai, M.P., Shen, T.W., Luft, J.C., DeSimone, J.M., Pulmonary Delivery of Butyrylcholinesterase as a

Model Protein to the Lung. Mol Pharmaceutics 13:5 (2016) 1626-1635.

6. Fromen, C.A., Rahhal, T.B., Robbins, G.R., Kai, M.P., Shen, T.W., Luft, J.C., DeSimone, J.M., Nanoparticle Surface Charge Impacts Distribution, Uptake and Lymph Node Trafficking by Pulmonary Antigen-Presenting Cells, Nanomed. Nanotechnol, Biol, Med 12:3 (2016) 677-687. Featured Cover Article.

7. Kai, M.P., Brighton, H.E., Fromen, C.A., Shen, T.W., Luft, J.C., Luft, Y.E., Keeler, A.W., Robbins, G.R., Ting, J.P.Y., Zamboni, W.C., Bear, J.E., DeSimone, J.M., Tumor Presence Induces Global Immune Changes and Enhances Nanoparticle Clearance, ACS Nano 10:1 (2016) 861-870.

8. Sobczynski, D.J., Fish, M.B., Fromen, C.A., Carasco-Teja, M., Coleman, R.M., Eniola-Adefeso, O., Drug Carrier Interactions in Blood: A Critical Aspect for High-Efficient Vascular-Targeted Drug Delivery Systems, Therapeutic Delivery 6:8 (2015) 915-934.

9. Shen, T.W.*, Fromen, C.A.*, Kai, M.P., Luft, J.C., Rahhal, T.R., Robbins, G.R., DeSimone, J.M., Distribution and Cellular Uptake of PEGylated Polymeric Particles in the Lung Towards Cell-Specific Targeted Delivery, Pharm Res 32 (2015) 3248-3260.

10. Fish, M.B., Thompson, A.J., Fromen, C.A., Eniola-Adefeso, O., Emergence and Utility of Non-Spherical Particles in Biomedicine, Ind Eng Chem Fundam 56:16 (2015) 4043-4059.

11. Fromen, C.A.*, Robbins, G.R.*, Shen, T.W., Kai, M.P., Ting, J.P.Y., DeSimone, J.M., Controlled Analysis of Nanoparticle Charge on Mucosal and Systemic Antibody Responses Following Pulmonary Immunization, Proc Natl Acad Sci USA 112 (2015) 488-493. *co-first authors.

12. Fromen, C.A., Shen, T.W., Larus, A.E., Mack, P., Luft, J.C., Maynor, B.W., DeSimone, J.M., Synthesis and Characterization of Monodisperse Uniformly Shaped Respirable Aerosols, AIChE Journal 59:9 (2013) 3184-3194.

13. Garcia A., Mack P., Williams, S., Fromen, C.A., Shen, T.W., Pillai, J., Kuehl, P., Napier, M.E., DeSimone, J.M., Maynor, B.W., Microfabricated Engineered Particle Systems for Respiratory Drug Delivery and Other Pharmaceutical Applications, Journal of Drug Delivery (2011).

14. Wang, Y., Merkel, T.J., Chen, K.; Fromen, C.A., Betts, D.E., DeSimone, J.M., Generation of a Library

	of Particles Having Controlled Sizes and Shapes via the Mechanical Elongation of Master Templates, Langmuir 27 (2011) 524-528. 15. Cox, G.P., Marshall, K.L., Lambropoulos, J.C., Leitch, M., Fromen, C.A., Jacobs, S.D., Modeling the Effects of Microencapsulation on the Electro-Optic Behavior of Polymer Cholesteric Liquid Crystal Flakes, Journal of Applied Physics 106 (2009) 124911-1.
__Professional__ and/or __Research Experience__ (including Post Doctoral)*:	Assistant Professor, University of Delaware, Department of Chemical and Biomolecular Engineering Newark DE, Fall 2017-Present University of Michigan's President's Postdoctoral Fellow, Department of Chemical Engineering, University of Michigan, Ann Arbor MI, Fall 2014-Summer 2017
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Is this proposal being submitted elsewhere? (Check all that apply)	

Project Description

Project Description	
*Proposal Type:	NEW
*Proposal Due Date:	2018-01-15
*Proposal Begin Date:	2018-06-01
*Proposal End Date:	2019-05-31
*Proposal Status:	PEN
*Primary Sponsor:	2910
*Resubmission: Is this a resubmission of a prior year UDRF proposal?	No
*Significance of the __Proposed Work__ *(250 words or less):*	Despite centuries of use and widespread application, aerosol delivery of therapeutics remains limited to a small subset of diseases and active pharmaceutical ingredients, mainly restricted to small molecule delivery for asthma management. Respiratory diseases which would benefit from direct and localized treatment span a much larger landscape; chronic obstructive pulmonary disease (COPD), lower respiratory infections, and lung cancers alone globally contribute 7.8 million annual deaths, with a reported 117 million pulmonary cases (~37% of population, 2012) and over $88 billion in health care costs in the US(1, 2). To expand the application of aerosol

	delivery, novel drug delivery approaches are needed. In this proposal, we introduce the concept of nanoparticle immunoengineering for respiratory therapeutics(3). Abnormal immune responses lie at the heart of most respiratory diseases. Using engineered particles with controlled incorporation of biologically-active ligands, we aim to develop a new tool which can directly interface with the immune system and redirect responses. We seek to understand what features of the particle and lung immune system are most critical in controlling the response and use this understanding to develop new therapeutic approaches. This will enable us to optimize nanoparticle immune engineering for the lung with the ultimate goal of driving translational advances and introducing new treatment options for patients with respiratory diseases.
*Description of **Proposed Research** or **Scholarly Activity** *(1250 words or less):*	Background: Nanoparticle-driven immune engineering via aerosol therapeutics represents a new approach to treat respiratory diseases, which remain a significant cause of morbidity and mortality worldwide(1, 3). To date, few nanoparticle formulations have been explored for lung administration and even fewer successfully translated to the clinic, stemming from interference by white blood cells, also known as phagocytic immune cells(4, 5). Interactions with these cells, historically viewed as undesirable, provide a new pathway for therapeutic intervention. The same cells which sequester nanoparticles are also responsible for regulating the local immune environment(5-7). Immune dysregulation has been implicated in every human disease; engineered particles which control particle-cellular interactions at the lung mucosa represents a new tool to directly interface with the immune system and correct aberrant responses(8). Optimization of pulmonary immune-engineering approaches requires consideration of the unique environment. Notably, the lung has an abundance of antigen presenting cells (APCs), such as macrophages and dendritic cells (DC), which phagocytose foreign materials at the air-lung interface. There are a number of lung-specific APC populations(9, 10). Some subsets are well understood; for example, the role of alveolar macrophages in particle clearance, antigen presentation, and homeostasis has been well-established(9-12). However, other specialized subsets have only recently been identified (Figure 1), due to historic challenges in differentiating these populations(13, 14). Thus, there are many remaining questions as to the division of labor between these cells, their significance in different disease conditions,

and their interactions with other adjacent cell populations at the mucosal interface(15-18). Advancing this understanding is critical to develop new therapeutics; APCs are poised as the gatekeepers to lung regulation and lung DC-subsets are likely cellular targets for therapeutic intervention(19).

Engineered particles are a key tool for probing the biological function of these cells, as well as directing desirable immune responses. APC populations naturally engulf engineered particles, enabling simultaneous tracking of cells and particles following phagocytosis(13). To further modulate the response, engineered particles can be designed to co-deliver multiple molecules, including antigens, PAMP (pathogen-associated molecular patterns) adjuvants, and other ligands(19-21). Orchestrating complex interactions with the immune system requires delivery of these molecules in precise sequence to the correct cells. While limited particle-driven immune-modulation has been attempted in the lung, recent work has demonstrated empirical proof of concept immune-stimulatory nanoparticles that promote adaptive responses(22, 23), tolerance(24), and immune skewing(25). Parallel lung advances in this area will require a systematic investigation of the specific lung mechanisms involved in response to isolated particle and/or molecular cues.

Approach Overview:

In this proposed research, we will develop design rules for aerosol particle carriers to engineer immune responses in the lung. We will develop a series of precisely engineered particles with a variety of physiochemical properties and screen interactions with recently identified lung dendritic cell (DC) subsets. Simultaneously, we will incorporate stimulatory and tolerizing ligands to develop new respiratory therapeutics. This proposed research requires application of chemical engineering fundamentals, incorporating aspects of molecular design, kinetics, transport, and systems scale-up. The outcomes of this work are two-fold: 1) generate advances in core knowledge of lung cell physiology and pathophysiology following therapeutic particle administration and 2) establish global design rules of pulmonary engineered particles needed to control lung immune responses.

AIM 1: Use engineered particles to probe lung biology.

Stemming from previous work (Figure 2), where particle surface charge was found to dramatically

impact lung DC distribution(26), we will screen a range of particle sizes and surface chemistries to evaluate their DC uptake. Polymeric particles will be fabricated in house with emulsion based approaches of multiple sizes, surface charges, and elasticity to elucidate the complex interplay of these variables on lung DC interactions. Using previously established fabrication methods(27), particles will be made of a poly(ethylene glycol) diacrylate backbone at controlled weight percent to vary particle stiffness, with a maleimide-functionalized fluorescent dye for imaging and 2- carboxyethyl or 2- aminoethyl methacrylate for added surface charge and chemical handles incorporated into the particle. Following fabrication, particles will be rigorously characterized with dynamic light scattering (DLS), UV-vis, and various forms of optical and electron microscopy, and screened for stability, cytotoxicity, endotoxin, and cellular in vitro uptake in lung cells(22, 28).

Particles will then be applied to the airway of mice through a liquid orotracheal instillation, providing uniform distribution and decoupling particle features from their aerosol properties(26, 29). Following a single administration, we will evaluate particle distribution at a range of established time points between 2 hr and 1 week. At each time point, we will use flow cytometry to identify particle association with DC subsets and correlate to histological sectioning in both lung tissue and regional draining lymph nodes. Importantly, these investigations will be performed on lungs in varied immune environments. We will explore particle uptake and distribution in healthy, wild type mice of two different strains, including C57BL/6 (Th1-prone) and BALBc (Th2-prone) mice, as these strains capture two extremes for cellular nanoparticle uptake propensity(30). We will then evaluate nanoparticle uptake in established lung disease airway models, including allergy, fibrosis, hypertension, and non-small cell lung cancer (NSCLC) to investigate pathophysiological changes to particle distribution in the airway(30, 31). Kinetic knowledge of particle association and clearance following pulmonary delivery in these disease conditions will establish potential targets for therapeutic intervention and advance core knowledge of lung DC subset function.

AIM 2: Engineer pulmonary formulations for controlled lung immune response.

In parallel to the identification of optimal platforms developed in Aim 1, we will systematically incorporate immune modulatory ligands to control local immune responses with these cells. Precise cues are needed to orchestrate immune responses which begin with a controlled interaction between cell surface receptors

	and particle ligand presentation during phagocytosis. Our first efforts to control this interaction will continue from our previously published work designing particle surfaces with PAMP toll-like receptor (TLR) agonists (Figure 3)(28). TLRs are found on the surface of APCs and can initiate an inflammatory signaling cascade needed to modulate Th2-skewed environments, such as those occurring in asthma and cancer(32, 33). In addition to TLR-ligand addition to the particle, we will also explore markers of self, including CD47 and phosphatidylserine, which are known to promote tolerance in certain immune settings(34, 35). In both sides of this work, we will evaluate the role of ligand surface density incorporation on the particle's ability to modulate the cell response. We will first modify particles fabricated in Aim 1 to incorporate CpG, imiquimod, Poly(I:C) (all TLR agonists), CD47, and phosphatidylserine and tune reaction conditions to modify surface incorporation(32-35). From this series of particles with varied ligand surface density, we will utilize a variety of in vitro cellular assays to evaluate the kinetics of cellular environment change due to particle stimulation, especially in comparison to the soluble molecule delivery. Stimulatory TLR agonists will be evaluated for their ability to direct pro-inflammatory responses in cultured APCs, while tolerizing ligands will be evaluated for their ability to generate anti-inflammatory responses, both evaluated by cellular surface molecule expression and cytokine profiles. Following our in vitro screens, we will down-select candidate therapeutics. Dispersible powders will be fabricated and evaluated for lung deposition using a Next Generation Impactor, as well as feasibility of particle-driven lung modulation in vivo(36, 37). While extensive in vivo studies are outside the scope of this proposal, pilot studies in asthma and fibrosis disease models (from Aim 1) will be pursued for preliminary data. Through the completion of this aim, we will establish initial design rules of particle surfaces to drive immune responses; combined with results from Aim 1, this work will provide a critical foundation towards immunoengineering the lung immune environment.
Upload References:	20180111_references.pdf
Upload Figures/Tables and or timeline (no more than 1 page):	20180111_figures.pdf

Other Required Information

Other Required Information	

*Indicate Plans for Submission of this **Project to Other Funding Sources** *(250 words or less):*	The work proposed here will lay a critical foundation in two different focus areas which are anticipated to develop into long term research projects in the lab. The first focus area is the advancement of basic science understanding of lung dendritic cells, which is of great interest to respiratory scientists in a variety of clinically-facing fields. As such, this work is expected to be of interest to the NIH (NHLBI and/or III study sections), American Lung Association, PhRMA Foundation, and American Thoracic Society. The second focus area is the mechanistic understanding of the physiochemical design of nanoparticles which drive lung immune responses. This aspect of the work will be submitted for funding requests to the NIH (NIBIB) and, most notably, the foundation of an NSF Career proposal. Finally, the data obtained in various in vivo disease models will provide preliminary findings in the development of new treatments of lung cancer, pulmonary fibrosis, and asthma. Full proposals will be developed in each of these focused disease areas and targeted to a number of private foundations with funding opportunities focused on novel therapeutic development and early career science development, including the Lungevity (cancer), Pulmonary Fibrosis, and Sandler (asthma) Foundations.
Research Support for Current Grants	
*Agency:	n/a
*Amount Received:	$0
*Start Date:	n/a
*End Date:	n/a
*Add Another Research Support for Current Grants:	No
Research Support for Pending Grants	
*Agency:	NIH-seed funding for pilot COBRE (UD Chemistry)
*Amount Requested:	$47,500
*Start Date:	1/15/2018
*End Date:	5/31/2018
*Add Another Research Support for Pending Grants:	No
Additional Information in Support of Proposal *(500 words or less):*	
*Executive Summary *(250 words or less)*:	In this proposed research, we outline an approach to optimize nanoparticle immunoengineering therapeutics to treat respiratory diseases. Given the continued global prevalence of lung diseases, novel treatment approaches are needed to improve patient outcomes. Using engineered particles with controlled

	incorporation of biologically-active ligands, we aim to develop new tools which can directly interface with the lung immune system and redirect responses needed to treat respiratory diseases. We will develop a series of precisely engineered particles with a variety of physiochemical properties and screen interactions with key lung immune cell subsets. Simultaneously, we will incorporate stimulatory and tolerizing ligands to develop new respiratory therapeutics. The outcomes of this work are two-fold: 1) generate advances in core knowledge of lung cell physiology and pathophysiology following therapeutic particle administration and 2) establish global design rules of pulmonary engineered particles needed to control lung immune responses. To perform this work, we are requesting funds to support one graduate student for a year and disposable lab supplies needed to perform this research. The proposed work builds on the PI's previously published work in nanoparticle therapeutics and pulmonary drug delivery and will generate critical preliminary data to for full proposals to the National Institutes of Health, American Lung Association, and the Lungevity, Pulmonary Fibrosis, and Sandler Foundations.

Budget

Budget	
*Upload Budget Justification	UDRF Fromen_Budjust_010918.pdf
*Budget Category:	GRADST
*Budget Amount:	32379
*Sponsor Amount:	22379
*Budget Cost Share (Institution):	10000
*Budget Cost Share (Third Party):	0
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Budget Amount:	2621
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Document Title	Question	Date Uploaded
UDRF Fromen_Budjust_010918.pdf	BUDGETUpload Budget Justification	1/11/2018 9:37 PM
20180111_figures.pdf	PD Upload FiguresTables and or timeline no more than 1 page	1/11/2018 1:39 PM
20180111_references.pdf	PD Upload References	1/11/2018 1:39 PM
nsf-biosketchCAF.pdf	Upload CV	1/11/2018 8:41 AM

Application Summary of : Tanis, Jessica

Cover Page

Proposal Data	
*Proposal ID:	18A00xxx
*Version ID:	V101
Faculty should provide their applicable Departmental Administrator with a budget and justification so that a record in UD's Grant Management System, People Soft (PS) may be initiated. Once completed use your PS number and version V101 above and click on the button to access that information.	
Cover Page	
*Employee ID:	
*Email:	JTANIS@UDEL.EDU
*First Name:	Jessica
Middle Name Initial:	E
*Last Name:	Tanis
*Hire Date:	04/01/2016
*Proposal ID:	18A00xxx
*Proposal Title:	UDRF TANIS 2018

*Proposal Title (Long):	Investigating the Impact of Diet on Amyloid-beta Toxicity in C. elegans
Education	
*Department:	Biological Sciences (02590)
*College:	Arts and Sciences (AS)
*Rank:	Assistant Professor (2C1001)
*Rank Date:	01/04/2016
*Degree:	PhD
*Year:	2008
Tenured Faculty Name *(for UDRF-SI)*:	
*Dept Admin Name:	Parman,Traci F
*Dept Admin Email:	TPARMAN@UDEL.EDU
*Contract & Grant Specialist Name:	Gaydos,Jennifer
*Chair Name:	Boyd,Ethna Fidelma
*Chair Email:	FBOYD@UDEL.EDU
*Dean Name:	Pelesko,John
*Dean Email:	PELESKO@UDEL.EDU
*Discipline:	Cell Biology / Genetics
Honors:*	2018 University of Delaware nominated ORAU Ralph E Powe Junior Faculty Enhancement Award applicant 2016 University of Delaware nominated Searle Scholar applicant 2012-2014 American Heart Association 12POST11940054 Postdoctoral fellow, Department of Physiology, University of Pennsylvania 2010-2012 NIH F32 AR060128 Postdoctoral fellow, Department of Physiology, University of Pennsylvania 2008-2009 NIH Institutional Training Grant T32 DK007259 Postdoctoral fellow, Physiology Department, Yale University 2008 John Spangler Nicholas Prize, outstanding thesis award, Mol. Cell and Dev. Biology Department, Yale University 2004-2007 National Science Foundation Graduate Research Fellowship 2002–2003 Chairman's Fellowship, Yale University 2002 Magna Cum Laude with Highest Honors in Biology, Muhlenberg College
Applicant's Relevant Publications:*	A complete list of the applicant's publications can be found at: https://www.ncbi.nlm.nih.gov/sites/myncbi/1Lcg5q3lb42Q_/bibliography/51590548/public/?sort=date&direction=ascending 1. Collins KM, Bode A, Fernandez RW, Tanis JE, Brewer JC, Creamer MS, Koelle MR. 2016. Activity of the C. elegans egg-laying behavior circuit is controlled by competing activation and feedback inhibition. Elife e21126. PubMed PMID: 27849154; PubMed Central PMCID: PMC5142809.

	2. Vais H, Mallilankaraman K, Mak DO, Hoff H, Payne R, Tanis JE, Foskett JK. 2016. EMRE Is a Matrix Ca(2+) Sensor that Governs Gatekeeping of the Mitochondrial Ca(2+) Uniporter. Cell Rep, 14(3):403-10. PubMed PMID: 26774479; PubMed Central PMCID: PMC4731249. 3. Vais H, Tanis JE, Müller M, Payne R, Mallilankaraman K, Foskett JK. 2015. MCUR1, CCDC90A, Is a Regulator of the Mitochondrial Calcium Uniporter. Cell Metab, 22(4):533-5. PubMed PMID: 26445506. 4. Vingtdeux V, Tanis JE, Chandakkar P, Zhao H, Dreses-Werringloer U, Campagne F, Foskett JK and Marambaud P. 2014. Effect of the CALHM1 G330D and R154H human variants on the control of cytosolic Ca2+ and Aß levels. PLOS One, 9(11):e112484. PubMed PMID: 25386646; PubMed Central PMCID: PMC4227689. 5. Tanis JE, Ma Z, Krajacic P, He L, Foskett JK and Lamitina T. 2013. CLHM-1 is a functionally conserved and conditionally toxic Ca2+-permeable ion channel in C. elegans. J Neurosci, 33:12275-86. PubMed PMID: 23884934; PubMed Central PMCID: PMC3721838. 6. Krajacic P*, Pistilli EE*, Tanis JE*, Khurana TS and Lamitina T. 2013 FER-1/Dysferlin promotes cholinergic signaling at the neuromuscular junction in C. elegans and mice. Biol Open, 2:1245-52. PubMed PMID: 24244862; PubMed Central PMCID: PMC3828772. (* indicates equal contributions) 7. Tanis JE, Bellemer A, Moresco JJ, Forbush B and Koelle MR. 2009. The potassium chloride cotransporter KCC-2 coordinates development of inhibitory neurotransmission and synapse structure in C. elegans. J Neurosci, 29:9943-54. PubMed PMID: 19675228; PubMed Central PMCID: PMC2737711. 8. Tanis JE, Moresco JJ, Lindquist RA and Koelle MR. 2008. Regulation of serotonin biosynthesis by the G proteins Galphao and Galphaq controls serotonin signaling in Caenorhabditis elegans. Genetics, 178:157-169. PubMed PMID: 18202365; PubMed Central PMCID: PMC2206068.
*__Professional__ and/or __Research Experience__ (including Post Doctoral):	2016–pres. Assistant Professor, University of Delaware 2013–2016 Research Associate, laboratory of Dr. J. Kevin Foskett, University of Pennsylvania 2009–2013 Postdoctoral Fellow, laboratory of Dr. Todd Lamitina, University of Pennsylvania 2008–2009 Postdoctoral Fellow, laboratory of Dr. Biff Forbush, Yale University 2003–2008 Graduate Fellow, laboratory of Dr. Michael Koelle, Yale University 2000–2002 Undergraduate honors research, labs of Dr. Wightman and Dr. McCain, Muhlenberg College
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proposal being submitted elsewhere? (Check all that apply)	

Project Description

Project Description	
*Proposal Type:	NEW
*Proposal Due Date:	2018-01-15
*Proposal Begin Date:	2018-06-01
*Proposal End Date:	2019-05-31
*Proposal Status:	PEN
*Primary Sponsor:	2910
*Resubmission: Is this a resubmission of a prior year UDRF proposal?	No
*Significance of the **Proposed Work** *(250 words or less):*	Late-onset Alzheimer's disease (LOAD) causes the most common type of dementia in elderly individuals and has profound effects on quality of life for more than 5 million people in the United States. Based on the aging population, it has been projected that by 2050, LOAD will account for 1.6 million deaths per year among Americans 65 years and older(1). LOAD is a progressive neurodegenerative disorder characterized by extraneuronal lesions formed of amyloid-beta (Aß) oligomers in the brain(2). This histological feature coupled with genetic evidence support the hypothesis that Aß is a causative factor in disease pathogenesis(3). Individuals with LOAD also exhibit mitochondrial dysfunction and disruptions in calcium (Ca2+) homeostasis(4,5). The link between Aß accumulation and alterations in mitochondrial function, as well as the resulting impact on LOAD pathogenesis, is not well understood. We are using the nematode C. elegans as a model system to identify factors that affect Aß accumulation and toxicity in vivo. Expression of toxic human Aß1-42 in C. elegans causes fully penetrant, age-dependent paralysis(6). We have discovered that the type of E. coli diet that Aß-expressing animals consume alters paralysis rate. Our preliminary genetic data have led us to hypothesize that consumption of HB101 E. coli activates the mitochondrial unfolded protein response (UPRmt), protecting against Aß toxicity. The goal of our research is to determine how diet affects UPRmt activation, Aß abundance, mitochondrial morphology, and mitochondrial function in Aß-expressing C.

	elegans, which will shed light on the impact of diet on Aß toxicity.
*Description of **Proposed Research** or **Scholarly Activity** *(1250 words or less):*	Background: While an increase in toxic Aß oligomers is a pathological marker of LOAD, how Aß accumulation leads to loss of neurites, synaptic dysfunction and finally, neuron death remains unresolved. Other features of LOAD include a reduction in mitochondrial density, abnormalities in mitochondrial ultrastructure and accumulation of mitochondrial proteins in the cytoplasm(4,7). Currently, the connection between Aß accumulation and mitochondrial dysfunction is unclear. Aß has been shown to aggregate in the mitochondria which could cause changes in energy production(4,8). Alternatively, Aß aggregates may disrupt communication between the endoplasmic reticulum and mitochondria, leading to dysregulation of Ca2+ homeostasis(9,10). Maintenance of protein homeostasis at a cellular level requires specific unfolded protein response mechanisms (UPRs) that are present in the cytosol, endoplasmic reticulum (UPRer) and mitochondria (UPRmt) to help cells process misfolded proteins. Activation of the UPRmt is induced by aggregation of misfolded mitochondrial proteins, imbalance of electron transport chain subunits, reactive oxygen species and pathogenic bacteria(11,12). In the model organism C. elegans, activation of the UPRmt leads to transcriptional upregulation of the mitochondrial chaperones hsp-6 and hsp-60 to restore mitochondrial homeostasis(13). Accumulation of Aß, but not the aggregation prone protein GFPdeg, decreases transcription of hsp-6 and hsp-60 and disrupts mitochondrial morphology(14–16). This suggests that alterations in mitochondrial integrity and function due to Aß accumulation are not simply a non-specific response to protein aggregation. Preliminary data: To identify factors that influence Aß toxicity, we are utilizing a transgenic strain of C. elegans in which toxic human Aß1-42 is expressed in the body wall muscles, resulting in time-dependent paralysis(6). These transgenic animals have consistently been used to identify genes and pharmacological agents that influence Aß accumulation and toxicity(17). Strikingly, we found that the type of E. coli diet that these Aß-expressing animals consumed altered time to paralysis, with animals grown on OP50 E. coli becoming paralyzed faster than those grown on HB101 E. coli (Figure 1). To determine the mechanism by which diet altered Aß toxicity we took a candidate gene approach. Since alterations in the insulin signaling, UPRer, UPRmt, heat shock response, and membrane damage response pathways have previously been shown to affect Aß toxicity and/or

accumulation(15,16,18–21), we crossed the Aß transgene into daf-16, sgk-1, rict-1, pek-1, ire-1, atf-6, phb-2, hsf-1 and kgb-1 mutants. We predicted that if a gene was required for the dietary effect on Aß toxicity, then Aß-induced paralysis in that mutant background would be similar for animals grown on OP50 and HB101. We found that the diet-induced shift in paralysis was eliminated in the phb-2 mutant, which exhibits robust activation of the UPRmt (Figure 2). Loss of phb-2 slowed paralysis of Aß animals grown on OP50 and HB101, but the effect of the phb-2 mutation and diet was not additive. A diet-induced shift in paralysis was still observed in atf-6 and rict-1 mutants, which also exhibit slowed Aß-induced paralysis compared to the control (data not shown). Together, these results suggest that loss of phb-2 specifically eliminates the effect of diet on Aß toxicity.

Research Plan: Our broad goal is to elucidate mechanisms that protect against pathogenic effects triggered by Aß accumulation. Based on our preliminary results, we hypothesize that diet-induced activation of the UPRmt by ingestion of HB101 E. coli is protective, reducing Aß toxicity. We will use transgenic C. elegans to define how diet affects stimulation of the UPRmt (Aim 1), Aß accumulation and mitochondria function (Aim 2). Our work has potential to provide insight into how diet influences cellular response to toxic Aß as well as the link between Aß accumulation and the UPRmt.

Aim 1: Determine the influence of E. coli diet on UPRmt activation in Aß–expressing C. elegans
Our preliminary data suggests that HB101 diet leads to upregulation of the UPRmt. The main UPRmt regulator is the transcription factor ATFS-1, which translocates to the nucleus and activates response genes to maintain stoichiometry of electron transport chain complex subunits during mitochondrial stress. We hypothesize that Aß animals that ingest HB101 will exhibit either an upregulation of atfs-1 transcription and/or an increase in ATFS-1 translocation to the nucleus compared to those that consume OP50. atfs-1 transcript levels in Aß-expressing animals fed HB101 or OP50 will be determined 14 hrs after the fourth larval stage (L4), before onset of severe paralysis, using real-time quantitative reverse transcription PCR. We will also measure transcript levels of the hsp-6 and hsp-60 mitochondrial chaperones to quantitatively compare the level of UPRmt induction in Aß animals that consume different diets(22). ATFS-1 translocation will be assessed by examining the localization of ATFS-1 tagged with GFP (ATFS-1::GFP transgene wgIs675(23), Caenorhabditis Genetics Center) in Aß worms animals fed HB101 or OP50 14 hours post L4. If we observe an increase in ATFS-1 transcript levels or nuclear localization in Aß animals grown on

HB101 as predicted, we will perform the same experiments with wild-type animals to determine if this is dependent on Aß expression.

Mitochondrial stress in neurons activates the UPRmt in the intestine, suggesting that a released signal can activate stress response in distant tissues(24). To determine in which cell(s) the UPRmt is activated in, we will generate single copy insertion (SCI) transgenes to express phb-2 in the intestine using the ges-1 promoter or Aß-accumulating muscles using the myo-3 promoter. We will determine where PHB-2 signaling is sufficient to restore the diet-induced shift in paralysis by crossing the SCI transgenes into the Aß-expressing phb-2 mutant and performing paralysis assays (see Figure 2). Based on the potential protective effect of UPRmt activation in cells accumulating Aß, we predict that phb-2 expression solely in the muscles of the phb-2 mutant will restore the diet-dependent shift in Aß-induced paralysis.

Aim 2: Define the impact of diet on Aß accumulation, mitochondrial morphology, and mitochondrial function
Aß aggregation begins with the formation of soluble oligomers, which develop into protofibrils and finally mature insoluble fibrils(25). While the severity of LOAD likely correlates with soluble oligomers instead of aggregated plaque Aß, the precise molecular identity and cellular target of toxic Aß species remains unclear(26). To determine if the delayed paralysis observed in Aß animals fed HB101 correlates with a reduction in Aß oligomers and/or fibrils compared to the Aß animals fed OP50, we will perform Aß immunoblotting with the 6E10 antibody which detects all forms of Aß, including monomers, soluble oligomers, aggregates and fibrils(15), as well as the A11 antibody (Invitrogen) which specifically recognizes aggregation-prone soluble oligomers(27) using described protocols(28). We will also perform immunohistochemistry to visualize Aß load (6E10 antibody) and soluble oligomeric aggregates (A11 antibody), imaging stained age-staged Aß animals grown on HB101 or OP50 bacteria. Finally, we will determine the effect the phb-2 mutation, predicting that the activation of the UPRmt in the phb-2 mutant will reduce Aß accumulation regardless of diet.

Accumulation of Aß disrupts mitochondrial morphology(15). We will cross a transgene that constitutively expresses mito-GFP in the body-wall muscles (ccIs4251(29), Caenorhabditis Genetics Center) into the Aß animals and analyze mitochondria morphology in animals grown on different E. coli to determine if the HB101 diet is protective. Mitochondria will be imaged with fluorescence microscopy and categorized as intact, disorganized, or complex(29). To assess the impact

	of diet on mitochondrial function in Aß-expressing animals, we will measure steady-state ATP levels every four hours following the temperature upshift using existing protocols(30). This will enable us to determine if Aß-induced paralysis correlates with reduced ATP levels and if the HB101 diet protects against mitochondrial dysfunction. Timeline: We expect these experiments can be completed in one year by PhD candidate Andy Lam working as a research assistant (Table 1).
Upload References:	UDRF References Tanis.pdf
Upload Figures/Tables and or timeline (no more than 1 page):	UDRF figures Tanis final.pdf

Other Required Information

Other Required Information	
*Indicate Plans for Submission of this **Project to Other Funding Sources** *(250 words or less):*	Support from the UDRF would lead to the generation of data that can be presented in a manuscript and used in the submission of an R01 proposal to the NIH - National Institute of Aging (NIA), likely for the October 2018 or February 2019 deadline. The results obtained from this project will be coupled with other data that are already collected. Briefly, bacterial diet also affects healthspan as Aß animals that consume HT115 E. coli paralyze at the same rate as those that consume HB101 E. coli, however, the animals exposed to HB101 exhibit extremely uncoordinated locomotion many hours before complete paralysis occurs. In addition, we are currently performing RNA sequencing to assess global gene expression changes in Aß animals fed HB101 compared to OP50 using start-up funds. Based on my discussions with Program Officers at the NIH Regional Seminar (Baltimore MD, October 2017), this project is of great interest to NIA as there is a goal to expand Alzheimer's research in all systems. Depending on the specific results, potential NIA Funding Opportunities include the standard Research Project Grant (Parent R01 PA-16-160), Role of Age-Associated Metabolic Changes in Alzheimer's Disease (PAR-17-031), and Capturing Complexity in the Molecular and Cellular Mechanisms Involved in the Etiology of Alzheimer's Disease (PAR-15-358). In addition, it is possible that specific Funding Opportunity Announcements (FOAs) of relevance to this project will be posted.
Research Support for Current Grants	

*Agency:	National Institute on Deafness and other Communication Disorders (NIDCD); R03 DC014328
*Amount Received:	$471,340
*Start Date:	03/01/2015
*End Date:	02/28/2018
*Add Another Research Support for Current Grants:	Yes
*Agency:	National Institute of General Medical Sciences (NIGMS) and the state of Delaware; INBRE Pilot Project Supported by P20 GM103446
*Amount Received:	$249,600
*Start Date:	12/01/2016
*End Date:	11/30/2018
*Add Another Research Support for Current Grants:	Yes
*Agency:	National Institute of General Medical Sciences (NIGMS) and the state of Delaware; Core Access Award
*Amount Received:	$3,950
*Start Date:	11/01/2017
*End Date:	3/31/2018
Research Support for Pending Grants	
*Agency:	ORAU Ralph E Powe Junior Faculty Enhancement Award
*Amount Requested:	$10,000
*Start Date:	6/1/2018
*End Date:	5/31/2019
*Add Another Research Support for Pending Grants:	No
Additional Information in Support of Proposal *(500 words or less):*	Mentoring: The PI started as a Tenure-Track Assistant Professor in the Biological Sciences Department at the University of Delaware (UD) in August 2016. Since that time she has set up her lab, recruited one M.S. student, two Ph.D. students, three undergraduates (one senior thesis student), one Postdoc, and one technician. In addition, Dr. Tanis is serving on thesis committees for nine M.S. students, two Ph.D. students and three undergraduates and was the outside reader of a Ph.D. dissertation for a Delaware State University (DSU) student. Dr. Tanis has been selected as a trainer for the Chemistry-Biology Interface (CBI) program, which exposes graduate students to interdisciplinary research, and participates in the annual Delaware Neuroscience Symposium. Since starting at UD, she has presented her research to the Department of Chemistry and Biochemistry at UD and the Biology Department at DSU.

	Funding: The PI is currently funded by an R03 from the National Institute on Deafness and other Communication Disorders (DC014328) as well as INBRE Pilot Project and Core Access Awards, supported by the National Institute of General Medical Sciences (P20 GM103446) and the state of Delaware. Laboratory research: Dr. Tanis is dedicated to conducting interdisciplinary biomedical research. She has continuously been drawn to use C. elegans and her >10 years of experience with this model system will enable the success of her research plan. Given Dr. Tanis' experience studying the mitochondrial uniporter as a postdoc she also has the knowledge of mitochondrial function required to carry out the research plan. The proposed work developed as an offshoot of the Tanis lab's study of the C. elegans homolog of the calcium homeostasis modulator ion channel CALHM1, which may play a protective role in LOAD pathogenesis. Many of the techniques proposed to study dietary effects on Aß toxicity are also utilized by students studying CALHM channels. Research facilities: The Tanis laboratory consists of 655 sq. ft. of space on the 2nd floor of Wolf Hall at UD. In addition to standard laboratory equipment, the lab is equipped with four Zeiss Stemi 508 stereomicroscopes, Zeiss AxioZoom V16 and AxioObserver D1 fluorescence microscopes, which both connect to a ZEN 2.3 Digital Imaging System and Axiocam 702 mono camera and a Tritech Research MINJ-1000D microINJECTOR system to create transgenics. Lab computers have GraphPad, DNASTAR, and ZEN software, used for data analysis, DNA sequence work and image analysis, respectively. C. elegans imaging experiments will be conducted at the UD BioImaging Center, which provides multiple microscopy and analysis platforms. RNA sequencing will be performed at the UD Sequencing and Genotyping Center on the Illumina HiSeq2500 and data analysis will be performed by Shawn Polson at the UD Center for Bioinformatics and Computational Biology. Support environment: The PI is mentored by Dr. Randy Duncan in the Department of Biological Sciences as well as CBI and Delaware Neuroscience faculty. Dr. Tanis is an active member of the Junior Investigators Network, participating in weekly meetings that provide grant writing and mentorship advice.
*Executive Summary *(250 words or less)*:	Late-onset Alzheimer's disease (LOAD), a neurodegenerative brain disorder that causes cognitive impairment in elderly individuals, affects

	more than 24 million individuals worldwide. Given the great personal, social and economic burdens associated with LOAD, it is important to understand the factors that contribute to disease pathogenesis in order to develop appropriate therapeutics. Our research uses a C. elegans model of Alzheimer's disease to identify factors that reduce accumulation of toxic Aß, a causative factor in LOAD. We discovered that the type of E. coli diet that these animals consume alters Aß-induced paralysis rate. Based on our study of this in different C. elegans genetic backgrounds, we hypothesize that consumption of specific E. coli activates the mitochondrial unfolded protein response, reducing Aß toxicity. Our proposed work uses a multifaceted approach including genetics, imaging, biochemistry, and behavioral studies to define the role of diet on Aß accumulation and mitochondrial function. Our study of mechanisms that reduce of Aß toxicity using an in vivo system is in line with the NIH mission to expand and accelerate research on the etiology of Alzheimer's disease and related dementias as called for by the National Alzheimer's Project Act (NAPA). The National Institute on Aging has specific funding set aside to achieve the goals of NAPA, and Congress demonstrated continued dedication to this area of research this past year by passing a $400 million increase for Alzheimer's research funding in the FY2017 budget. Our research is also of interest to private foundations including the Alzheimer's Association.

Budget

Budget	
*Upload Budget Justification	Budget justification UDRF.pdf
*Budget Category:	GRADST
*Budget Amount:	26144
*Sponsor Amount:	25000
*Budget Cost Share (Institution):	1144
*Budget Cost Share (Third Party):	0
Budget Category:	OTHER
Budget Amount:	1500
Sponsor Amount:	0
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Budget Cost Share TP Sum:	0

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UDRF References Tanis.pdf	PD Upload References	1/17/2018 10:48 AM
NSF biosketch for UDRF.pdf	Upload CV	1/17/2018 10:48 AM

Application Summary of : Samimi-Sadeh, Naomi

Cover Page

Proposal Data	
*Proposal ID:	18A00xxx
*Version ID:	V101
Faculty should provide their applicable Departmental Administrator with a budget and justification so that a record in UD's Grant Management System, People Soft (PS) may be initiated. Once completed use your PS number and version V101 above and click on the button to access that information.	
Cover Page	
*Employee ID:	
*Email:	NSADEH@UDEL.EDU
*First Name:	Naomi
Middle Name Initial:	
*Last Name:	Samimi-Sadeh
*Hire Date:	07/01/2016
*Proposal ID:	18A00xxx
*Proposal Title:	UDRF S-SADEH 2018
*Proposal Title (Long):	Assessing stability and change in inhibitory brain networks related to psychopathology and risky behavior
Education	
*Department:	Psychological & Brain Sciences (02577)
*College:	Arts and Sciences (AS)
*Rank:	Assistant Professor (2C1001)
*Rank Date:	01/07/2016
*Degree:	Ph.D.
*Year:	2012
Tenured Faculty Name *(for UDRF-SI)*:	
*Dept Admin Name:	Powell,Carolyn Faye
*Dept Admin Email:	CPOWELL@UDEL.EDU
*Contract & Grant Specialist Name:	Ehmann,Julie Fitzgerald

*Chair Name:	Simons,Robert F
*Chair Email:	RSIMONS@UDEL.EDU
*Dean Name:	Pelesko,John
*Dean Email:	PELESKO@UDEL.EDU
*Discipline:	Clinical Science
*Honors:	2016 - Donald F. Klein Early Career Investigator Award (Finalist), Anxiety & Depression Association of America 2015 - Rising Star Designation, Association for Psychological Science 2015 - Early Career Achievement Award, American Psychological Association 2014 - Career Development Leadership Award, Anxiety & Depression Association of America 2014 - Continuing Education Grant, American Psychology-Law Society 2013 - Robert E. Harris Memorial Award, University of California, San Francisco (Honors a psychology fellow for excellence in clinical services & research) 2010 - Sarah C. Mangelsdorf Award, University of Illinois (Honors a female student for demonstrating the potential to be an academic leader) 2010 - Frederick & Ruby Kanfer Award, University of Illinois (Awarded for scholarship that integrates basic science & clinical practice) 2009 - List of Teachers Ranked Excellent, University of Illinois 2009 - Graduate College Travel Award, University of Illinois 2008 - American Psychological Association Research Scholarship, American Psychological Foundation/ Council of Graduate Departments of Psychology 2008 - Smadar Levin Award, Society for Research in Psychopathology
*Applicant's Relevant Publications:	(10 of 44 peer-reviewed publication selected; H-index = 21) Sadeh, N., Wolf, E.J., Logue, M.W., Hayes, J.P., Stone, A., Griffin, L.M., Schichman, S.A., & Miller, M.W. (2016). Epigenetic variation at SKA2 predicts suicide phenotypes and internalizing psychopathology. Depression and Anxiety, 33(4), 308-315.

Sadeh, N., Wolf, E.J., Logue, M.W., Lusk, J., Hayes, J.P., McGlinchey, R.E., Milberg, W.P., Stone, A., Schichman, S.A., & Miller, M.W. (2016). Polygenic risk for externalizing psychopathology and executive dysfunction in trauma-exposed veterans. Clinical Psychological Science, 4(3), 545-558.

Sadeh, N., Spielberg, J.M., Logue, M.W., Wolf, E.J., Smith, A.K., Lusk, J., Hayes, J.P., Sperbeck, E., Milberg, W.P., McGlinchey, R.E., Salat, D.H., Carter, W.C., Stone, A., Schichman, S.A., Humphries, D.E., Miller, M.W. (2016). SKA2 methylation is associated with decreased prefrontal cortical thickness and greater PTSD severity among trauma-exposed veterans. Molecular Psychiatry, 21(3), 357–363.

Sadeh, N. & Baskin-Sommers, A. (2017). Risky, impulsive, and self-destructive behavior Questionnaire (RISQ): A validation study. Assessment, 24(8), 1080-1094.

Sadeh, N., Spielberg, J.M., Miller, M.W., Milberg, W.P., Salat, D.H., Amick, M., Fortier, C. & McGlinchey, R.E. (2015). Neurobiological indicators of disinhibition in posttraumatic stress disorder. Human Brain Mapping, 36(8), 3076-3086.

Sadeh, N.,+ Spielberg, J.M. +, Warren, S.L., Miller, G.A., & Heller, W. (2014). Aberrant neural connectivity during emotional processing associated with posttraumatic stress. Clinical Psychological Science, 2(6), 748-755.

Sadeh, N., Spielberg, J.M., Heller, W., Herrington, J.D., Engels, A.S., Warren, S.L., Crocker, L.D., Sutton, B.P., & Miller, G.A. (2013). Emotion disrupts neural activity during selective attention in psychopathy. Social Cognitive, and Affective Neuroscience, 8(3), 235-246.

Sadeh, N., Javdani, S., Finy, M.S., & Verona, E. (2011). Gender differences in emotional risk for self- and other-directed violence among externalizing adults. Journal of Consulting & Clinical Psychology, 79(1), 106-117.

Sadeh, N. & Verona, E. (2012). Visual complexity attenuates emotional processing in psychopathy: Implications for fear-potentiated startle deficits. Cognitive, Affective, & Behavioral Neuroscience, 12(2), 346-360.

Sadeh, N. & McNiel, D.E. (2013). Facets of anger, childhood sexual victimization, and gender as predictors of suicide attempts in psychiatric patients after hospital discharge. Journal of Abnormal Psychology, 122(3), 879-890.

***Professional** and/or **Research Experience** (including Post Doctoral):*	2016-Present: Assistant Professor, University of Delaware, Department of Psychological and Brain Sciences, Newark, DE 2014-2016: Assistant Professor, Boston University School of Medicine, Department of Psychiatry, Boston, MA 2013-2016: Principal Investigator, Behavioral Science Division, National Center for PTSD, VA Boston Healthcare System, Boston, MA 2012-2013: Postdoctoral Fellow, Dale E. McNiel, Ph.D. (Mentor), Department of Psychiatry, University of California, San Francisco, CA 2011-2012: Pre-doctoral Internship, Clinical Psychology Training Program, University of California, San Francisco, CA 2005-2012: Doctor of Philosophy, Clinical Psychology, University of Illinois at Urbana-Champaign, Champaign, IL 2000-2004: Bachelor of Arts, Psychology, University of Wisconsin-Madison, Madison, WI
Upload: A two-page CV, following the NSF format for biological information, is also requested. An example and template: CLICK HERE	
*Upload CV:	Samimi-Sadeh_NSF Biosketch.docx
Is this proposal being submitted elsewhere? (Check all that apply)	

Project Description

Project Description	
*Proposal Type:	NEW
*Proposal Due Date:	2018-01-15
*Proposal Begin Date:	2018-06-01
*Proposal End Date:	2019-05-31
*Proposal Status:	DRF
*Primary Sponsor:	2910
*Resubmission: Is this a resubmission of a prior year UDRF proposal?	No
*Significance of the **Proposed Work** *(250 words or less):*	The capacity for self-control is one of the strongest predictors of psychological and physical well-being, with 80-90% of self-control in everyday life relying on the ability to inhibit unhealthy impulses and urges (Baumeister et al., 1994). Poor inhibitory control negatively impacts health in numerous ways,

	including by increasing engagement in risky and impulsive behaviors that are associated with premature death and disease (e.g., reckless driving, drug use). Notably, inhibitory control failure is a feature of a diverse array of mental disorders (e.g., substance use, posttraumatic stress) and other harmful behaviors (e.g., suicide, violence). Decades of research have culminated in a wealth of knowledge about the brain regions involved in supporting inhibitory control. It is also known that certain situations make it more difficult to control impulsive urges (e.g., experiencing intense negative emotions or mental fatigue), especially for individuals with mental illness. However, less is known about how brain networks support inhibition across these different challenging situations in individuals with mental illness. The objective of this proposal is to begin to fill this gap in the literature by establishing how inhibitory neural networks function across different challenging contexts in a clinical sample of adults with mental illness. This research has the potential to significantly advance current knowledge by (i) delineating how inhibitory control neural networks adapt (or fail to adapt) to support self-control in challenging contexts across mental disorders and (ii) establishing the stability and predictive power of these neural networks for explaining changes in symptoms of mental illness over time.
*Description of **Proposed Research** or **Scholarly Activity** *(1250 words or less):*	Although much is known about the brain regions involved in inhibitory control (Criaud & Boulinguez, 2013), no study to date has investigated how brain networks functionally reconfigure to support inhibition across contexts that typically compromise such control. Three common situations known to challenge inhibition are (i) when cognitive resources are taxed or impaired (e.g., after effort depletion or alcohol consumption), (ii) when encountering immediate temptations or rewards, and (iii) when experiencing negative mood states (Baumeister, 2014; Heatherton & Wagner, 2011). Importantly, the proposed research is designed to systematically examine inhibitory control brain networks in each of these contexts. Existing research on inhibition has almost uniformly examined only coupling between pairs of brain regions, which does not take into account the role brain regions play in larger brain networks. In other words, studies have looked at connections rather than networks. Data from our research team using graph theory metrics (Spielberg et al., 2015) found that the global brain network (i.e., connectivity between all brain regions) meets demand for inhibitory control by reconfiguring into an

organization with greater communication efficiency (i.e., Global Efficiency), optimization for specialized processing (i.e., Transitivity), and robustness to disruption (i.e., Assortativity). These findings highlight the insight that can be gained from examining the entire brain network and support the use of graph theory metrics to assess network organization and function. However, these findings are preliminary and require replication and extension. Indeed, there is mounting concern that the conclusions of neuroimaging studies are based on unreliable and biased results (Poldrack et al., 2016). Given that using graph theory metrics to assess neural functioning is a relatively new area of study, it is important to evaluate the reliability and validity of these measures. To address this issue, we will determine replicability by assessing the 3-month test-retest reliability of the identified neural networks and graph properties.

The majority of research on inhibitory control in pathological samples has focused exclusively on one or two diagnoses in a given study, despite substantial evidence that inhibitory failure manifests across diverse mental disorders and public health problems (Goschke, 2014; Nigg, 2000). This approach limits understanding of how control deficits may contribute to multiple symptoms and pathological behaviors and explain patterns of comorbidity among disorders. We will address this gap by investigating relations between inhibitory neural network function and clusters of mental disorders known to share common etiologies and risk factors, specifically externalizing disorders and emotional disorders.

Specific Aims.
Ongoing research in my lab, supported by a NIH-funded COBRE grant, is investigating (i) how functional brain networks supporting inhibitory control adapt to challenging contexts and (ii) the relevance of these networks for predicting self-control, psychiatric symptoms, and risky behavior. It involves collecting MRI and clinical assessment data on a cohort of healthy adults (N = 100; 50% female) and reassessing a subset of this group after 3 months (N=50) to examine the reliability of the neural findings. Another piece of this research is to collect data on a clinical sample of adults with mental illness to investigate how inhibitory control brain networks function across diverse forms of psychopathology (N=100, 50% female).

One limitation of the current project is that the clinical sample is not being followed over time. Longitudinal assessment of these individuals would provide valuable information on whether neural network metrics of inhibition can predict changes in mental

health symptoms and future engagement in risky behavior. It would also advance understanding on the reliability of neural metrics of inhibition in individuals with mental illness. The specific aims described below are designed to fill these gaps:

Specific Aim 1: Establish the replicability of disturbances in inhibitory neural network functioning related to mental illness. We will perform a 3-month follow-up assessment on a subset (N = 50) of the clinical sample (using the same MRI tasks and protocol). Inhibitory network functioning will be assessed using neural network organization (indexed using graph theory metrics) and network connectivity strength during tasks that measure inhibitory control in different challenging contexts (see MRI assessment below). Hypothesis: Disturbances in neural network functioning that were associated with mental illness at the baseline assessment will also be observed at follow-up.

Specific Aim 2: Evaluate whether disturbances in inhibitory neural network functioning at baseline predict future mental health symptoms and risky behavior. We will perform a brief clinical assessment (via phone or email) every 4 weeks for 3 months to re-evaluate engagement in harmful behaviors (e.g., risk-taking, self-harm, substance use) and mental health symptoms linked to inhibitory control problems and use the baseline MRI to predict these clinical outcomes. Hypothesis: Disturbances in neural network functioning identified at baseline will predict engagement in risky behaviors (drug use, risky sex, aggressive behavior) and changes in mental health symptoms (e.g., increased levels of posttraumatic stress) at follow-up.

Specific Aim 3: Examine whether changes in inhibitory neural network functioning within individuals (from baseline to follow-up) predict changes in risky behavior and mental health symptoms over the same time period. We will use the MRI and clinical assessment data collected at baseline and 3-month follow-up for these analyses. Hypothesis: Changes in neural network functioning from baseline to follow-up will correlate with fluctuations in risky behaviors/ mental health over time.

Methods
Participants. 50 adults who participated in an initial MRI/clinical assessment and have a history of an externalizing disorder (e.g., substance dependence, antisocial personality disorder) or emotional disorder (e.g., anxiety, depression, posttraumatic stress) will be recruited to participate in a 3-month follow-up study. Inclusion criteria are: ages 18-55 and English as a first language. Exclusion criteria are: head injury

with loss of consciousness for over 30 minutes or lasting effects, current psychosis, serious medical or neurological condition, current pregnancy, metallic implants or other contraindications to MRI. These criteria will ensure that participants can understand the measures and protect participant safety.

Measures.
1. Clinical Assessment: To supplement the intensive clinical assessment done at baseline, participants will complete a battery of self-report questionnaires every 4 weeks for 3 months to assess health-related and risky behaviors, mental health symptoms, and emotional processes (e.g., difficulty with emotion regulation, perceived stress).

2. MRI Assessment: Three months after their initial MRI assessment, participants will return to complete a second MRI scan to collect data on functional and structural brain networks. Functional connectivity will be assessed during Go/No-Go tasks designed to index inhibition in different contexts:
• Negative Mood Induction: participants respond to Go/No-Go stimuli superimposed on aversive pictures (e.g., mutilated bodies)

• Exposure to Reward Cues: participants respond to Go/No-Go stimuli superimposed on rewarding pictures (e.g., erotic couples)

• Cognitive Resource Depletion: participants respond to Go/No-Go stimuli superimposed on neutral pictures while completing a concurrent working memory task (n-back task)

• Neutral Context: participants respond to Go/No-Go stimuli superimposed on neutral pictures (no emotional or cognitive manipulation)

The Go/No-Go task represents one of the most widely-studied and well-validated inhibitory control tasks available (Nigg, 2000; Wright et al., 2014), including in research on the neural basis of inhibition.

Expected Outcomes.
The proposed research would provide key preliminary data on the replicability of disruptions in inhibitory control brain networks related to mental illness and other costly clinical problems. Further, it would provide a crucial initial test of whether graph theory metrics of inhibitory control brain networks can predict changes in mental health symptoms and health-related behaviors over time. These data would provide a strong foundation for a R01 grant application designed to examine how inhibitory control networks go awry in mental illness and whether graph theory metrics are useful biomarkers

	for predicting fluctuations in mental health symptoms and risky behaviors over time.
Upload References:	UDRF_Sadeh_Winter 2018_REF.docx
Upload Figures/Tables and or timeline (no more than 1 page):	UDRF_Sadeh_Winter 2018_Tables.docx

Other Required Information

Other Required Information	
*Indicate Plans for Submission of this **Project to Other Funding Sources** *(250 words or less):*	Data from this project will be used as pilot and feasibility data for a larger R01 application to the National Institute of Mental Health and as a NARSAD Young Investigator Award. Given their relevance for understanding risk for suicidal and self-harming behaviors, data from this project will be used to submit an application to the American Foundation for Suicide Prevention, specifically the Young Investigator Innovation Grant. Additionally, a proposal focusing on understanding the role of inhibitory control brain networks in psychopathology characterized by violent and aggressive behavior will be submitted to The Harry Frank Guggenheim Foundation Research Grant mechanism.
Research Support for Current Grants	
*Agency:	National Institute of General Medical Sciences
*Amount Received:	$1,214,255
*Start Date:	09/11/2017
*End Date:	08/31/2022
*Add Another Research Support for Current Grants:	No
Research Support for Pending Grants	
*Agency:	National Institute of Mental Health
*Amount Requested:	$1,915,324
*Start Date:	04/01/2018
*End Date:	03/31/2023
*Add Another Research Support for Pending Grants:	No
Additional Information in Support of Proposal *(500 words or less):*	Laboratory Facilities. My laboratory space consists of six recently renovated rooms in Wolf Hall at the University of Delaware (approximately 836 sq. ft.). These rooms are dedicated for various research activities, including running research participants (behavioral testing and clinical interviewing), data entry and analysis, and programming, as well as

workstations for research personnel (graduate students, project coordinator, other study staff). These rooms also contain locked file cabinets for securing data and are linked directly to the main server.

Computing Facilities: The lab has two Linux neuroimaging-dedicated analysis machines located in Wolf 411 (machine 1: 8-core Xeon cpu, 48GB RAM, 16TB disk space; machine 2: 12-core Xeon cpu, 48GB RAM, 11TB disk space). For data storage/backup, the lab has a Thecus N12000 NAS with 36TB of disk space located in the department server room (temperature and humidity controlled). There are gigabit Ethernet connections between all three machines, allowing for rapid communication. Finally, the lab owns a 24-core node (128GB RAM) in one of UD's supercomputing clusters. Thus, the lab has immediate priority for processing on this node (access to all other cluster nodes is available, but is allocated on a first come, first served basis).

Clinical Facilities. I am a faculty member in the Psychological and Brain Science Department's Clinical Science program, which maintains an in-house Psychological Services Clinic (PSC) that offers mental health services to individuals in the community and trains graduate students. The PSC is a valuable resource for recruiting clinical samples of individuals seeking mental health treatment. It is located approximately 0.5 miles from my laboratory space and the neuroimaging facilities. I am also a licensed clinical psychologist with the requisite training and expertise to conduct research with clinical samples.

Neuroimaging Facilities. UD's Center for Biomedical and Brain Imaging (CBBI) is a state-of-the-art 11,600-square-foot facility, housing the state's first research dedicated MRI scanner, which is located in the building adjacent to the Sadeh lab. The centerpiece of the CBBI is a Siemens 3T Magnetom Prisma equipped with a 64 channel, phased-array head coil. The Prisma will allow for extremely powerful scanning capabilities, for example, ultra-fast fMRI and 514-directions diffusion imaging. The imaging suite is equipped with MR-compatible visual and auditory stimulation equipment, eye-tracking, response devices, and Biopac physiological measurement hardware. To harness the power of the Prisma, the CBBI has licensed key research acquisition protocols, including multi-band fMRI and diffusion protocols from the Center for Magnetic Resonance Research at University of Minnesota (the same protocols used by the Human Connectome Project) and a multi-echo MPRAGE protocol from the Martinos Center at Mass General Hospital. Additional CBBI resources include

	conference/ teaching facilities, bench-top imaging instruments, and a mock scanner.
*Executive Summary *(250 words or less)*:	Poor inhibitory control negatively impacts health in numerous ways, including by conferring risk for a diverse range of psychopathology and increasing risky and impulsive behaviors that are associated with premature death and disease. The objectives of this application are to determine how functional brain networks supporting inhibitory control respond to situational challenges in adults with mental disorders and to evaluate the relevance of these brain network adaptations for predicting fluctuations in mental health symptoms and risky behaviors over time. The specific aims of the application are 1) to evaluate the replicability of disturbances in inhibitory neural networks related to mental disorders, 2) to assess whether disturbances in neural network functioning predict clinical problems over a 3-month period, and 3) to examine whether changes in inhibitory neural network functioning predict changes in clinical problems over the same time period. The project involves collecting additional neuroimaging and clinical assessment data on a well-characterized cohort of adults with mental illness (N = 50) three months after their initial assessment. The knowledge gained from this research is expected to ultimately aid in the treatment of inhibition failures in mental illness by leading to a deeper understanding of the brain networks that support successful inhibitory control.

Budget

Budget	
*Upload Budget Justification	UDRF_BUDGET JUST_SAMIMI SADEH.docx
*Budget Category:	OTHER
*Budget Amount:	30000
*Sponsor Amount:	25000
*Budget Cost Share (Institution):	5000
*Budget Cost Share (Third Party):	0
Budget Category:	PARTINC
Budget Amount:	5000
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Budget Cost Share TP:	
Budget Amount Sum:	25000
Sponsor Amount Sum:	25000
Budget Cost Share IN Sum:	10000
Budget Cost Share TP Sum:	0

Document Title	Question	Date Uploaded
UDRF_BUDGET JUST_SAMIMI SADEH.docx	BUDGETUpload Budget Justification	12/22/2017 9:22 PM
UDRF_Sadeh_Winter 2018_Tables.docx	PD Upload FiguresTables and or timeline no more than 1 page	12/22/2017 9:01 PM

UDRF_Sadeh_Winter 2018_REF.docx	PD Upload References	12/20/2017 8:30 PM
Samimi-Sadeh_NSF Biosketch.docx	Upload CV	12/20/2017 7:59 PM