Research Advisory Committee

Meeting of June 19, 2017

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Crowdfunding Project Descriptions Reviews: The votes and comments of the review panels are captured on this spreadsheet which is attached separately and best read on computer screen.

AMERICAN BRAIN FOUNDATION	Research Advisory Committee June 19, 2017 10:00 a.m. – 11:00 a.m. CT Conference call: 866-740-1260; Access code: 9286317
Committee Members	Carsten Bonnemann, MD; Merit Cudkowicz, MD; Robert Griggs, MD; Shafali Jeste, MD; John Morris, MD; Raymond Roos, MD; Ralph Sacco, MD; Ira Shoulson, MD; Eugene Scharf, MD; Lisa DeAngelis, MD; Christy Phelps, Deputy ED AAN
Staff	Jane Ransom, Shelly Collins Rucks, Suzi Sherman, Natalie Baumgartner

	AGENDA ITEM	*PRESENTED BY*
10:00 a.m.	Welcome	Dr. Griggs, Chair
	Approve Minutes of April 25, 2017 Meeting	Dr. Griggs
10:05	Crowdfunding a) Projects posted to date b) Pending projects c) Crowdfunding with partner organizations d) Marketing plan	Dr. Griggs
10:25	Major Giving	Shelly Rucks, Director of Development
10:40	Clinical Research Training Scholarships & Sustainable Growth a. 2017 Successes b. Challenges i. Funding Foundation's Operations ii. Scholarship increase from $130,000 to $150,000	Jane Ransom, Executive Director
11:00	Adjourn	

American Brain Foundation
Research Advisory Committee Meeting
April 25, 2017
7:45 – 8:45 a.m. ET
In Person

In attendance: Merit Cudkowicz, MD; Robert Griggs, MD; Ralph Sacco, MD; Ira Shoulson, MD; Eugene Scharf, MD

Staff: Jane Ransom, Shelly Rucks, Suzi Sherman, Natalie Baumgartner

Excused: Carsten Bonnemann, MD; Shafali Jeste, MD; John Morris, MD; Raymond Roos, MD; Lisa DeAngelis, MD; Christy Phelps, Deputy ED AAN.

Dr. Griggs welcomed everyone and discussed the agenda for the meeting. Dr. Griggs asked that the Research Advisory Committee minutes from March 20, 2017, be reviewed.

MOTION to approve the minutes from March 20,2017.

Approved (Unanimous).

1. **Presentations of Crowdfunding at Annual Meeting:** Dr. Griggs highlighted the crowdfunding site launch and the presentations at NINDS, the Experiential Learning Stage, and the Frontiers Plenary. He mentioned how the crowdfunding site was created, its benefits, who should apply, how to apply, and how much it costs ABF. Dr. Griggs went on to explain how crowdfunding campaigns can work and the importance of making each project publicly readable.

   Discussion: The Committee could see that a lot of hard work had been put into each project and were excited to hear that projects were written for a more general audience. There was concern that the website, overall, may not be catering to the donor, which might cost ABF donations. There was a desire to make the website more user-friendly.

   The Committee acknowledged that "$24,000,000 Raised" (on the website) is an impressive number, but that it was unclear that the sum had been raised over the lifetime of ABF. They also did not understand why there was only a 90-day window for crowdfunding.

   Ms. Ransom said that 90 days is the standard in the world of crowdfunding campaigns. Putting a cap on the campaign creates a sense of urgency for donors. But, she acknowledged that the ABF is learning as it progresses and is open to changing the length of campaigns. Ms. Ransom also mentioned that ABF's Digital Strategist would support marketing efforts for each project.

   The Committee encouraged the ABF to present or create an early success on the crowdfunding site to prove that it is a viable donations platform. The Committee also

seemed to agree that they needed access to analytics to know where donations were coming from (i.e. social networks, organizations, individuals).

2. **Behind-the-Scenes Look at Crowdfunding Site:** Ms. Sherman highlighted the features of the new website and crowdfunding site. She featured a behind-the-scenes look at how the applications come in and how the review process is handled.

3. **Feedback on Crowdfunding Site and Next Steps:** Ms. Ransom asked the Committee for input from the Committee on establishing project milestones, rotation of projects equally on home page vs. highlighting crowd-pleasing projects, and review of instructions for application process.

   The Committee agreed that application instructions will require a "wait and see" approach with awareness for applicant feedback. The Committee also felt it important to have one quick win, which would require the prioritization of an individual project over others to call attention to successes. Milestones need to be considered, but the Committee seemed to prefer a two-stage payment process to project holders to ensure oversight.

   The Committee felt that it was important to look at these projects as "pilot projects" that might need revisions. However, it is important to make clear to researchers that their money is coming from people who are investing in their project and in their success.

4. **Crowdfunding & Major Donor Fundraising:** Ms. Rucks is open to questions concerning all current and future fundraising efforts.

5. **Adjourn** at 8:47 a.m. ET.

	Manav Vyas University of Toronto	**Ania Busza** University of Rochester Medical School	**Kent Werner** Cogentis Therapeutics	**Charlene Ong** Massachusetts General Hospital/ Brigham and Women's Hospital/ Harvard Medical School	**Adam Mecca** Yale University	**James Noble** Columbia University
ALS & Neuromuscular						
Autism & Neurodevelopment						
Brain & Nerve Tumors				X		
Brain & Spine Trauma				X		X
Dementia-Alzheimer's, LBD, Other			X		X	
Headache & Pain						
Movement Disorders			X			
MS & Autoimmune Disease						
Neurogenetic Disease						
Neuroinfectious Disease						
Neurorehabilitation		X				
Seizure Disorders						
Sleep Disorders						
Stroke & Vascular Diseases	X	X		X		
Technology & Innovation				X		
Other						X

Yellow = Pending Projects

	Gordon Smith University of Utah	**Aaron Boes** University of Iowa	**Matt Bianchi** Massachusetts General Hospital/ Brigham and Women's Hospital/ Harvard Medical School	**Bakhos Tannous** Massachusetts General Hospital/ Brigham and Women's Hospital/ Harvard Medical School	**Sean Rose** The Sports Neurology Clinic at The CORE Institute	**Bradford Worrall** University of Virginia
ALS & Neuromuscular	X					
Autism & Neurodevelopment		X				
Brain & Nerve Tumors		X		X		
Brain & Spine Trauma					X	
Dementia- Alzheimer's, LBD, Other						
Headache & Pain						
Movement Disorders						
MS & Autoimmune Disease						
Neurogenetic Disease						
Neuroinfectious Disease						
Neurorehabilitation						
Seizure Disorders						
Sleep Disorders			X			
Stroke & Vascular Diseases						X
Technology & Innovation	X		X			
Other						

Yellow = Pending Projects

	Dolores Vasquez Sanroman Oklahoma State University	**Eugene Scharf** University of Rochester Medical School	**Kumar Pichumani** Houston Methodist Research Institute & Hospital	**William Renthal** Harvard Medical School
ALS & Neuromuscular				
Autism & Neurodevelopment				
Brain & Nerve Tumors			X	
Brain & Spine Trauma				
Dementia-Alzheimer's, LBD, Other				
Headache & Pain				X
Movement Disorders				
MS & Autoimmune Disease				
Neurogenetic Disease				
Neuroinfectious Disease				
Neurorehabilitation	X			
Seizure Disorders				
Sleep Disorders	X			
Stroke & Vascular Diseases		X		
Technology & Innovation	X		X	
Other				

Yellow = Pending Projects

To: Robert Griggs MD, Jane Ransom
Re: ABF Crowdfunding platform risk
From: Gene Scharf MD

I. Problem statement:

The American Brain Foundation neuroscience crowd-funding platform disrupts the conventional mechanisms of charitable giving and therefore may appear as a risk to individual disease focused foundations by the perception of diverting donor funds and research proposals in areas of overlap.

II. Purpose statement:

Create a unique solution that can:

1. Align and serve the common interests of multiple independent neuroscience themed foundations.
2. Create buy-in from multiple independent neuroscience foundations to support the American Brain Foundation crowd funding platform.

III. Proposed solution:

By **opening the platform and inviting campaigns initiated by non-profits,** the American Brain Foundation can strategically position itself not as a competitor with other foundations for a fixed sum of donations but instead as a **facilitator or broker** connecting and extending the influence of foundations with tenable research ventures in need of financial support. Operating as a low-cost/low-risk intermediary between a public donor pool and an organization, the ABF Research exchange simultaneously functions as a proxy fundraiser for private foundations while elevating itself to the sole and universal space for high quality neuroscience crowdfunding thus incentivizing the sustainability of the both the ABF and the listing organization. Promoting this unique function redefines the ABF Crowdfunding platform as the universal neuroscience crowdfunding exchange and defuses concerns about competition and diversion.

Private foundations through their participation in the ABF exchange benefit by:

1. Access to additional funding and charitable contributions without bearing the cost and risk of establishing, competing, and maintaining similar models of fundraising.
2. Positive branding and professional association with ABF and AAN.
3. Access to AAN scientific review of proposals.
4. Heightened public visibility for the organization and its researchers.

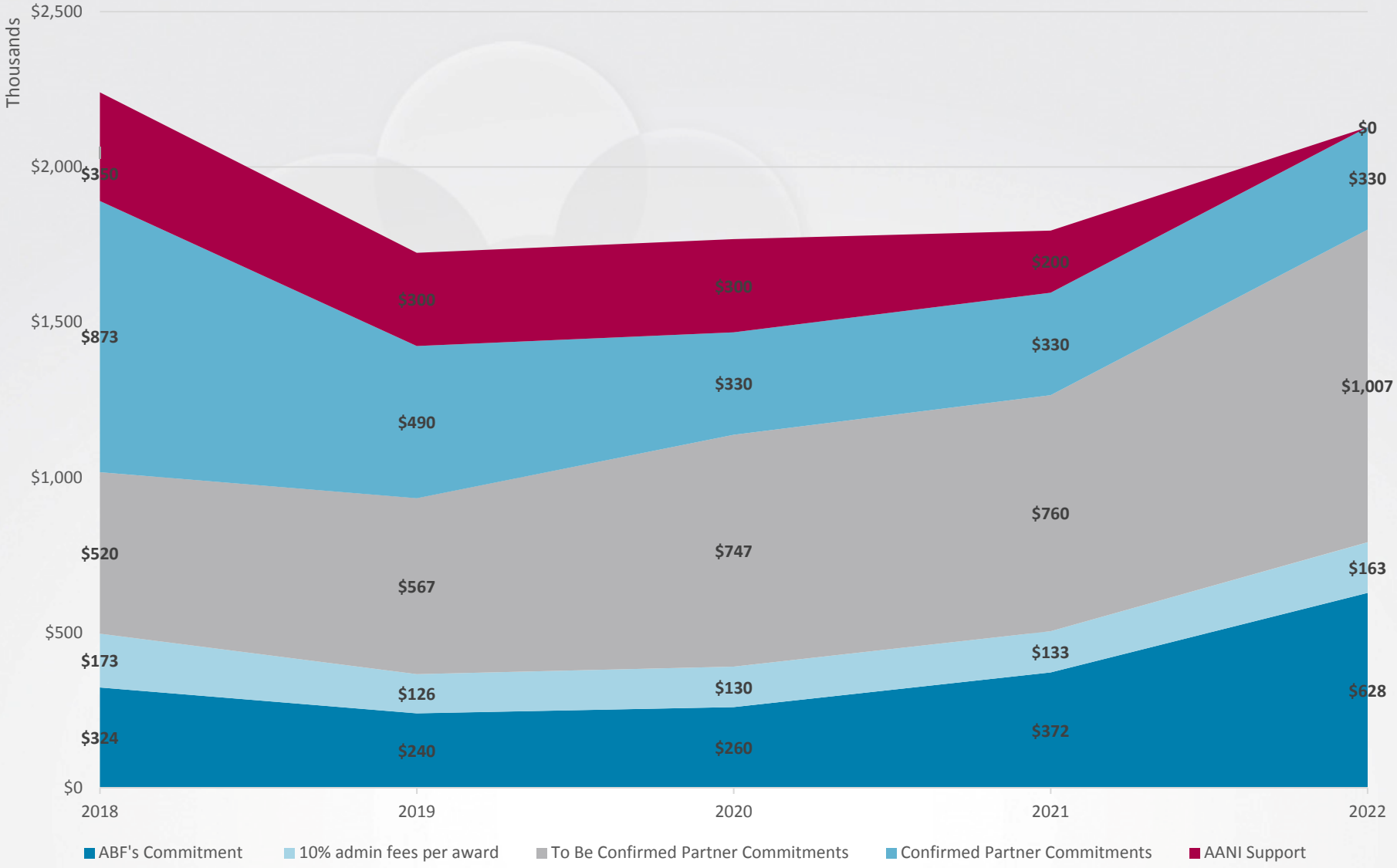
To illustrate the concept imagine an organization, ABC Foundation, receives a research funding proposal. This proposal is credible but is not a high enough priority to be funded. Instead of rejecting the proposal, ABC Foundation asks the researcher to apply to be posted on the ABF crowdfunding site with documentation that the project has the full support of thel ABC Foundation. If the project is accepted for crowdfunding by the ABF, the ABF agrees to include branding from the ABC Foundation, showing its full support for the campaign. If the campaign is funded, then ABC Foundation awards the sum to the initial applicant.

IV. Deliverable

The American Brain Foundation Deliverable:

1. Commitment from one to two large leading nonprofit foundations to list at least one project as proof of concept.
2. Commitment from at least two small boutique disease focused organizations to submit a project as proof of concept.

5 Year Research Program Forecast



AMERICAN BRAIN FOUNDATION

	2018	2019	2020	2021	2022
Research Program Total	$2,210,200	$1,693,200	$1,737,200	$1,764,700	$2,098,000

Assumptions:

1. YTD AANI support is $1.5M and the ABF is forecasting to use $350,000 in 2017 leaving $1.15M for 2018-2022
2. In cases where the ABF has more than one award with a partner in any given year, AANI admin fee is $5K total (per partnership) instead of per award
3. 2018 is based on actual commitments of 14 CRTSs/CSDAs, 2019-2022 is based on benchmarks agreed upon with AANI
   a) 2019 = 10 CRTSs/CSDAs;
   b) 2020 = 11 CRTSs/CSDAs;
   c) 2021 = 11 CRTSs/CSDAs;
   d) 2022 = 12 CRTSs/CSDAs
4. In 2019, the cost of a CRTS increased to $150,000
5. "Confirmed Partner Commitments" includes the MBRF's 10% admin fee (per award), therefore "10% admin fee" excludes the MBRF's 10% fee to avoid double counting

AMERICAN BRAIN FOUNDATION

Aaron D. Boes

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(319) 331-5479 • aaron-boes@uiowa.edu

CURRENT POSITION

7/2016 - Current	Assistant Professor Departments of Pediatrics, Neurology & Psychiatry University of Iowa Hospitals and Clinics Iowa City, IA

ADDITIONAL AFFILIATIONS

7/2016 - Current	Non-Clinical Staff \ Courtesy Staff (Research Collaborator) Massachusetts General Hospital Harvard University, Boston, MA

EDUCATION & WORK EXPERIENCE

7/2014 – 6/2016	Attending, Pediatric Neurologist Massachusetts General Hospital Harvard University, Boston, MA
7/2014 – 6/2016	Clinical Neuroscience Fellow & Staff Physician Neuropsychiatry & Noninvasive Brain Stimulation Berenson Allen Center for Noninvasive Brain Stimulation Beth Israel Deaconess Medical Center Harvard University, Boston, MA
7/2013 - 6/2014	Chief Pediatric Neurology Resident Massachusetts General Hospital Harvard University, Boston, MA
7/2011 - 6/2013	Pediatric Neurology Resident Massachusetts General Hospital \ Brigham and Women's Harvard University, Boston, MA
6/2009 - 6/2011	Pediatric Resident Rady Children's Hospital University of California San Diego, San Diego, CA
8/2003 - 5/2009	Scholar, Medical Scientist Training Program M.D. Carver College of Medicine; Ph.D. Neuroscience University of Iowa, Iowa City, IA
8/1999 - 5/2003	Bachelors of Science with Honors and High Distinction Integrative Physiology \ Exercise Science University of Iowa, Iowa City, IA
2001 Spring	Traveling Scholar The University of Wales, Swansea, Wales, UK

HONORS, AWARDS, & OUTSTANDING ACHIEVEMENTS

2016	Biological Psychiatry Travel Fellowship Award
2016	S. Weir Mitchell Award for outstanding achievement in neurology research + $1000 cash prize, American Academy of Neurology & American Brain Foundation
2015	Primary mentor for manuscript awarded Saul R. Korey Award for American Academy of Neurology Best Medical Student Essay, awarded to mentee David Fischer
2013 - 2015	Received highest teaching rating, 'Excellent' by Harvard Medical School students, Neuroanatomy Laboratory
2014	First author on manuscript awarded the prestigious S. Weir Mitchell Award by the American Academy of Neurology
2014, 2015	American Academy of Neurology Scholarship recipient, nominated by Partners Neurology, BIDMC Neurology
2013	Cobb Award & Cash Prize for Best Poster Presentation, Boston Society of Neurology and Psychiatry Cobb Assembly
2011	Named "Highly Cited Author" in 2011 by Social Cognitive and Affective Neuroscience
2008	American Academy of Neurology Saul R. Korey Award, Best medical student essay in experimental neurology
2008	Cognitive Neuroscience Society, Graduate Students Present Award (9 of 300 applicants awarded)
2007, 2008	Wisconsin Symposium on Emotion Scholar Travel Award (15 awarded per year)
2007	Human Brain Mapping Conference, Highest Ranking Abstract (top 65 of 1566) & Travel Fellow Award
2007	NINDS Neuroscience Career Symposium Travel Award
2005	Medical Student Representative, American Academy of Neurology Conference, Miami, FL
2003	University of Iowa Dean's List
2002	Honors Thesis Travel Award
2002	Golden Key National Honor Society Inductee
2002	Czech Heritage Scholarship Award

2002	Phi Beta Kappa Honor Society Inductee
2000	Nile Kinnick Leadership Award

PUBLICATIONS

1. **Boes AD**, Murko V, Wood JL, Langbehn DR, Canady J, Richman L, Nopoulos P: Social function in boys with cleft lip and palate: relationship to ventral frontal cortex morphology. *Behav Brain Res* 2007, 181(2):224-231. PMID: 17537526.

2. **Boes AD**, McCormick LM, Coryell WH, Nopoulos P: Rostral anterior cingulate cortex volume correlates with depressed mood in normal healthy children. *Biol Psychiatry* 2008, 63(4):391-397. PMID: 17916329.

3. **Boes AD**, Tranel D, Anderson SW, Nopoulos P: Right anterior cingulate: a neuroanatomical correlate of aggression and defiance in boys. *Behav Neurosci* 2008, 122(3):677-684. PMID: 18513137.

4. **Boes AD**, Bechara A, Tranel D, Anderson SW, Richman L, Nopoulos P: Right ventromedial prefrontal cortex: a neuroanatomical correlate of impulse control in boys. *Soc Cogn Affect Neurosci* 2009, 4(1):1-9. PMID: 19015086.

5. Van Der Plas EA, **Boes AD**, Wemmie JA, Tranel D, Nopoulos P: Amygdala volume correlates positively with fearfulness in normal healthy girls. *Soc Cogn Affect Neurosci* 2010, 5(4):424-431. PMID: 20150341.

6. Nopoulos P, **Boes AD**, Jabines A, Conrad AL, Canady J, Richman L, Dawson JD: Hyperactivity, impulsivity, and inattention in boys with cleft lip and palate: relationship to ventromedial prefrontal cortex morphology. *J Neurodev Disord* 2010, 2(4):235-242. PMID: 22127933.

7. **Boes AD**, Mehta S, Rudrauf D, Van Der Plas E, Grabowski T, Adolphs R, Nopoulos P: Changes in cortical morphology resulting from long-term amygdala damage. 2011, *Soc Cogn Affect Neurosci* 2012, 7(5):588-595. PMID: 21896493.

8. **Boes AD**, Grafft AH, Joshi C, Chuang NA, Nopoulos P, Anderson SW: Behavioral effects of congenital ventromedial prefrontal cortex malformation. *BMC Neurol,* 2011, 11:151. PMID: 22136635.

9. **Boes AD**, Grafft A, Espe-Pfeifer P, Rowe J, Stein MT: Manipulative and antisocial behavior in an 11-year-old boy with epilepsy. *J Dev Behav Pediatr* 2012, 33(4):365-368. PMID: 22566031

10. **Boes AD,** Duhaime AC, Caruso P, Fischl B: FreeSurfer is useful for the early detection of Rasmussen's encephalitis. *Dev Med Child Neurol.* 2015, PMID: 26174006

11. **Boes AD**, Prasad, S, Pascual-Leone, A, Liu H, Liu Q, Caviness, VS, Fox, MD: Network localization of neurological symptoms from focal brain lesions. *Brain,* 2015, Oct;138:3061-75, PMID: 26264514.

12. Stern AP, **Boes AD**, Haller CS, Bloomingdale K, Pascual-Leone A, Press D. Psychiatrists' attitudes toward transcranial magnetic stimulation. *Biological Psychiatry*, 2015 S0006-3223(15) 659-9, PMID: 26435222

13. Rubio B**, **Boes AD****°**, Laganiere S, Rotenberg A, Jeurissen D, Pascual-Leone, A: Noninvasive Brain Stimulation in Pediatric ADHD: A Review. *Journal of Child Neurology*, 2016, 31(6), p784-796

    ** Indicates authors contributed equally **°** Indicates corresponding author

14. Fischer DB, Perez DL, Prasad S, Rigolo L, O'Donnell L, Acar D, Meadows M, Baslet G, **Boes AD**, Golby AJ, Dworetzky, BA. Right inferior longitudinal fasciculus lesions disrupt visual-emotional integration. *Social Cognitive and Affective Neuroscience, 2016, 11(6): 945-951.*

15. Sutterer M, Bruss J, **Boes AD**, Voss MW, Bechara A, Tranel D. Canceled connections: Lesion-derived network mapping helps explain differences in performance on a complex decision-making task. *Cortex, 2016, 78: 31-43*

16. Laganiere S, **Boes AD**, Fox MD. Network localization of hemichorea-hemiballismus. *Neurology,* 2016. 86 (23): 2187-2195

17. Fischer DB,** **Boes AD**,** Demertzi A, Evrard HC, Laureys S, Edlow BL, Liu H, Saper CB, Pascual-Leone A, Fox MD, Geerling JC. A human brain network derived from coma-causing brainstem lesions. 2016. 687 (23) 2427 -2434

    *** Indicates authors contributed equally*

18. **Boes AD**, Stern AP, Bernstein M, et al. H-Coil Repetitive Transcranial Magnetic Stimulation Induced Seizure in an Adult with Major Depression: A Case Report. Brain Stimul. 2016 Apr 19.

19. Kelly MS, Oliveira-Maia AJ, Bernstein M, Stern AP, Press DZ, Pascual-Leone A, & **Boes, AD.** Initial response to transcranial magnetic stimulation treatment for depression predicts subsequent response. Journal of Clinical Neuropsychiatry. *Epub ahead of print.*

SELECTED CHAPTERS \ ABSTRACTS \ ADDITIONAL PUBLISHED WORKS

1. **Boes AD**, Crawford, J. Rady Children's Hospital Housestaff Manual, Neurology Section. 2010– 2011

2. **Boes AD**, Caviness, VS: Neuroanatomy and Lesion Localization. Book Chapter in Handbook of Pediatric Neurology, 1st edition. Ed. Kathy Sims, Lippincott. 2014

3. **Boes AD**. Contributing author and reviewer for McGraw-Hill Clinical Access \ AccessMedicine Online Edition, Neurology and Pediatric Neurology Content. 2013 - 2015.

4. **Boes AD,** SS Ayache, JP Lefaucheur, A Pascual-Leone, MD Fox. Predicting the network effects of central pain lesions using resting-state functional

connectivity MRI. Resting State MRI Conference, Massachusetts Institute Technology, Boston. *Article in prep*

5. **Boes AD,** Weigand A, Lan MJ, Liston C, Dubin MJ, Pascual-Leone A, Fox MD. Effective rTMS therapy for depression is associated with increased volume of the left subgenual cortex. Brain Stimulation, Vol 8 Issue 5, Page e1.

6. **Boes AD**, Noninvasive Brain Stimulation. Invited review for The Sage Encyclopedia of Intellectual and Developmental Disorders. Chapter submitted.

7. **Boes AD,** Fischer DB, Geerling JC, Saper CB, Fox MD. Hypothalamus-derived sleep- and wake-promoting networks in the human brain. Abstract accepted, 2016 American Academy of Neurology Conference, Vancouver Canada. Article in prep.

8. **Boes AD**, Greve D, Weigand A, Lan MJ, Liston C, Fischl B, Pascual-Leone A, Dubin MJ, Fox MD. Left Dorsolateral Prefrontal Cortex Thickness Increases With Effective rTMS Treatment of Depression. Abstract accepted, 2016 American Neuropsychiatry Association, San Diego, CA

9. Kuceyeski A, Labar DR, Nearing D, Tsagaris Z, Silverstein J, Pepper-Lane H, **Boes AD**, Fox MD, Thickbroom G, Edwards DJ. Predicting motor function after stroke using MRI-based lesion-overlap and transcranial magnetic stimulation metrics. 2016 Human Brain Mapping Conference.

SELECTED INVITED LECTURES AND PRESENTATIONS

1. **Boes AD** (2016) “Left Dorsolateral Prefrontal Cortex Thickness Increases With Effective rTMS Treatment of Depression.” American Neuropsychiatry Association Meeting, San Diego, CA.

2. **Boes AD** (2015) “Pediatric Neurology Emergencies” Child Neurology Course, Harvard Medical School Continuing Medical Education.

3. **Boes AD** (2015) “Network localization of neurological symptoms: from hallucinations to coma.” Neurology Grand Rounds, Massachusetts General Hospital, Boston, MA.

4. **Boes AD** (2015) “Network localization of neurological symptoms” Platform Presentation ‘Neural Circuits and Neuromodulation’ American Academy of Neurology, Washington DC.

5. **Boes AD** (2014 - 2015) “Clinical Applications of TMS in Pediatrics, Transcranial Magnetic Stimulation Course, Harvard Continuing Medical Education Series, Boston, MA.

6. **Boes AD** (2014) “Lesion-based network analysis.” Gabrieli Laboratory, Massachusetts Institute of Technology, Boston, MA.

7. **Boes AD** (2013) “Neural correlates of peduncular hallucinosis.” Mayo Clinic Pediatric Neurology Noon Conference Series.

8. **Boes AD** (2013) “Neural correlates of peduncular hallucinosis.” Neurology Grand Rounds, University of Wisconsin, Madison, WI.

9. **Boes AD** (2013) “Neuroanatomy and neural networks of peduncular hallucinosis.” Platform Presentation, ‘Disturbances of Linguistic, Social, and Other Processes’ American Academy of Neurology. San Diego, CA.

10. **Boes AD** (2010) “Structural neural correlates of depressed mood and fearfulness in children and adolescents.” Invited speaker for Biological Psychiatry Symposium, New Orleans, LA.

11. **Boes AD** (2010) “Antisocial behavior following early-onset ventromedial prefrontal cortex lesion.” American Society for Clinical Investigation / American Academy of Pediatrics Joint Meeting. Chicago, IL.

12. **Boes AD** (2008) “Impulse control and the ventromedial prefrontal cortex.” Graduate Student Award Presentation, Cognitive Neuroscience Society. San Francisco, CA.

TEACHING

2014, 2015	Instructor, Intensive Course in Transcranial Magnetic Stimulation, Harvard Continuing Medical Education Course. 5 day course offered three times per year.
2013 – 2015	Instructor, Laboratory for Nervous System Anatomy, Human Organ Systems, Harvard Medical School

THE UNIVERSITY OF IOWA, Iowa City, IA

2008 Spring	Instructor, Medical Neuroscience Small Group
2007 Spring	Teaching Assistant, Medical Neuroscience Laboratory
2007 Spring	Tutor, Medical Student Counseling Center
2000 - 2003	Tutor, New Dimensions in Learning, Provided tutoring services to underserved and underrepresented students
2000 Spring	Class Research Coordinator, I-Notes, Principles of Biology and Drugs: Their Action, Nature, and Use

PROFESSIONAL MEMBERSHIP & ACTIVITIES

2014, 2015	Co-Chair, TMS Society Pediatric Subcommittee
2008 - Current	Ad-hoc reviewer, including *Cerebral Cortex*, *Biological Psychiatry*, *Neuropsychologia, Annals of Neurology, Sleep*
2005 - Current	American Academy of Neurology Member
2008	American Medical Association Student Member
2007 - 2009	Organization of Human Brain Mapping

2007 - 2009	Cognitive Neuroscience Society
2002 - 2007	Society for Neuroscience

SERVICE AND ADMINISTRATIVE PARTICIPATION

2016	Physician Scientist Mentoring Program, Boston University
2015 - 2016	Course Director for Child Neurology Conference Series, Massachusetts General Hospital
2014-2015	Participated in Resident Selection Committee, Pediatric Neurology, Massachusetts General Hospital
2007-2008	Volunteer Medical Examiner, Free Medical Clinic
2007 Summer	Volunteer Medical Examiner, Free Mental Health Clinic
2006 - 2007	Executive Committee Member, Brain Awareness Week, UI Brain Discovery Fair Planning and Organization
2004 - 2005	President, Medical Student Interest Group in Neurology
2002 - 2003	Undergraduate Representative, UI Student Government Research Council
2002 - 2003	Patient Guide, Free Medical Clinic of Iowa City

GRANT SUPPORT

Completed

2003 – 2005	NIGMS T32GM007337, Medical Scientist Training Program, PI: Steven Lentz. Role: Trainee
2005 - 2008	NINDS/NIA T32NS007421. Neuroscience Training Program. PI: Daniel Tranel. Role: Trainee
2013 - 2015	R25 Grant. NIH/NINDS R25NS065743-05. Mentor: Alvaro Pascual-Leone, M.D., Ph.D.
2014 - 2016	Sidney R. Baer, Jr. Clinical & Research Fellowship, Neuropsychiatry & Noninvasive Brain Stimulation

Current

2016 - 2017	K12 Child Health Research Career Development Award 4K12HD027748-24

Pending

2017 - 2020	Child Neurology Career Development K12
2017	Aiming for a Cure Foundation Grant

THE UNIVERSITY OF IOWA

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March 10, 2017

American Brain Foundation
201 Chicago Ave
Minneapolis, MN 55415

RE: Proposal created by investigator Dr. Aaron Boes

This letter serves as Institutional Assurance that The University of Iowa fully supports the work of Dr. Aaron Boes, in particular this proposal for "Investigating the neural basis of Posterior Fossa Syndrome." The appropriate programmatic and administrative personnel at the University of Iowa approve this proposal submission and will support the administrative work necessary, should this proposal be funded.

Thank you for considering Dr. Boes for this award. We are very grateful for the opportunity to seek the important and generous support of the American Brain Foundation to further the research work of our faculty.

Sincerely,

Mary Blackwood
Acting for Daniel Reed

Daniel Reed
Vice President for Research & Economic Development

Boes - American Brain Foundation Grant

Grant Start Date 7/1/2017

Personnel	**Effort**	**Cal. Months**
Image Processing Analyst (Joel Bruss)	5%	0.6
Psychologist (Amanda Graft)	4%	0.4

MRI - 1 hour	3 Per Subject
Participant Compensation + Travel	$100 per visit

Base Salary		Requested Salary	Fringe	7/1/2017-06/30/2018 Year 1	7/1/2018-06/30/2019 Year 2	7/1/2019-06/30/2020 Year 3
$ 53,040		$ 2,652	$ 629	$ 3,281	$ 3,346	$ 3,413
$ 89,000		$ 3,212	$ 761	$ 3,973	$ 4,053	$ 4,134
				$ 7,254	**$ 7,399**	**$ 7,547**
Subject costs						
$ 615	Per hour			**$ 25,830**	**$ 23,985**	**$ 23,985**
$ 300	Per Subject			**$ 1,400**	**$ 1,300**	**$ 1,300**
			Total Costs	**$ 34,484**	**$ 32,684**	**$ 32,832**

Participant Breakout	**30 Total**	14	13	13

	Total
$	10,040
$	12,160
$	22,200
$	73,800
$	4,000
$	100,000

Title: **Posterior Fossa Syndrome in a Medulloblastoma population: analysis by functional MRI imaging**

Sponsor Name: **None**

PI Name: **Jones, Robin** Protocol #: **2014P001592** Type: **New Protocol**

Date Received: **August 13, 2014**

Study Staff

Name	Role	Degree	Organization	Citi Certified
Abrams, Annah	Co-Investigator	MD	MGH > Psychiatry	6/12/2013
Boes, Aaron	Co-Investigator	MD, Ph.D	MGH > Neurology > Neurology Chief Funds	10/9/2012
Gallotto, Sara	Research Coordinator/Manager		MGH > Radiation Oncology	5/1/2013
Jones, Robin	Principal Investigator	MD	MGH > Neurology	11/13/2013
Pulsifer, Margaret	Co-Investigator	Ph.D	MGH > Psychiatry	9/30/2012
Yock, Torunn	Co-Investigator	MD	MGH > Radiation Oncology	3/9/2012

Signatures

PI Name: Jones, Robin, M, MD
Authenticated: August 04, 2014

Sponsor Funding: None

Select the source of funding that will be used to support the proposed research:

- ○ Government / Foundation / Other Non-Profit
- ○ Corporate
- ○ Institutional Award
- ○ Department Funds
- ⊙ None

Is this the primary source of funding?

○ Yes ○ No ⊙ Not applicable

Health / Medical Records

1. Purpose

Briefly describe the purpose of the research:

Medulloblastoma represents the most common malignant cerebellar posterior fossa tumor in children.

Posterior fossa syndrome is seen postoperatively in approximately 25% of patients with medulloblastoma. To date, we have treated 180 medulloblastoma patients with proton beam radiotherapy at the Francis H. Burr Proton Therapy Center (FHBPTC). Data acquired as part of the clinical and research protocols related to the treatment at the FHBPTC has included standard brain MRI imaging pre- and post-operatively, as well as neuropsychological testing. MRI functional connectivity imaging is a tool that can map networks in the human brain. Anatomical predictors of posterior fossa syndrome are not well understood.

We propose to retrospectively investigate the patterns of cerebellar functional connectivity in pediatric medulloblastoma patients using data from MRI images collected as part of treatment protocols at the FHBPTC. We will look at functional connectivity patterns of the lesions using a normative database to determine what regions in the brain are normally connected to this lesion site in the normal population.

We will analyze the data in both patients affected with posterior fossa syndrome as well as age-matched controls from our sample population. In addition, we will incorporate results of neuropsychological analysis to identify variables that may contribute to outcome.

Data resulting from this research will be used for the following. Check all that apply.

- ☑ Publication
- ☑ Oral Presentation
- ☐ Other

Will data resulting from this research ever be submitted to the FDA?

○ Yes ⊙ No

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2. Study Population

Describe the study population, e.g., age, gender, diagnosis. Note: Healthcare providers may be considered subjects if you are studying provider behavior or performance, or analyzing patient outcomes based on provider. In such cases, you must consider the privacy risks and privacy rights of providers.

We will include pediatric patients treated at MGH for medulloblastoma age 0-21 years, inclusive of males and females, from 1/2002 to 12/2014. The age-matched controls are patients from the IRB-approved data repository called "MGH Pediatric Radiation Oncology Database".

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3. Source of Health / Medical Information

Indicate:

☑ Partners Sites

Partners Sites - Check all that apply:

☐ BWH
☐ Faulkner
☑ MGH
☐ NWH
☐ NSMC
☐ PCHI
☐ SRH
☐ McLean
☑ Other

Enter the other sources of health / medical information and move to the box on the right.

IRB #2005P000087 MGH Pediatric Radiation Oncology Database

☐ Non-Partners Sites

---

4. Data To Be Collected / Obtained

Check all that apply.

Administrative:

☐ Billing data
☐ Coded encounter data (diagnoses, procedures, dates)
☑ Demographic data (age, gender, vital status)
☑ Personal data (name, address, PCP)

Health / Medical:

☑ Allergies
☑ Discharge Summary
☐ Doctors Orders
☑ History / Physical
☐ Immunizations

☑ Medication List

☑ Office / Clinic Notes

☑ Operative / Procedure Notes (e.g. endoscopy)

☐ Pharmacy

☑ Problem List

Health/Medical Reports/Results:

☐ Blood Bank

☑ Laboratory

☑ Pathology reports (reports only). Complete the Excess Human Material form for use of tissue/slides instead of this form.

☑ Radiology

Sensitive/Personal Information:

☐ HIV Status

☑ Mental Health

☐ Reproductive History (e.g., abortions)

☐ Sexual Behavior/Sexually Transmitted Diseases

☐ Substance Abuse (e.g., drug or alcohol abuse)

☐ Other potentially stigmatizing behaviors

Will any Sensitive/Personal Information listed above be collected?

◉ Yes ○ No

Explain why the sensitive/personal data checked above is needed to achieve the goals of the study:

Posterior fossa syndrome is a common problem defined by mutism, ataxia and emotional lability. We will need to review their mental health information to better define the emotional symptoms that present in patients with posterior fossa syndrome in order to correlate the anatomic location of the injury in the cerebellum and brainstem with the symptomology.

Other Health/Medical Information:

☑ Other

Specify:

Neuropsychological measures which are a part of the standard medical records and assessments in children with brain tumors.

Have you created a data collection form or other tool for data collection?

○ Yes ◉ No

Enter specific data variables needed to achieve the goals of your study. Enter one variable and move to the box on the right. Repeat for all variables.

gender

age at treatment
name
medical record number
tumor size
M stage
ataxia grade
mutism grade
CN abnormalities
dysarthria
other neurologic findings
MRI preop date
MRI post op Date
operation date
VP shunt/EVD status
hydrocephalus
handedness
other surgical complications
Neuropsychological measures
emotional lability grade

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5. Data To Be Requested From The Following Time Period (Encounter Dates)

Indicate the time period over which the health / medical information was / will be created as part of clinical care.

From (mm/yyyy):

01/2002

To (mm/yyyy):
For future data, use anticipated project end date.

12/2014

NOTE: This information is needed for the IRB to determine whether the research use of the health/medical information meets the criteria for an exemption from the requirement for IRB review. For more information about HUMAN SUBJECTS RESEARCH or EXEMPT RESEARCH, see the policy 'Exempt Human-Subjects Research.'

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6. Protected (Identifiable) Health Information

PHI refers to health/medical information that is accompanied by any of the listed 18 HIPAA identifiers or by a code where the key to the code that links to the identifiers is accessible to investigators. DE-IDENTIFIED

DATA (without any identifiers or codes that link back to individuals) are not considered PHI, and are not subject to HIPAA regulations.

Will you be recording any of the identifiers listed above with the data or using a code to link the data to any of the identifiers? If yes, than under the HIPAA Privacy Rule provisons the data cannot be considered de-identified and authorization from the subject or a waiver of authorization must be granted by the IRB. When answering this question, consider the need for recording dates or retaining direct identifiers, such as name and/or medical record number, to link data from multiple sources, to avoid duplicating records, or for QA purposes. NOTE: If you are recording medical record number or other identifiers, even if temporarily for QA purposes or to avoid duplicating records, then answer "Yes".

◉ Yes ○ No

Check the identifiers that will be recorded with or linked by code to the data.

☑ Name

☐ Social Security Number

☑ Medical record number

☐ Address by street location

☐ Address by town / city / zipcode

☑ Dates (except year), e.g., date of birth; admission / discharge date; date of procedure; date of death

☐ Telephone number

☐ Fax number

☐ Electronic email address

☐ Web URLs

☐ Internet protocol (IP) address

☐ Health plan beneficiary number

☐ Account number

☐ Certificate / license number

☐ Vehicle identification number and serial number, including license plate number

☐ Medical device identifiers and serial numbers

☐ Biometric identifiers (finger and voice prints)

☐ Full face photographic image

☐ Any other identifier; or combination of identifiers likely to identify the subject (e.g., Pathology Accession #)

Explain why it would be impossible to conduct the research without access to and use of identifiable health / medical information. For example, the data cannot be obtained from electronic health / medical records or databases without access to identifiers or identifiers are needed for prospective data collection.

This in formation is required to initially identify patients with posterior fossa syndrome for this retrospective review. Then we will use the demographics to

match medulloblastoma patients who have not been affected by posterior fossa syndrome for the control group. We also need dates to calculate exact age at the time of treatment.

Will identifiers be removed from the data and destroyed after all of the data has been collected, the study has been completed, or all regulatory and sponsor obligations have been met, consistent with regulatory and institutional research record keeping requirements? For guidance, see the PHRC Recordkeeping and Record Retention Requirements document.

⊙ Yes ○ No

NOTE: Federal regulations mandate that, under a Waiver of Consent / Authorization, identifiers be destroyed as early as possible. De-identified datasets may be retained indefinitely.

6A. Waiver of Informed Consent / Authorization

Explain why the risk to subjects, specifically the risk to privacy, is no more than minimal risk. When addressing this question, describe the measures you have put in place to protect the privacy of subjects and confidentiality of the data; for example: (1) identifiable health information will be stored on a computer on the Partners network with password protections enabled and anti-virus software or an encrypted laptop, with access to data limited to study staff; (2) name and/or medical record number will be replaced with a study ID or code and the key to the code stored in a password protected file; (3) direct identifiers, such as name and medical record number, will be removed once all of the data is collected and analysis performed on de-identified data.

We request a waiver of consent for those patients entered into the database retrospectively, as the use of the requested protected health information (PHI) involves no more than a minimal risk to the privacy of the individual patients based on the following:
(1) we will protect the identifiers from improper use and disclosure by storing the information on a password-protected database which can be accessed only by study personnel, all of whom have completed training in HIPAA guidelines and requirements;
(2) we will destroy the identifiers at the earliest opportunity consistent with the conduct of the proposed clinical research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law; and
(3) the requested PHI will not be reused nor disclosed to any other person or entity, except as required by law or for authorized oversight of the research study.

Explain why the research could not practicably be carried out without the waiver of consent / authorization. When addressing this question, consider the difficulty in locating individuals who may

have moved, the number of subjects and cost and use of limited resources of locating individuals and sending letters and consent forms, and the impact on the scientific validity of the study if you could use only data of individuals from whom you were able to obtain informed consent.

The research cannot practicably be carried out without the waiver of consent given that many of the patients to be included in the study cannot be contacted, either because they have expired or changed address. In addition, informed consent for this research project would compromise the integrity and completeness of the data because many busy patients simply don't have time for a process (read the
consent form, understand and acquiesce and send it back) which doesn't have a direct beneficial or adverse effect on them. The likelihood that we would lose valuable information in this setting is quite high.

NOTE: "Only in a few research studies would it be impossible to obtain informed consent; however in many studies the financial cost would be prohibitive and a potentially poor use of limited research resources." Ensuring Voluntary Informed Consent and Protecting Privacy and Confidentiality, National Bioethics Advisory Commission.

Explain why the rights and welfare of the subjects will not be adversely affected by the waiver of consent / authorization. When addressing this question, consider the individual's right to privacy and the measures you have put in place to protect the privacy of subjects and confidentiality of any data and any health/medical implications for subjects; for example: (1) identifiable data will be stored securely with access limited to study staff; (2) information resulting from this study will not have any important health/medical implications for subjects.

The rights and welfare of the subjects in this study will not be adversely affected by the waiver of consent, as the data will be maintained in a password-protected database which can be accessed only by study personnel. All study personnel have completed training in HIPAA guidelines and requirements; accordingly, they will strictly maintain the confidentiality of the data and will protect the privacy of all patients entered into the database. Moreover, in any reports or presentation of data, there will be no disclosure of any possible patient identifiers.

NOTE: If the research uncovers information about the subjects that has important health / medical implications for them, contact the PHRC to discuss the appropriate process for providing subjects with additional pertinent information.

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7. Research Data

How will research data be recorded and stored?

☑ Electronically

Electronic Research Data

What type of device will the research data be accessed and stored on? Check all that apply.

☑ Desktop computer

☐ Portable device i.e., Laptop, Netbook, Tablet, iPod computer, Cell/Smart phone

☐ USB Flash/Thumb, External Hard Drive

☐ Other device

Portable devices can include cell phone/smart phones, laptops, iPad/tablet computers, iPods or any other electronic device that can communicate wirelessly. For information on portable device security, refer to the Partners Portable Device Security Handbook (PHS Internal only link)

Where is the primary storage location of the device(s)? For example, the laptop is stored in office 123 on White 1 and is secured to a desk with a laptop lock or the hard drive is stored in a locked cabinet in office 123 on White 1 and access is limited to study staff only.

All electronic data contianing patient identifiers will be stored on a Partner's password-protected Desktop computer.

Who will have access to the electronic research data?

The PI and study staff.

NOTE: All computers and portable devices must have password protections enabled; All computers must have active anti-virus software; Laptops, tablet, netbook computers, and USB Flash/Thumb drives must be full disk encrypted; If data will be transmitted outside the Partners firewall, data must be encrypted during transit with the use of SSL/https.

Will data be uploaded to a website/server?

○ Yes ⊙ No

☐ Paper

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8. Sending Health / Medical Information to Collaborators Outside Partners

Will any health / medical information be sent to collaborators outside Partners?

○ Yes ⊙ No

HIPAA And Tracking Disclosures Of Identifiable Health Information (PHI)

1. Disclosures of PHI to persons or entities outside Partners without the written authorization of the subject must be tracked in accordance with Partners policy "Accounting of Disclosures" (PHS Intranet link). NOTE: A code derived from the subject's name is considered identifiable, for example, a code that contains subject initials.

2. Tracking is NOT required for disclosure of LIMITED DATA SETS under a DATA USE AGREEMENT. For more information about LIMITED DATA SETS and DATA USE AGREEMENTS, refer to Partners policy "Limited Data Sets Policy/Data Use Agreements" (PHS Intranet link).

NOTE: Partners (PHS) is the HIPAA covered entity. PHS includes BWH, Faulkner, MGH, McLean, PCHI, SRH, NSMC, and NWH, among others. PHS does not include other Harvard affiliated hospitals, such as BIDMC, DFCI, HSPH, CHB, or MEEI.

Review - (85) Full Application Review	
Review	
Acceptance Due Date	3/13/2017
Due Date	3/13/2017
Status	Submitted
Status Date	3/13/2017
Sent Date	3/13/2017
Received Date	3/13/2017
Visible From	3/13/2017
Visible To	12/31/2017
Request	
Name (Full)	Dr. Aaron Boes
Organization Name	University of Iowa
Type	Other Research Projects
Project Budget	$221,627.00
Exisiting Funding / In-Kind Support	$121,627.00
Requested Amount	$100,000.00
Project Title	Investigating the neural basis of posterior fossa syndrome
General focus	Brain & Nerve Tumors Autism & Neurodevelopment
Specific Disease Focus	Posterior fossa syndrome
Project Description	Project Description The goal of treating a child with a brain tumor is not simply to prolong life, but rather to maximize the child's quality of life and help them realize their long-term potential. Here we propose to study cognitive problems that commonly occur as a surgical complication in children with brain tumors of the cerebellum. By understanding the anatomy of this problem using an innovative neuroimaging approach this study could have an immediate clinical impact by improving the surgical approach to childhood cerebellum tumors. One of the most common sites for brain tumors in children is the cerebellum, a structure in the back of the brain that is essential for coordination of movements and cognition. 1 in every 4 children having a tumor removed from the cerebellum experiences an often-dramatic onset of major cognitive difficulties after the surgery. These post-surgical difficulties may include an inability to speak (mutism), emotional lability, and a host of other problems in behavior and cognition. The duration of symptoms is highly variable, ranging from days to several months or even lifelong disability. This constellation of symptoms following cerebellum surgery is known as posterior fossa syndrome; it has been known and written about in the medical literature for over 60 years but there have not been any strategies that have proven effective in preventing it or treating it. Given the limitations in our knowledge the onset of posterior fossa syndrome is a legitimate cause of major anxiety at a vulnerable time in the child's treatment course, not only for the child experiencing symptoms, but also the family and the care team. Here, we propose to investigate the anatomy of posterior fossa syndrome using a neuroimaging approach called voxel-based lesion symptom mapping. The clinical course of 115

	children with cerebellum tumors will be reviewed, including detailed neuropsychological test results performed before and after the surgery. The anatomical site of the surgical resection will be mapped onto a reference brain and statistically compared between children who had posterior fossa syndrome versus those that did not. This will provide the first large-scale map of the regions of the cerebellum that are critical for developing posterior fossa syndrome. This large dataset is made possible through a unique collaboration between pediatric neuro-oncology teams at the University of Iowa Hospitals and Clinics and Harvard's Massachusetts General Hospital.
Specific Aims	Aim 1. Perform lesion-symptom mapping of posterior fossa syndrome (PFS). We will use a large existing database of structural MRI (clinical scans) and neuropsychological test results from pediatric patients before and after cerebellum tumor resection to localize posterior fossa symptoms. In addition, the cerebro-cerebellar networks disrupted by the lesion will be inferred using resting-state functional connectivity MRI from a publically available pediatric connectome dataset. Hypothesis: The profile of post-surgical neuropsychiatric deficits in PFS can be predicted based on lesion location and the associated cerebro-cerebellar network(s). Aim 2. Perform longitudinal imaging of posterior fossa syndrome recovery We will use pre- and post-surgical multimodal high-resolution MRI along with detailed neuropsychological testing to longitudinally assess the neural substrates of cognitive impairment in posterior fossa syndrome and the network modifications associated with functional recovery. Hypothesis: Disruption of specific inter-hemispheric cerebro-cerebellar networks will correlate with domain-specific cognitive symptoms (e.g. connectivity between right postero-lateral cerebellum hemisphere and left-sided cortical language areas will be disrupted in the presence of language deficits) and these networks will regain a modified functional connectivity pattern in association with functional improvements.
Milestones	- Trace lesion location of over 100 pediatric patients with cerebellar tumor resections and analyze lesion location relative to neuropsychological outcomes. - Collect data from the initial 5 patients with cerebellar tumor resection to longitudinally monitor recovery and imaging correlates of recovery.
Feedback	
Yes/No	Yes
Review Long Notes	No comments.

UNIVERSITY of IOWA
CARVER COLLEGE
OF MEDICINE

University of Iowa Health Care

Aaron Boes, MD, PhD

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March 7, 2017

I have no conflicts of interest for financial disclosures to report.

Sincerely,

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Director, Noninvasive Brain Stimulation Clinical Program
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Aaron D. Boes

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CURRENT POSITION

7/2016 - Current	Assistant Professor Departments of Pediatrics, Neurology & Psychiatry University of Iowa Hospitals and Clinics Iowa City, IA

ADDITIONAL AFFILIATIONS

7/2016 - Current	Non-Clinical Staff \ Courtesy Staff (Research Collaborator) Massachusetts General Hospital Harvard University, Boston, MA

EDUCATION & WORK EXPERIENCE

7/2014 – 6/2016	Attending, Pediatric Neurologist Massachusetts General Hospital Harvard University, Boston, MA
7/2014 – 6/2016	Clinical Neuroscience Fellow & Staff Physician Neuropsychiatry & Noninvasive Brain Stimulation Berenson Allen Center for Noninvasive Brain Stimulation Beth Israel Deaconess Medical Center Harvard University, Boston, MA
7/2013 - 6/2014	Chief Pediatric Neurology Resident Massachusetts General Hospital Harvard University, Boston, MA
7/2011 - 6/2013	Pediatric Neurology Resident Massachusetts General Hospital \ Brigham and Women's Harvard University, Boston, MA
6/2009 - 6/2011	Pediatric Resident Rady Children's Hospital University of California San Diego, San Diego, CA
8/2003 - 5/2009	Scholar, Medical Scientist Training Program M.D. Carver College of Medicine; Ph.D. Neuroscience University of Iowa, Iowa City, IA
8/1999 - 5/2003	Bachelors of Science with Honors and High Distinction Integrative Physiology \ Exercise Science University of Iowa, Iowa City, IA
2001 Spring	Traveling Scholar The University of Wales, Swansea, Wales, UK

HONORS, AWARDS, & OUTSTANDING ACHIEVEMENTS

2016	Biological Psychiatry Travel Fellowship Award
2016	S. Weir Mitchell Award for outstanding achievement in neurology research + $1000 cash prize, American Academy of Neurology & American Brain Foundation
2015	Primary mentor for manuscript awarded Saul R. Korey Award for American Academy of Neurology Best Medical Student Essay, awarded to mentee David Fischer
2013 - 2015	Received highest teaching rating, 'Excellent' by Harvard Medical School students, Neuroanatomy Laboratory
2014	First author on manuscript awarded the prestigious S. Weir Mitchell Award by the American Academy of Neurology
2014, 2015	American Academy of Neurology Scholarship recipient, nominated by Partners Neurology, BIDMC Neurology
2013	Cobb Award & Cash Prize for Best Poster Presentation, Boston Society of Neurology and Psychiatry Cobb Assembly
2011	Named "Highly Cited Author" in 2011 by Social Cognitive and Affective Neuroscience
2008	American Academy of Neurology Saul R. Korey Award, Best medical student essay in experimental neurology
2008	Cognitive Neuroscience Society, Graduate Students Present Award (9 of 300 applicants awarded)
2007, 2008	Wisconsin Symposium on Emotion Scholar Travel Award (15 awarded per year)
2007	Human Brain Mapping Conference, Highest Ranking Abstract (top 65 of 1566) & Travel Fellow Award
2007	NINDS Neuroscience Career Symposium Travel Award
2005	Medical Student Representative, American Academy of Neurology Conference, Miami, FL
2003	University of Iowa Dean's List
2002	Honors Thesis Travel Award
2002	Golden Key National Honor Society Inductee
2002	Czech Heritage Scholarship Award

2002 Phi Beta Kappa Honor Society Inductee

2000 Nile Kinnick Leadership Award

PUBLICATIONS

1. **Boes AD**, Murko V, Wood JL, Langbehn DR, Canady J, Richman L, Nopoulos P: Social function in boys with cleft lip and palate: relationship to ventral frontal cortex morphology. *Behav Brain Res* 2007, 181(2):224-231. PMID: 17537526.

2. **Boes AD**, McCormick LM, Coryell WH, Nopoulos P: Rostral anterior cingulate cortex volume correlates with depressed mood in normal healthy children. *Biol Psychiatry* 2008, 63(4):391-397. PMID: 17916329.

3. **Boes AD**, Tranel D, Anderson SW, Nopoulos P: Right anterior cingulate: a neuroanatomical correlate of aggression and defiance in boys. *Behav Neurosci* 2008, 122(3):677-684. PMID: 18513137.

4. **Boes AD**, Bechara A, Tranel D, Anderson SW, Richman L, Nopoulos P: Right ventromedial prefrontal cortex: a neuroanatomical correlate of impulse control in boys. *Soc Cogn Affect Neurosci* 2009, 4(1):1-9. PMID: 19015086.

5. Van Der Plas EA, **Boes AD**, Wemmie JA, Tranel D, Nopoulos P: Amygdala volume correlates positively with fearfulness in normal healthy girls. *Soc Cogn Affect Neurosci* 2010, 5(4):424-431. PMID: 20150341.

6. Nopoulos P, **Boes AD**, Jabines A, Conrad AL, Canady J, Richman L, Dawson JD: Hyperactivity, impulsivity, and inattention in boys with cleft lip and palate: relationship to ventromedial prefrontal cortex morphology. *J Neurodev Disord* 2010, 2(4):235-242. PMID: 22127933.

7. **Boes AD**, Mehta S, Rudrauf D, Van Der Plas E, Grabowski T, Adolphs R, Nopoulos P: Changes in cortical morphology resulting from long-term amygdala damage. 2011, *Soc Cogn Affect Neurosci* 2012, 7(5):588-595. PMID: 21896493.

8. **Boes AD**, Grafft AH, Joshi C, Chuang NA, Nopoulos P, Anderson SW: Behavioral effects of congenital ventromedial prefrontal cortex malformation. *BMC Neurol,* 2011, 11:151. PMID: 22136635.

9. **Boes AD**, Grafft A, Espe-Pfeifer P, Rowe J, Stein MT: Manipulative and antisocial behavior in an 11-year-old boy with epilepsy. *J Dev Behav Pediatr* 2012, 33(4):365-368. PMID: 22566031

10. **Boes AD,** Duhaime AC, Caruso P, Fischl B: FreeSurfer is useful for the early detection of Rasmussen's encephalitis. *Dev Med Child Neurol.* 2015, PMID: 26174006

11. **Boes AD**, Prasad, S, Pascual-Leone, A, Liu H, Liu Q, Caviness, VS, Fox, MD: Network localization of neurological symptoms from focal brain lesions. *Brain,* 2015, Oct;138:3061-75, PMID: 26264514.

12. Stern AP, **Boes AD**, Haller CS, Bloomingdale K, Pascual-Leone A, Press D. Psychiatrists' attitudes toward transcranial magnetic stimulation. *Biological Psychiatry*, 2015 S0006-3223(15) 659-9, PMID: 26435222

13. Rubio B**, **Boes AD****°**, Laganiere S, Rotenberg A, Jeurissen D, Pascual-Leone, A: Noninvasive Brain Stimulation in Pediatric ADHD: A Review. *Journal of Child Neurology*, 2016, 31(6), p784-796

    ** Indicates authors contributed equally **°** Indicates corresponding author

14. Fischer DB, Perez DL, Prasad S, Rigolo L, O'Donnell L, Acar D, Meadows M, Baslet G, **Boes AD**, Golby AJ, Dworetzky, BA. Right inferior longitudinal fasciculus lesions disrupt visual-emotional integration. *Social Cognitive and Affective Neuroscience, 2016, 11(6): 945-951.*

15. Sutterer M, Bruss J, **Boes AD**, Voss MW, Bechara A, Tranel D. Canceled connections: Lesion-derived network mapping helps explain differences in performance on a complex decision-making task. *Cortex, 2016, 78: 31-43*

16. Laganiere S, **Boes AD**, Fox MD. Network localization of hemichorea-hemiballismus. *Neurology,* 2016. 86 (23): 2187-2195

17. Fischer DB,** **Boes AD**,** Demertzi A, Evrard HC, Laureys S, Edlow BL, Liu H, Saper CB, Pascual-Leone A, Fox MD, Geerling JC. A human brain network derived from coma-causing brainstem lesions. 2016. 687 (23) 2427 -2434

    *** Indicates authors contributed equally*

18. **Boes AD**, Stern AP, Bernstein M, et al. H-Coil Repetitive Transcranial Magnetic Stimulation Induced Seizure in an Adult with Major Depression: A Case Report. Brain Stimul. 2016 Apr 19.

19. Kelly MS, Oliveira-Maia AJ, Bernstein M, Stern AP, Press DZ, Pascual-Leone A, & **Boes, AD.** Initial response to transcranial magnetic stimulation treatment for depression predicts subsequent response. Journal of Clinical Neuropsychiatry. *Epub ahead of print.*

SELECTED CHAPTERS \ ABSTRACTS \ ADDITIONAL PUBLISHED WORKS

1. **Boes AD**, Crawford, J. Rady Children's Hospital Housestaff Manual, Neurology Section. 2010– 2011

2. **Boes AD**, Caviness, VS: Neuroanatomy and Lesion Localization. Book Chapter in Handbook of Pediatric Neurology, 1st edition. Ed. Kathy Sims, Lippincott. 2014

3. **Boes AD**. Contributing author and reviewer for McGraw-Hill Clinical Access \ AccessMedicine Online Edition, Neurology and Pediatric Neurology Content. 2013 - 2015.

4. **Boes AD,** SS Ayache, JP Lefaucheur, A Pascual-Leone, MD Fox. Predicting the network effects of central pain lesions using resting-state functional

connectivity MRI. Resting State MRI Conference, Massachusetts Institute Technology, Boston. *Article in prep*

5. **Boes AD,** Weigand A, Lan MJ, Liston C, Dubin MJ, Pascual-Leone A, Fox MD. Effective rTMS therapy for depression is associated with increased volume of the left subgenual cortex. Brain Stimulation, Vol 8 Issue 5, Page e1.

6. **Boes AD**, Noninvasive Brain Stimulation. Invited review for The Sage Encyclopedia of Intellectual and Developmental Disorders. Chapter submitted.

7. **Boes AD,** Fischer DB, Geerling JC, Saper CB, Fox MD. Hypothalamus-derived sleep- and wake-promoting networks in the human brain. Abstract accepted, 2016 American Academy of Neurology Conference, Vancouver Canada. Article in prep.

8. **Boes AD**, Greve D, Weigand A, Lan MJ, Liston C, Fischl B, Pascual-Leone A, Dubin MJ, Fox MD. Left Dorsolateral Prefrontal Cortex Thickness Increases With Effective rTMS Treatment of Depression. Abstract accepted, 2016 American Neuropsychiatry Association, San Diego, CA

9. Kuceyeski A, Labar DR, Nearing D, Tsagaris Z, Silverstein J, Pepper-Lane H, **Boes AD**, Fox MD, Thickbroom G, Edwards DJ. Predicting motor function after stroke using MRI-based lesion-overlap and transcranial magnetic stimulation metrics. 2016 Human Brain Mapping Conference.

SELECTED INVITED LECTURES AND PRESENTATIONS

1. **Boes AD** (2016) "Left Dorsolateral Prefrontal Cortex Thickness Increases With Effective rTMS Treatment of Depression." American Neuropsychiatry Association Meeting, San Diego, CA.

2. **Boes AD** (2015) "Pediatric Neurology Emergencies" Child Neurology Course, Harvard Medical School Continuing Medical Education.

3. **Boes AD** (2015) "Network localization of neurological symptoms: from hallucinations to coma." Neurology Grand Rounds, Massachusetts General Hospital, Boston, MA.

4. **Boes AD** (2015) "Network localization of neurological symptoms" Platform Presentation 'Neural Circuits and Neuromodulation' American Academy of Neurology, Washington DC.

5. **Boes AD** (2014 - 2015) "Clinical Applications of TMS in Pediatrics, Transcranial Magnetic Stimulation Course, Harvard Continuing Medical Education Series, Boston, MA.

6. **Boes AD** (2014) "Lesion-based network analysis." Gabrieli Laboratory, Massachusetts Institute of Technology, Boston, MA.

7. **Boes AD** (2013) "Neural correlates of peduncular hallucinosis." Mayo Clinic Pediatric Neurology Noon Conference Series.

8. **Boes AD** (2013) “Neural correlates of peduncular hallucinosis.” Neurology Grand Rounds, University of Wisconsin, Madison, WI.

9. **Boes AD** (2013) “Neuroanatomy and neural networks of peduncular hallucinosis.” Platform Presentation, ‘Disturbances of Linguistic, Social, and Other Processes’ American Academy of Neurology. San Diego, CA.

10. **Boes AD** (2010) “Structural neural correlates of depressed mood and fearfulness in children and adolescents.” Invited speaker for Biological Psychiatry Symposium, New Orleans, LA.

11. **Boes AD** (2010) “Antisocial behavior following early-onset ventromedial prefrontal cortex lesion.” American Society for Clinical Investigation / American Academy of Pediatrics Joint Meeting. Chicago, IL.

12. **Boes AD** (2008) “Impulse control and the ventromedial prefrontal cortex.” Graduate Student Award Presentation, Cognitive Neuroscience Society. San Francisco, CA.

TEACHING

2014, 2015	Instructor, Intensive Course in Transcranial Magnetic Stimulation, Harvard Continuing Medical Education Course. 5 day course offered three times per year.
2013 – 2015	Instructor, Laboratory for Nervous System Anatomy, Human Organ Systems, Harvard Medical School

THE UNIVERSITY OF IOWA, Iowa City, IA

2008 Spring	Instructor, Medical Neuroscience Small Group
2007 Spring	Teaching Assistant, Medical Neuroscience Laboratory
2007 Spring	Tutor, Medical Student Counseling Center
2000 - 2003	Tutor, New Dimensions in Learning, Provided tutoring services to underserved and underrepresented students
2000 Spring	Class Research Coordinator, I-Notes, Principles of Biology and Drugs: Their Action, Nature, and Use

PROFESSIONAL MEMBERSHIP & ACTIVITIES

2014, 2015	Co-Chair, TMS Society Pediatric Subcommittee
2008 - Current	Ad-hoc reviewer, including *Cerebral Cortex*, *Biological Psychiatry*, *Neuropsychologia, Annals of Neurology, Sleep*
2005 - Current	American Academy of Neurology Member
2008	American Medical Association Student Member
2007 - 2009	Organization of Human Brain Mapping

2007 - 2009	Cognitive Neuroscience Society
2002 - 2007	Society for Neuroscience

SERVICE AND ADMINISTRATIVE PARTICIPATION

2016	Physician Scientist Mentoring Program, Boston University
2015 - 2016	Course Director for Child Neurology Conference Series, Massachusetts General Hospital
2014-2015	Participated in Resident Selection Committee, Pediatric Neurology, Massachusetts General Hospital
2007-2008	Volunteer Medical Examiner, Free Medical Clinic
2007 Summer	Volunteer Medical Examiner, Free Mental Health Clinic
2006 - 2007	Executive Committee Member, Brain Awareness Week, UI Brain Discovery Fair Planning and Organization
2004 - 2005	President, Medical Student Interest Group in Neurology
2002 - 2003	Undergraduate Representative, UI Student Government Research Council
2002 - 2003	Patient Guide, Free Medical Clinic of Iowa City

GRANT SUPPORT

Completed

2003 – 2005	NIGMS T32GM007337, Medical Scientist Training Program, PI: Steven Lentz. Role: Trainee
2005 - 2008	NINDS/NIA T32NS007421. Neuroscience Training Program. PI: Daniel Tranel. Role: Trainee
2013 - 2015	R25 Grant. NIH/NINDS R25NS065743-05. Mentor: Alvaro Pascual-Leone, M.D., Ph.D.
2014 - 2016	Sidney R. Baer, Jr. Clinical & Research Fellowship, Neuropsychiatry & Noninvasive Brain Stimulation

Current

2016 - 2017	K12 Child Health Research Career Development Award 4K12HD027748-24

Pending

2017 - 2020	Child Neurology Career Development K12
2017	Aiming for a Cure Foundation Grant

Letter of Intent Form

Prefix

First Name

Aaron

Last Name

Boes

Suffix

Title

Assistant Professor

Institution

University of Iowa

Office Address

University of Iowa Hospitals and Clinics
W278 General Hospital
200 Hawkins Drive

City

Iowa City

State

Iowa

Postal Code

52246

E-mail

aaron-boes@uiowa.edu

Office Phone

3193538587

Office Fax

Project Details

Project Title

Investigating the neural basis of posterior fossa syndrome

General focus

Brain & Spinal Cord Tumors
Autism & Neurodevelopment

Specific Disease Focus

Posterior fossa syndrome

Project Description

The goal of treating a child with a brain tumor is not simply to prolong life, but rather to maximize the child's quality of life and help them realize their long-term potential. Here we propose to study cognitive problems

that commonly occur as a surgical complication in children with brain tumors of the cerebellum. By understanding the anatomy of this problem using an innovative neuroimaging approach this study could have an immediate clinical impact by improving the surgical approach to childhood cerebellum tumors.

One of the most common sites for brain tumors in children is the cerebellum, a structure in the back of the brain that is essential for coordination of movements and cognition. 1 in every 4 children having a tumor removed from the cerebellum experiences an often-dramatic onset of major cognitive difficulties after the surgery. These post-surgical difficulties may include an inability to speak (mutism), emotional lability, and a host of other problems in behavior and cognition. The duration of symptoms is highly variable, ranging from days to several months or even lifelong disability. This constellation of symptoms following cerebellum surgery is known as posterior fossa syndrome; it has been known and written about in the medical literature for over 60 years but there have not been any strategies that have proven effective in preventing it or treating it. Given the limitations in our knowledge the onset of posterior fossa syndrome is a legitimate cause of major anxiety at a vulnerable time in the child's treatment course, not only for the child experiencing symptoms, but also the family and the care team.

Here, we propose to investigate the anatomy of posterior fossa syndrome using a neuroimaging approach called voxel-based lesion symptom mapping. The clinical course of 115 children with cerebellum tumors will be reviewed, including detailed neuropsychological test results performed before and after the surgery. The anatomical site of the surgical resection will be mapped onto a reference brain and statistically compared between children who had posterior fossa syndrome versus those that did not. This will provide the first large-scale map of the regions of the cerebellum that are critical for developing posterior fossa syndrome. This large dataset is made possible through a unique collaboration between pediatric neuro-oncology teams at the University of Iowa Hospitals and Clinics and Harvard's Massachusetts General Hospital.

How will your project contribute to the treatment, prevention or cure of a neurological disease(s)?

This study will provide unprecedented information about which region or regions of the cerebellum are most critical to the development of posterior fossa syndrome. This anatomical knowledge will be paramount for optimizing the surgical approach to pediatric brain tumors of the cerebellum, such that this region may be avoided whenever possible within the constraints of the primary goal of tumor removal. Moreover, our novel approach for studying brain lesions that takes into account the network connectivity of the lesion site may provide insight regarding novel rehabilitation strategies such as using noninvasive neuromodulation applied to regions of the cerebral cortex that normally interact with the site of the lesion.

Project Budget

Total expense budget

An estimated total is acceptable.

450,000

Value of existing funding or in-kind support

What portion of the above total expense has funding already received or promised?

16,627

Portion to be raised through crowdfunding

How much are you seeking from the crowdfunding platform?

433,373

Attachments and Verifications

Financial Disclosures & Conflicts of Interest Form

Boes disclosure statement.pdf

CV of Principal Investigator

Boes CV 2017.pdf

I understand that the American Brain Foundation will not post approved projects for crowdfunding until documentation of IRB approval or exemption is provided.

Yes

THE UNIVERSITY OF IOWA

Division of Sponsored Programs
2 Gilmore Hall
Iowa City, Iowa 52242-1320
319-335-2123 *Fax* 319-335-2130
dsp@uiowa.edu
http://research.uiowa.edu/dsp

March 10, 2017

American Brain Foundation
201 Chicago Ave
Minneapolis, MN 55415

RE: Proposal created by investigator Dr. Aaron Boes

This letter serves as Institutional Assurance that The University of Iowa fully supports the work of Dr. Aaron Boes, in particular this proposal for "Investigating the neural basis of Posterior Fossa Syndrome." The appropriate programmatic and administrative personnel at the University of Iowa approve this proposal submission and will support the administrative work necessary, should this proposal be funded.

Thank you for considering Dr. Boes for this award. We are very grateful for the opportunity to seek the important and generous support of the American Brain Foundation to further the research work of our faculty.

Sincerely,

Mary Blackwood
Acting for Daniel Reed

Daniel Reed
Vice President for Research & Economic Development

Boes - American Brain Foundation Grant

Grant Start Date 7/1/2017

Personnel	**Effort**	**Cal. Months**
Image Processing Analyst (Joel Bruss)	5%	0.6
Psychologist (Amanda Graft)	4%	0.4

MRI - 1 hour	3 Per Subject
Participant Compensation + Travel	$100 per visit

Base Salary		Requested Salary		Fringe		7/1/2017-06/30/2018 Year 1		7/1/2018-06/30/2019 Year 2		7/1/2019-06/30/2020 Year 3
$ 53,040	$	2,652	$	629	$	3,281	$	3,346	$	3,413
$ 89,000	$	3,212	$	761	$	3,973	$	4,053	$	4,134
					$	**7,254**	**$**	**7,399**	**$**	**7,547**
Subject costs										
$ 615	Per hour				**$**	**25,830**	**$**	**23,985**	**$**	**23,985**
$ 300	Per Subject				**$**	**1,400**	**$**	**1,300**	**$**	**1,300**
			Total Costs		**$**	**34,484**	**$**	**32,684**	**$**	**32,832**

Participant Breakout	**30 Total**	14	13	13

	Total
$	10,040
$	12,160
$	22,200
$	73,800
$	4,000
$	100,000

Title: **Posterior Fossa Syndrome in a Medulloblastoma population: analysis by functional MRI imaging**

Sponsor Name: **None**

PI Name: **Jones, Robin** Protocol #: **2014P001592** Type: **New Protocol**

Date Received: **August 13, 2014**

Study Staff

Name	Role	Degree	Organization	Citi Certified
Abrams, Annah	Co-Investigator	MD	MGH > Psychiatry	6/12/2013
Boes, Aaron	Co-Investigator	MD, Ph.D	MGH > Neurology > Neurology Chief Funds	10/9/2012
Gallotto, Sara	Research Coordinator/Manager		MGH > Radiation Oncology	5/1/2013
Jones, Robin	Principal Investigator	MD	MGH > Neurology	11/13/2013
Pulsifer, Margaret	Co-Investigator	Ph.D	MGH > Psychiatry	9/30/2012
Yock, Torunn	Co-Investigator	MD	MGH > Radiation Oncology	3/9/2012

Signatures

PI Name: Jones, Robin, M, MD
Authenticated: August 04, 2014

Sponsor Funding: None

Select the source of funding that will be used to support the proposed research:

- ○ Government / Foundation / Other Non-Profit
- ○ Corporate
- ○ Institutional Award
- ○ Department Funds
- ⊙ None

Is this the primary source of funding?

○ Yes ○ No ⊙ Not applicable

Health / Medical Records

1. Purpose

Briefly describe the purpose of the research:

Medulloblastoma represents the most common malignant cerebellar posterior fossa tumor in children.

Posterior fossa syndrome is seen postoperatively in approximately 25% of patients with medulloblastoma. To date, we have treated 180 medulloblastoma patients with proton beam radiotherapy at the Francis H. Burr Proton Therapy Center (FHBPTC). Data acquired as part of the clinical and research protocols related to the treatment at the FHBPTC has included standard brain MRI imaging pre- and post-operatively, as well as neuropsychological testing. MRI functional connectivity imaging is a tool that can map networks in the human brain. Anatomical predictors of posterior fossa syndrome are not well understood.

We propose to retrospectively investigate the patterns of cerebellar functional connectivity in pediatric medulloblastoma patients using data from MRI images collected as part of treatment protocols at the FHBPTC. We will look at functional connectivity patterns of the lesions using a normative database to determine what regions in the brain are normally connected to this lesion site in the normal population.

We will analyze the data in both patients affected with posterior fossa syndrome as well as age-matched controls from our sample population. In addition, we will incorporate results of neuropsychological analysis to identify variables that may contribute to outcome.

Data resulting from this research will be used for the following. Check all that apply.

- ☑ Publication
- ☑ Oral Presentation
- ☐ Other

Will data resulting from this research ever be submitted to the FDA?

○ Yes ⊙ No

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2. Study Population

Describe the study population, e.g., age, gender, diagnosis. Note: Healthcare providers may be considered subjects if you are studying provider behavior or performance, or analyzing patient outcomes based on provider. In such cases, you must consider the privacy risks and privacy rights of providers.

We will include pediatric patients treated at MGH for medulloblastoma age 0-21 years, inclusive of males and females, from 1/2002 to 12/2014. The age-matched controls are patients from the IRB-approved data repository called "MGH Pediatric Radiation Oncology Database".

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3. Source of Health / Medical Information

Indicate:

☑ Partners Sites

Partners Sites - Check all that apply:

☐ BWH
☐ Faulkner
☑ MGH
☐ NWH
☐ NSMC
☐ PCHI
☐ SRH
☐ McLean
☑ Other

Enter the other sources of health / medical information and move to the box on the right.

IRB #2005P000087 MGH Pediatric Radiation Oncology Database

☐ Non-Partners Sites

---

4. Data To Be Collected / Obtained

Check all that apply.

Administrative:

☐ Billing data
☐ Coded encounter data (diagnoses, procedures, dates)
☑ Demographic data (age, gender, vital status)
☑ Personal data (name, address, PCP)

Health / Medical:

☑ Allergies
☑ Discharge Summary
☐ Doctors Orders
☑ History / Physical
☐ Immunizations

☑ Medication List

☑ Office / Clinic Notes

☑ Operative / Procedure Notes (e.g. endoscopy)

☐ Pharmacy

☑ Problem List

Health/Medical Reports/Results:

☐ Blood Bank

☑ Laboratory

☑ Pathology reports (reports only). Complete the Excess Human Material form for use of tissue/slides instead of this form.

☑ Radiology

Sensitive/Personal Information:

☐ HIV Status

☑ Mental Health

☐ Reproductive History (e.g., abortions)

☐ Sexual Behavior/Sexually Transmitted Diseases

☐ Substance Abuse (e.g., drug or alcohol abuse)

☐ Other potentially stigmatizing behaviors

Will any Sensitive/Personal Information listed above be collected?

⊙ Yes ○ No

Explain why the sensitive/personal data checked above is needed to achieve the goals of the study:

Posterior fossa syndrome is a common problem defined by mutism, ataxia and emotional lability. We will need to review their mental health information to better define the emotional symptoms that present in patients with posterior fossa syndrome in order to correlate the anatomic location of the injury in the cerebellum and brainstem with the symptomology.

Other Health/Medical Information:

☑ Other

Specify:

Neuropsychological measures which are a part of the standard medical records and assessments in children with brain tumors.

Have you created a data collection form or other tool for data collection?

○ Yes ⊙ No

Enter specific data variables needed to achieve the goals of your study. Enter one variable and move to the box on the right. Repeat for all variables.

gender

age at treatment
name
medical record number
tumor size
M stage
ataxia grade
mutism grade
CN abnormalities
dysarthria
other neurologic findings
MRI preop date
MRI post op Date
operation date
VP shunt/EVD status
hydrocephalus
handedness
other surgical complications
Neuropsychological measures
emotional lability grade

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5. Data To Be Requested From The Following Time Period (Encounter Dates)

Indicate the time period over which the health / medical information was / will be created as part of clinical care.

From (mm/yyyy):

01/2002

To (mm/yyyy):
For future data, use anticipated project end date.

12/2014

NOTE: This information is needed for the IRB to determine whether the research use of the health/medical information meets the criteria for an exemption from the requirement for IRB review. For more information about HUMAN SUBJECTS RESEARCH or EXEMPT RESEARCH, see the policy 'Exempt Human-Subjects Research.'

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6. Protected (Identifiable) Health Information

PHI refers to health/medical information that is accompanied by any of the listed 18 HIPAA identifiers or by a code where the key to the code that links to the identifiers is accessible to investigators. DE-IDENTIFIED

DATA (without any identifiers or codes that link back to individuals) are not considered PHI, and are not subject to HIPAA regulations.

Will you be recording any of the identifiers listed above with the data or using a code to link the data to any of the identifiers? If yes, than under the HIPAA Privacy Rule provisons the data cannot be considered de-identified and authorization from the subject or a waiver of authorization must be granted by the IRB. When answering this question, consider the need for recording dates or retaining direct identifiers, such as name and/or medical record number, to link data from multiple sources, to avoid duplicating records, or for QA purposes. NOTE: If you are recording medical record number or other identifiers, even if temporarily for QA purposes or to avoid duplicating records, then answer "Yes".

◉ Yes ○ No

Check the identifiers that will be recorded with or linked by code to the data.

☑ Name

☐ Social Security Number

☑ Medical record number

☐ Address by street location

☐ Address by town / city / zipcode

☑ Dates (except year), e.g., date of birth; admission / discharge date; date of procedure; date of death

☐ Telephone number

☐ Fax number

☐ Electronic email address

☐ Web URLs

☐ Internet protocol (IP) address

☐ Health plan beneficiary number

☐ Account number

☐ Certificate / license number

☐ Vehicle identification number and serial number, including license plate number

☐ Medical device identifiers and serial numbers

☐ Biometric identifiers (finger and voice prints)

☐ Full face photographic image

☐ Any other identifier; or combination of identifiers likely to identify the subject (e.g., Pathology Accession #)

Explain why it would be impossible to conduct the research without access to and use of identifiable health / medical information. For example, the data cannot be obtained from electronic health / medical records or databases without access to identifiers or identifiers are needed for prospective data collection.

This in formation is required to initially identify patients with posterior fossa syndrome for this retrospective review. Then we will use the demographics to

match medulloblastoma patients who have not been affected by posterior fossa syndrome for the control group. We also need dates to calculate exact age at the time of treatment.

Will identifiers be removed from the data and destroyed after all of the data has been collected, the study has been completed, or all regulatory and sponsor obligations have been met, consistent with regulatory and institutional research record keeping requirements? For guidance, see the PHRC Recordkeeping and Record Retention Requirements document.

⊙ Yes ○ No

NOTE: Federal regulations mandate that, under a Waiver of Consent / Authorization, identifiers be destroyed as early as possible. De-identified datasets may be retained indefinitely.

6A. Waiver of Informed Consent / Authorization

Explain why the risk to subjects, specifically the risk to privacy, is no more than minimal risk. When addressing this question, describe the measures you have put in place to protect the privacy of subjects and confidentiality of the data; for example: (1) identifiable health information will be stored on a computer on the Partners network with password protections enabled and anti-virus software or an encrypted laptop, with access to data limited to study staff; (2) name and/or medical record number will be replaced with a study ID or code and the key to the code stored in a password protected file; (3) direct identifiers, such as name and medical record number, will be removed once all of the data is collected and analysis performed on de-identified data.

We request a waiver of consent for those patients entered into the database retrospectively, as the use of the requested protected health information (PHI) involves no more than a minimal risk to the privacy of the individual patients based on the following:
(1) we will protect the identifiers from improper use and disclosure by storing the information on a password-protected database which can be accessed only by study personnel, all of whom have completed training in HIPAA guidelines and requirements;
(2) we will destroy the identifiers at the earliest opportunity consistent with the conduct of the proposed clinical research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law; and
(3) the requested PHI will not be reused nor disclosed to any other person or entity, except as required by law or for authorized oversight of the research study.

Explain why the research could not practicably be carried out without the waiver of consent / authorization. When addressing this question, consider the difficulty in locating individuals who may

have moved, the number of subjects and cost and use of limited resources of locating individuals and sending letters and consent forms, and the impact on the scientific validity of the study if you could use only data of individuals from whom you were able to obtain informed consent.

The research cannot practicably be carried out without the waiver of consent given that many of the patients to be included in the study cannot be contacted, either because they have expired or changed address. In addition, informed consent for this research project would compromise the integrity and completeness of the data because many busy patients simply don't have time for a process (read the
consent form, understand and acquiesce and send it back) which doesn't have a direct beneficial or adverse effect on them. The likelihood that we would lose valuable information in this setting is quite high.

NOTE: "Only in a few research studies would it be impossible to obtain informed consent; however in many studies the financial cost would be prohibitive and a potentially poor use of limited research resources." Ensuring Voluntary Informed Consent and Protecting Privacy and Confidentiality, National Bioethics Advisory Commission.

Explain why the rights and welfare of the subjects will not be adversely affected by the waiver of consent / authorization. When addressing this question, consider the individual's right to privacy and the measures you have put in place to protect the privacy of subjects and confidentiality of any data and any health/medical implications for subjects; for example: (1) identifiable data will be stored securely with access limited to study staff; (2) information resulting from this study will not have any important health/medical implications for subjects.

The rights and welfare of the subjects in this study will not be adversely affected by the waiver of consent, as the data will be maintained in a password-protected database which can be accessed only by study personnel. All study personnel have completed training in HIPAA guidelines and requirements; accordingly, they will strictly maintain the confidentiality of the data and will protect the privacy of all patients entered into the database. Moreover, in any reports or presentation of data, there will be no disclosure of any possible patient identifiers.

NOTE: If the research uncovers information about the subjects that has important health / medical implications for them, contact the PHRC to discuss the appropriate process for providing subjects with additional pertinent information.

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7. Research Data

How will research data be recorded and stored?

☑ Electronically

Electronic Research Data

What type of device will the research data be accessed and stored on? Check all that apply.

☑ Desktop computer

☐ Portable device i.e., Laptop, Netbook, Tablet, iPod computer, Cell/Smart phone

☐ USB Flash/Thumb, External Hard Drive

☐ Other device

Portable devices can include cell phone/smart phones, laptops, iPad/tablet computers, iPods or any other electronic device that can communicate wirelessly. For information on portable device security, refer to the Partners Portable Device Security Handbook (PHS Internal only link)

Where is the primary storage location of the device(s)? For example, the laptop is stored in office 123 on White 1 and is secured to a desk with a laptop lock or the hard drive is stored in a locked cabinet in office 123 on White 1 and access is limited to study staff only.

All electronic data contianing patient identifiers will be stored on a Partner's password-protected Desktop computer.

Who will have access to the electronic research data?

The PI and study staff.

NOTE: All computers and portable devices must have password protections enabled; All computers must have active anti-virus software; Laptops, tablet, netbook computers, and USB Flash/Thumb drives must be full disk encrypted; If data will be transmitted outside the Partners firewall, data must be encrypted during transit with the use of SSL/https.

Will data be uploaded to a website/server?

○ Yes ⊙ No

☐ Paper

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8. Sending Health / Medical Information to Collaborators Outside Partners

Will any health / medical information be sent to collaborators outside Partners?

○ Yes ⊙ No

HIPAA And Tracking Disclosures Of Identifiable Health Information (PHI)

1. Disclosures of PHI to persons or entities outside Partners without the written authorization of the subject must be tracked in accordance with Partners policy "Accounting of Disclosures" (PHS Intranet link). NOTE: A code derived from the subject's name is considered identifiable, for example, a code that contains subject initials.

2. Tracking is NOT required for disclosure of LIMITED DATA SETS under a DATA USE AGREEMENT. For more information about LIMITED DATA SETS and DATA USE AGREEMENTS, refer to Partners policy "Limited Data Sets Policy/Data Use Agreements" (PHS Intranet link).

NOTE: Partners (PHS) is the HIPAA covered entity. PHS includes BWH, Faulkner, MGH, McLean, PCHI, SRH, NSMC, and NWH, among others. PHS does not include other Harvard affiliated hospitals, such as BIDMC, DFCI, HSPH, CHB, or MEEI.

UNIVERSITY of IOWA
CARVER COLLEGE
OF MEDICINE

University of Iowa Health Care

Aaron Boes, MD, PhD

Assistant Professor of Pediatrics, Neurology & Psychiatry
Director of Noninvasive Brain Stimulation Program
W278 GH, 200 Hawkins Drive
Iowa City, Iowa 52242
319-384-9264 ***Tel***

March 7, 2017

I have no conflicts of interest or financial disclosures to report.

Sincerely,

Aaron Boes, M.D., Ph.D.

ABF Full Application

Applicant Information

Prefix

Dr.

First Name

Aaron

Last Name

Boes

Suffix

Title

Assistant Professor

Institution Name

University of Iowa

E-mail

aaron-boes@uiowa.edu

Office Phone

(319) 353-8587

Office Fax

Project Details

Project Title

Investigating the neural basis of posterior fossa syndrome

Disease focus

Brain & Spinal Cord Tumors

Autism & Neurodevelopment

Specific Disease Focus

Posterior fossa syndrome

Project Summary/Abstract

In this grant Dr. Boes proposes to investigate the neural basis of posterior fossa syndrome, a condition in which children undergoing cerebellar tumor removal develop acute cognitive and neurobehavioral symptoms. In the first aim Dr. Boes proposes to perform lesion symptom mapping, a statistical approach to link specific neuropsychological deficits with lesion location using a large existing database. In the second aim Dr. Boes proposes a longitudinal neuroimaging study of pediatric patients undergoing neurosurgery of the cerebellum. Structural and functional imaging will be performed before and immediately after the surgery and three months later in order to assess the structural and functional imaging correlates of posterior fossa syndrome. Together, these aims combine to provide a novel and innovative use of state-of-the-art imaging to a vexing clinical condition. We are optimistic that a better understanding of the neural basis of

posterior fossa syndrome will lead to improved surgical care and potentially improved treatments for this condition.

Project Narrative

Mortality rates have steadily improved for treating pediatric brain tumors and it is increasingly important that treatments maximize long-term outcomes. The cerebellum is one of the most common sites of pediatric brain tumors and 1 in every 4 children having a tumor removed from the cerebellum experiences an often-dramatic onset of major cognitive difficulties after the surgery. Difficulties may include an inability to speak (mutism), emotional lability, and a host of other problems in behavior and cognition with highly variable rates of recovery. Here we propose to study the anatomy of this problem using state-of-the-art innovative neuroimaging approaches that combine lesion mapping and functional imaging. A better understanding of this common surgical complication could have an immediate clinical impact by improving the surgical approach to childhood cerebellum tumors.

Facilities and Equipment

The University of Iowa Hospitals and Clinics (UIHC) provides an ideal atmosphere to collaboratively conduct groundbreaking research in biomedicine that is transferred to exemplary clinical care. UIHC is the largest referral site in the state for childhood brain tumors and this research program will benefit from our strong interdisciplinary clinical program in neuro-oncology, which is housed in a brand new state-of-the-art Children's Hospital. All aspects of the current application were designed to utilize the strengths of successful researchers in pediatric neurology, neuropsychology, neurosurgery and neuroimaging. The Magnetic Resonance Research Facility has dedicated research MRIs at both 3 and 7 Tesla in a brand-new facility. The Iowa Neuroimaging Consortium is a fully staffed resource spanning 4,100 square feet in the College of Medicine. It includes image analysis technicians, system programmers, data core managers, and research assistants. It will provide much of the infrastructure. Finally, our laboratory has extensive experience in pediatric neuroimaging, lesion mapping, and evaluation of neuropsychological performance to ensure the proper collection and analysis of data.

Specific Aims

Aim 1. Perform lesion-symptom mapping of posterior fossa syndrome (PFS).

We will use a large existing database of structural MRI (clinical scans) and neuropsychological test results from pediatric patients before and after cerebellum tumor resection to localize posterior fossa symptoms. In addition, the cerebro-cerebellar networks disrupted by the lesion will be inferred using resting-state functional connectivity MRI from a publically available pediatric connectome dataset. Hypothesis: The profile of post-surgical neuropsychiatric deficits in PFS can be predicted based on lesion location and the associated cerebro-cerebellar network(s).

Aim 2. Perform longitudinal imaging of posterior fossa syndrome recovery

We will use pre- and post-surgical multimodal high-resolution MRI along with detailed neuropsychological testing to longitudinally assess the neural substrates of cognitive impairment in posterior fossa syndrome and the network modifications associated with functional recovery. Hypothesis: Disruption of specific inter-hemispheric cerebro-cerebellar networks will correlate with domain-specific cognitive symptoms (e.g. connectivity between right postero-lateral cerebellum hemisphere and left-sided cortical language areas will be disrupted in the presence of language deficits) and these networks will regain a modified functional connectivity pattern in association with functional improvements.

Research Strategy

Significance, Innovation, Approach, Timeline

Significance

Posterior fossa syndrome (PFS) includes cognitive and neurobehavioral symptoms that occur most commonly after surgical resection of cerebellum tumors in children (1, 2). It occurs in as many as 1 in 4 cerebellar surgeries in pediatric tumor patients (1,3) which is one of the most common sites of primary brain tumors in children. Both the severity and duration of symptoms is highly variable, ranging from days to lifelong disability (4 - 6). The mechanistic basis of PFS from a neuroanatomical and large-scale neural network perspective is poorly understood and has not been investigated using modern approaches for lesion-symptom mapping. However, such information has immediate clinical relevance, as greater anatomical knowledge of regions that contribute to PFS could inform the surgical approach and lead to better outcomes. Knowledge of the network-based correlates of PFS and its recovery may also inform innovative follow-up studies that use noninvasive brain stimulation in a targeted way to affected cerebro-cerebellar networks to augment recovery of function. More broadly, PFS provides a unique window from which to investigate the role of the cerebellum in cognitive development, which has major implications for understanding a variety of neurodevelopmental disorders in which the cerebellum is implicated, including ADHD, autism, and dyslexia (7, 8). As such, insights from this study may extend beyond PFS to a variety of neurodevelopmental conditions.

Innovation

During my residency training in child neurology I developed a novel method for investigating the network effects of focal brain lesions, termed lesion network mapping (9). This work was inspired by a patient encounter; a 17-year-old girl developed visual hallucinations after a punctate infarct to a non-visual region of the thalamus. Traditional lesion mapping of this patient and 22 others with visual hallucinations following subcortical infarcts revealed two weaknesses of traditional lesion mapping: 1) the lesions overlapped at multiple sites, raising the question of whether they failed to localize or localized along different nodes of a single functional network, and 2) the overlap sites occurred in

non-visual regions, but the leading hypothesis for the mechanism of peduncular hallucinosis is that these lesions have their functional effects remotely in higher-order visual cortices. It was unclear how or if these lesion sites related to cortical visual areas. A novel solution to address these two questions was to use the 3D volume of each lesion in a large normative database of functional connectivity MRI to investigate the networks associated with each lesion location, as a way to infer the remote sites impacted by the lesions. Using this approach, 22 of 23 lesions fell along a single network that had connectivity to the ventral extrastriate visual cortex, a region hypothesized to be involved in the generation of hallucinations. I was the lead author describing this novel method applied to four separate lesion syndromes, published in Brain in 2015 (9). The method is gaining momentum this year with an important validation study and several additional high impact publications using the method by our group and others.

The current proposal will build upon this innovative work through a variety of conceptual and technical improvements to lesion network mapping. First, this study will provide the first application of lesion network mapping in the pediatric population, which will require age-matched normative data. This approach will be important in investigating the hypothesis that cerebellar injury disrupts cognition through disruption of specific cerebro-cerebellar networks (10). Next, these experiments will provide the only study design to date of lesion network mapping that includes functional imaging before and after the onset of a lesion, such that predicted network effects of the lesion can be tested explicitly, a critical test of the technique's validity.

Approach

Aim 1. We propose to investigate the anatomy of PFS using a neuroimaging approach called voxel-based lesion symptom mapping. The clinical course of 115 children with cerebellum tumors will be reviewed, including detailed neuropsychological test results performed before and after the surgery. The anatomical site of the surgical resection will be mapped onto a reference brain and statistically compared between children who had PFS versus those that did not. This will provide the first large-scale map of the regions of the cerebellum that are critical for developing PFS. This large dataset is made possible through a unique collaboration between pediatric neuro-oncology teams at Iowa and Harvard's Massachusetts General Hospital.

Aim 2.

30 pediatric patients undergoing cerebellum tumor resection will be recruited prospectively to participate in a longitudinal study involving neuropsychological testing and neuroimaging at three time points, pre-surgical, immediate post-surgical, and three months later. MRI will include structural, diffusion tensor imaging & resting state functional connectivity MRI sequences.

Timeline

This study proposed here will be completed over a three year period (2017 - 2020). Additional funding in the form of an RO1 will be applied for in year 2 (2019).

List up to 5 milestones you will reach within the first 6 months of your study.

- Trace lesion location of over 100 pediatric patients with cerebellar tumor resections and analayze lesion location relative to neuropsychological outcomes.
- Collect data from the initial 5 patients with cerebellar tumor resection to longitudinally monitor recovery and imaging correlates of recovery.

Age of Population Group(s) that will potentially benefit from this research

(check boxes that apply)

Pediactric

Scientific Literature References

Reference 1

Catsman-Berrevoets, C. E.; Aarsen, F. K. The Spectrum of Neurobehavioural Deficits in the Posterior Fossa Syndrome in Children after Cerebellar Tumour Surgery. Cortex 2010, 46, 933--946.

Reference 2

Gadgil, N.; Hansen, D.; Barry, J.; Chang, R.; Lam, S. Posterior Fossa Syndrome in Children Following Tumor Resection: Knowledge Update. Surgical neurology international 2016, 7, S179-83.

Reference 3

Robertson, P. L.; Muraszko, K. M.; Holmes, E. J.; Sposto, R.; Packer, R. J.; Gajjar, A.; Dias, M. S.; Allen, J. C. Incidence and Severity of Postoperative Cerebellar Mutism Syndrome in Children with Medulloblastoma: A Prospective Study by the Children's O

Reference 4

Tamburrini, G.; Frassanito, P.; Chieffo, D.; Massimi, L.; Caldarelli, M.; Rocco, C. Di Cerebellar Mutism. Child's Nervous System 2015, 31, 1841--1851.

Reference 5

Gelabert-González, M.; Fernández-Villa, J. Mutism after Posterior Fossa Surgery. Review of the Literature. Clinical Neurology and Neurosurgery 2001, 103, 111--114.

Reference 6

Rønning, C.; Sundet, K.; Due-Tønnessen, B.; Lundar, T.; Helseth, E. Persistent Cognitive Dysfunction Secondary to Cerebellar Injury in Patients Treated for Posterior Fossa Tumors in Childhood. Pediatric neurosurgery 2005, 41, 15--21.

Reference 7

Wang, S. S.-H.; Kloth, A. D.; Badura, A. The Cerebellum, Sensitive Periods, and Autism. Neuron 2014, 83, 518--32.

Reference 8

Stoodley, C. J. The Cerebellum and Neurodevelopmental Disorders. The Cerebellum 2016, 15, 34--37.

Reference 9

Boes, A. D.; Prasad, S.; Liu, H.; Liu, Q.; Pascual-Leone, A.; Caviness, V. S.; Fox, M. D. Network Localization of Neurological Symptoms from Focal Brain Lesions. Brain : a journal of neurology 2015, 138, 3061--75.

Reference 10

Sagiuchi, T.; Ishii, K.; Aoki, Y.; Kan, S.; Utsuki, S.; Tanaka, R.; Fujii, K.; Hayakawa, K. Bilateral Crossed Cerebello-Cerebral Diaschisis and Mutism after Surgery for Cerebellar Medulloblastoma. Annals of Nuclear Medicine 2001, 15, 157--160.

Budget, Attachments and Acknowledgements

Budget

We recognize that changes may have occurred since the time you submitted your Letter of Intent. Please share the most recent accurate numbers below:

Total Project Budget

$221,627

Total existing funding or in-kind support

$121,627

Amount to be raised through crowdfunding campaign

$100,000

Evidence of institutional support (letter)

Boes-Institutional support.pdf

Full budget

Budget.xlsx

Documentation of IRB/IUCAC approval or exemption, if applicable.

Boes_IRB_posterior_fossa.pdf

Completed conflict of interest & disclosure form

Boes disclosure statement.pdf

I understand that the ABF will not list approved projects for general public crowdfunding campaigns until documentation of IRB/IUCAC approval or exemption is provided.

Yes

I understand that approval of the project to be shared on the crowdfunding campaign site is dependent on providing and working with the ABF staff to create the requisite materials that present the project in an engaging, easy-to-understand website presentation. I am amenable to working with the ABF staff to create such materials.

Yes

I understand that approval once a project has been completed, I will be required to submit a summary of my findings to be posted online (one page), and will submit this in a reasonably timely fashion. I also agree to submit a financial report, and to co-sign a thank you letter with the ABF that will be sent to donors.

Yes

I understand and agree that the ABF may share the information that I provide (including but not limited to the project description and relevant biographical/background details) in conversations with other potential funders outside the website to bolster fundraising efforts.

Yes

American Brain Foundation Release Agreement

American Brain Foundation
Release Agreement – Research

1. **Grant**. For good and valuable consideration, the receipt and sufficiency of which is hereby acknowledged, I grant to the

   American Brain Foundation ("ABF") and to the ABF's affiliates (including the American Academy of Neurology), and their respective contractors, agents, assigns, licensees, and successors (collectively, the "ABF Group"), a worldwide, royalty-free, perpetual, irrevocable right to take and use my image, likeness, voice, verbal statements, written testimonials and name and all images, videos, sound recordings, and written and verbal materials that I provide to the ABF (collectively, the "Materials "), in all forms and media, including composite or modified representations, for the purpose of promoting and supporting the missions of the ABF. For the avoidance of doubt, the Materials include all research project proposal information, project reports and other research-related information submitted to the ABF. I understand and agree that the ABF may publish the Materials on any and all media, including printed matter, promotional materials, e-mail, websites and social media platforms.
2. **Acknowledgement of Use**. I understand that the ABF Group may use the Materials on any and all media, including printed matter, promotional materials, e-mail, websites and social media platforms. I understand that the ABF's use of the Materials may intentionally or unintentionally give rise to the impression that either I or a family member suffers from brain/neurologic disease, and I nevertheless consent to this use. The ABF is not obligated to utilize any of the rights granted in this agreement. I waive the right to inspect or approve any uses of the Materials in connection with this grant.
3. **Warranty**. I warrant that I have the full power to enter into this agreement and to grant the aforementioned rights.
4. **Release**. I release the ABF Group from all liability for any claims that may arise regarding the use of Materials, including any claims of defamation, invasion of privacy, or infringement of moral rights, rights of publicity, or copyright. The ABF is permitted, although not obligated, to include my name as a credit in connection with any use of the Materials.**I have read and understood this agreement, I understand that it contains a release of liability, and I am over the age of 18**. This agreement expresses the complete understanding of the parties and shall be binding on me and my heirs, legal representatives and assigns. I understand that I am entering into a legally binding agreement and that clicking "I Accept" below shall have the same legal effect as my signature on this Release Agreement.

I Accept

Dear Applicant:

In the increasingly complex world of scientific publication, concerns about commercial influence and other possible conflicts make it important for authors to disclose all potential sources of bias. Our system of reviewing conflicts of interest aligns with the policies of the American Academy of Neurology and allows donors to judge whether conflicts exist. Please complete this form, referring to the definitions in the beginning regarding commercial entities, compensation, expert witness, and "immediate family member." At first glance, this task may seem onerous, but will likely take less than 10 minutes.

What to expect: You will be asked whether you have disclosures relating to each question (check yes or no) and will be provided a field in which to list the disclosures. Filling out the forms on the next few screens will be easiest if you have a list of the following items regarding your activity (either commercial or non-profit) and that of any immediate family members during the period of your project. Disclosures are required for any dollar amount, except for gifts valued under $1000. Names of commercial and non-profit entities are required along with specific roles, grant numbers for grants, and specific years. No dollar amounts need to be included. Please indicate complete names of sponsors or companies.

DEFINITIONS

Personal compensation:
Serving on a scientific advisory board
Gifts worth more than $1000
Travel funded by a commercial entity
Serving as a journal editor, associate editor, or on an editorial advisory board
Patents held or pending
Royalties from publishing
Honoraria for speaking engagements
Corporate appointments or consultancies
Speakers' bureaus
Clinical, neurophysiology, or imaging studies in your practice and % effort devoted if the result of this paper will benefit your practice, affiliated unit, or a sponsor

Research support:
Commercial research support
Government research support (including funding organization, grant number, and role)
Academic research support not attributed in the manuscript
Support from a non-profit foundation or society
Stock options for serving on a Board of Directors
License fee payments
Royalty payments from technology or inventions

Stocks, stock options, and royalties
Stock options in a company in which you are (were) an investigator
Stock options in medical industry

Legal proceedings
Expert testimony for a legal proceeding on behalf of industry
Affidavit for a legal proceeding on behalf of industry
Witness or consultant for a legal proceeding on behalf of industry

Optional non-financial
Non-financial disclosures you wish to share

Definitions of Terms in Disclosure Agreement
Commercial entity: A for-profit business that manufactures, distributes, markets, sells, or advertises pharmaceutical or scientific products or medical devices.
Compensation: Anything of monetary value including a salary, honorarium, stipend, gift, or payment of travel-related expenses.
Expert witness: A person who has provided expert medical testimony during a trial or administrative hearing, in a deposition or an affidavit, or in any other type of legal proceeding.
"Immediate family member": Any person who would benefit financially from the publication of the manuscript because of their relationship to the author. This includes a member of an applicant's immediate family or anyone else who has a significant relationship with the applicant.

Please provide all financial relationships (and those of your "immediate family members") from the past two years regardless of whether these relationships are related to the project described in your application.

FINANCIAL DISCLOSURE
Personal Compensation from Commercial and Non-Profit Entities that benefits you directly or indirectly. Within the past two years (and during the course of the study under consideration if the study exceeded two years), I or one of my "immediate family members" received personal compensation for the following:

All compensation received during the past two years regardless of the relationship to your project must be disclosed; for the period exceeding two years, only compensation relevant to the topic of the study needs to be disclosed.

1. Serving on a scientific advisory board or data safety monitoring board. List specific disclosures in the following format: (1) Commercial or non-profit entity (2) Commercial or non-profit entity... If none, please say "None":

None

2. Gifts (other than travel or compensation for consulting or for educational efforts) worth more than USD $1000. List specific disclosures in the following format: (1) Commercial or non-profit entity, brief description of gift, (2) Commercial or non-profit entity, brief description of gift... If none, please say "None":

None

3. Funding for travel or speaker honoraria to the individual from a commercial or non-profit entity not included in the study funding [Exclude CME activities and Grand Rounds]. List specific disclosures in the following format: (1) Commercial or non-profit entity, type of payment, (2) Commercial or non-profit entity, type of payment... If none, please say “None”:

None

4. Serving as a journal editor, an associate editor, or editorial advisory board member. This may include a journal published by your national medical/scientific organization. Please include regardless of whether you receive compensation. List specific disclosures in the following format: (1) Full journal name, role, year(s), (2) Full journal name... If none, please say “None”:

None

5. Patents issued or pending. List specific disclosures in the following format: (1) Brief description of invention/technology, (2) Brief description of invention/technology... If none, please say “None”:

None

6. Publishing Royalties (do not include honoraria for occasional writing). List specific disclosures in the following format: (1) Full title of work, full name of publisher, year(s) of publication (or receipt of royalties), (2) Full title of work... If none, please say “None”:

None

7. Employment. If you are currently employed by a commercial entity, please disclose below. In addition, if your past employment at a commercial entity is directly related to this manuscript, please disclose below. List specific disclosures in the following format: (1) Commercial entity, position, years (2) Commercial entity, position, years... If none, please say “None”:

None

8. Consultancies. List specific disclosures in the following format: (1) Commercial or non-profit entity, (2) Commercial or non-profit entity... If none, please say “None”:

None

9. Speakers' bureau. List specific disclosures in the following format: (1) Commercial or non-profit entity, (2) Commercial or non-profit entity... If none, please say “None”:

None

10. Other activities not covered in designations above (if in doubt, provide full disclosure). List specific disclosures in the following format: (1) Commercial or non-profit entity, brief description of activity, (2) Commercial or non-profit entity... If none, please say “None”:

None

11. Some studies have potential for financial gain for the project investigators or the sponsor. The following question seeks to provide transparency regarding any financial benefits to investigators or sponsors.

Do you perform clinical procedures or imaging studies in your practice or unit that overlap with the content of your proposed project, practice parameter, or clinical practice guideline and would your sponsor or this part of your practice or unit benefit if the conclusions were widely followed?
Note: This is the only item in this Agreement that applies to an interest that is related specifically to this particular study, practice parameter, or clinical practice guideline.

List specific disclosures in the following format: (1) Name of Practice or Research Unit, Clinical procedure/imaging study, % of effort (e.g. 35%), year(s), (2) Name of Practice or Research Unit, Clinical procedure/imaging study, % of effort (e.g., 35%)... If none, please say “None”:

None

RESEARCH SUPPORT
Within the past two years and during the course of the study under consideration if the study exceeded two years, I or one of my "immediate family members" received financial or material research support or compensation from the following:

All support received during the past two years regardless of the relationship to the study must be disclosed; for the period exceeding two years, only support relevant to the topic of the study needs to be disclosed.

12. Commercial entities. List specific disclosures in the following format: (1) Commercial entity, (2) Commercial entity... If none, please say “None”:

None

13. Government entities. List specific disclosures in the following format: (1) Sponsor/funding source, grant number(s), role, year(s), (2) Sponsor/funding source... If none, please say “None”:

NINDS-sponsored R25NS065743-05
Child Health Research Career Development Award 4K12HD027748-24

14. Academic entities other than those attributed in the manuscript. List specific disclosures in the following format: (1) Academic entity, (2) Academic entity... If none, please say “None”:

None

15. Foundations or societies (include grant number if required by funding agency). List specific disclosures in the following format: (1) Full name of Foundation or Society, (2) Full name of Foundation or Society... If none, please say “None”:

Aiming for a Cure Grant

STOCK, STOCK OPTIONS & ROYALTIES

In the past two years and during the course of the study under consideration if the study exceeded two years, I or one of my "immediate family members":

All revenues during the past two years regardless of the relationship to the study must be disclosed; for the period exceeding two years, only revenues relevant to the topic of the study needs to be disclosed.

16. Stock or stock options or expense compensation for serving on a board of directors. List disclosures in the following format: (1) Commercial entity, (2) Commercial entity... If none, please say “None”:

None

17. License fee payments. List specific disclosures in the following format: (1) Invention/technology, source of payment, (2) Invention/technology... If none, please say “None”:

None

18. Royalty payments or have contractual rights for receipt of future royalty payments from technology or inventions (this does not include royalties from publishing). List specific disclosures in the following format: (1) Technology/invention, source of payment, year(s), (2) Technology/invention... If none, please say “None”:

None

19. Stock or stock options in a commercial entity sponsoring research with which the author or "immediate family member" was involved as an investigator (Excludes investments in mutual funds held by the author or dependents). List specific disclosures in the following format: (1) Company, year(s), (2) Company, year... If none, please say “None”:

None

20. Stock or stock options in a commercial entity whose medical equipment or other materials related to the practice of medicine. (Exclude investments in mutual funds held by the author or dependents). List specific disclosures in the following format: (1) Company, year(s), (2) Company, year... If none, please say “None”:

None

LEGAL PROCEEDINGS

In the past two years and during the course of the study under consideration if the study exceeded two years, I or one of my "immediate family members" have (whether or not it pertains to the topic of the current study):

All compensation received during the past two years regardless of the relationship to the study must be disclosed; for the period exceeding two years, only compensation relevant to the topic of the study needs to be disclosed.

21. Given expert testimony, acted as a witness or consultant, or prepared an affidavit for any legal proceeding involving a commercial entity (do not include proceedings for individual patients). You may specify role, e.g., 'expert witness for plaintiff' if desired. (Include year only if activity is directly related to the present study.)

List specific disclosures in the following format: (1) Commercial entity, activity, year(s), (2) Commercial entity, activity, year(s)... If none, please say “None”:

None

OPTIONAL: NONFINANCIAL DISCLOSURE

22. I have chosen to declare one or more non-financial competing interests (e.g., special interest groups you represent or others that may be affected if your paper is published or that could be perceived as biasing the study; the corresponding author should be aware of conflicts of interest that Co-investigators or Contributors may have). Non-financial disclosures will not be published.

List specific disclosures, if none, please say “None”:

None

☑ I have completed this Disclosure Statement fully and to the best of my ability. I understand that all Applicants must complete this Disclosure Statement and that the information disclosed may be published if their project is accepted for crowdfunding.

By my electronic signature, I verify the completeness and accuracy of the contents of this form.

Click in the box above to add your electronic signature

03/18/2017

Date [03/18/2017]

April 7, 2017

Aaron Boes, MD
University of Iowa Hospitals and Clinics
W278 General Hospital
200 Hawkins Drive
Iowa City, Iowa 52246

Dear Dr. Boes,

Congratulations! On behalf of the American Brain Foundation, I am pleased to inform you that your project has been selected to post on the Foundation's crowdfunding site.

An email was sent requesting several documents. It is critical that you provide all of the requested documents in order for your project to be posted on the crowdfunding site.

As a reminder, you will have 90 days from when your project goes live on the site to raise the funds needed to complete your proposed project. Once the funds are raised, a gift agreement will be sent to you and your institution to review and sign. As soon as the American Brain Foundation receives the signed gift agreement, the first payment for your project will be sent to your institution. The final payment for your project will be sent after your progress report has been reviewed and approved by the Foundation.

Please respond to this letter with the name of and contact information for the contact at your institution that the Foundation should work with to process payments. Please send your response to grants@americanbrainfoundation.org.

Again, congratulations on being selected for this opportunity.

Sincerely,

Suzi Sherman
Program Officer, Research & Digital Grants

CC: Daniel Reed, VP Research & Economic Development

Review - (399) Full Application Review	
Review	
Acceptance Due Date	3/31/2017
Due Date	3/31/2017
Visible From	3/29/2017
Visible To	12/31/2017
Request	
Name (Full)	Dr. Ania Busza
Organization Name	University of Rochester Medical School
Type	Other Research Projects
Project Budget	$52,900.00
Exisiting Funding / In-Kind Support	$0.00
Requested Amount	$52,900.00
Project Title	A Surface EMG controlled Mixed Reality Smart glass for Motor Rehabilitation in Stroke Patients
General focus	Stroke & Vascular Diseases Neurorehabilitation
Specific Disease Focus	neuro-rehabilitation post-stroke
Project Description	Project Description Our goal is to create a mixed reality interface that senses electrical signals from muscles and maps muscle activity to a virtual arm. This approach may lead to new methods of motor rehabilitation for patients disabled from stroke. BACKGOUND: Each year 795,000 people suffer a stroke in the US, and 30-40% are left with a permanent disability. There is a great need for effective evidence-based neurorehabilitation strategies, and the American Heart Association and the NINDS have named novel brain-computer interfaces and earlier rehabilitation efforts as high priorities for research. OUR PROJECT: We will build a system where subjects control movements of a virtual arm (VA) displayed on a mixed reality interface (the Microsoft HoloLens headset). The movement of the VA will be controlled by electric signals from arm muscles (measured by surface electromyography, or sEMG). sEMG signals from healthy subjects will be used for initial baseline, then the system will be tested and further calibrated on stroke patients with weakness. We will run a pilot study evaluating our system in stroke patients, to obtain preliminary data for a future large-scale clinical trial. WHY THE sEMG-VA MAY BE MORE EFFECTIVE THAN CURRENT REHABILITATION TECHNIQUES: Studies on neuroplasticity suggest that effective rehab strategies involve multiple repetitions of goal-directed movements. Patients have better recovery rates when they practice more frequently, earlier, when the intensity of the movement matches their level of weakness, and when they are more motivated. Motor imagery (imagining performing movements with the affected limb) also appears to facilitate recovery. The sEMG-VA brings all of these features together. It provides the patient opportunity for frequent exercise early after their stroke, calibrated to their current level

	of weakness. The virtual arm movements triggered by weak muscle contractions will provide visual imagery of full arm movements, similar to motor imagery techniques. Finally, the virtual reality interface can be adapted with games to boost interest and motivation.
Specific Aims	SPECIFIC AIM 1: To develop a surface-EMG controlled Virtual Arm (sEMG-VA) in which movement of a virtual model arm is controlled by real-time surface EMG signals. We will focus on wrist flexion/extension of the model arm in our first prototype. SPECIFIC AIM 2: To develop a method of rapidly calibrating the sEMG-VA system such that it can be adapted to sEMG signals from muscles of varying strength. This will be critical in making the system effective for patients with different levels weakness and through several phases of recovery. SPECIFIC AIM 3: To assess the feasibility of using the sEMG-VA system on stroke patients in the inpatient and acute rehab setting. This preliminary study will provide information on tolerability, participation rates, and logistical challenges - all essential for proper design of a future larger clinical trial for efficacy.
Milestones	1. Prototype development -- we will develop the first prototype of our device, where surface EMG (sEMG) signals from the forearms of healthy volunteers will be able to control the wrist flexion/extension of a virtual arm displayed by the HoloLens 2. Device calibration -- we will develop an algorithm by which the device can be calibrated to each individual user, based off of the relative strength of each muscle group (such as wrist-extensors or wrist-flexors) for each day. 3. Preliminary feasibility/tolerability assessments-- We will start our preliminary trial looking at the feasibility of using the sEMG-VA device on acute/subacute patients during the first 3 weeks after their stroke.
Feedback	
Yes/No	Undecided
Review Long Notes	

Letter of Intent Form

Prefix

First Name

Ania

Last Name

Busza

Suffix

Title

Dr.

Institution

University of Rochester Medical School

Office Address

University of Rochester Medical Center
School of Medicine and Dentistry
601 Elmwood Ave, Box 681

City

Rochester

State

NY

Postal Code

14642

E-mail

Ania_Busza@urmc.rochester.edu

Office Phone

508-275-2530

Office Fax

Project Details

Project Title

A Surface EMG controlled Mixed Reality Smart glass for Motor Rehabilitation in Stroke Patients

General focus

Stroke & Vascular Diseases
Neuro-rehabilitation

Specific Disease Focus

neuro-rehabilitation post-stroke

Project Description

Our goal is to create a mixed reality interface that senses electrical signals from muscles and maps muscle activity to a virtual arm. This approach

may lead to new methods of motor rehabilitation for patients disabled from stroke.
BACKGOUND: Each year 795,000 people suffer a stroke in the US, and 30-40% are left with a permanent disability. There is a great need for effective evidence-based neurorehabilitation strategies, and the American Heart Association and the NINDS have named novel brain-computer interfaces and earlier rehabilitation efforts as high priorities for research.
OUR PROJECT: We will build a system where subjects control movements of a virtual arm (VA) displayed on a mixed reality interface (the Microsoft HoloLens headset). The movement of the VA will be controlled by electric signals from arm muscles (measured by surface electromyography, or sEMG). sEMG signals from healthy subjects will be used for initial baseline, then the system will be tested and further calibrated on stroke patients with weakness. We will run a pilot study evaluating our system in stroke patients, to obtain preliminary data for a future large-scale clinical trial.
WHY THE sEMG-VA MAY BE MORE EFFECTIVE THAN CURRENT REHABILITATION TECHNIQUES: Studies on neuroplasticity suggest that effective rehab strategies involve multiple repetitions of goal-directed movements. Patients have better recovery rates when they practice more frequently, earlier, when the intensity of the movement matches their level of weakness, and when they are more motivated. Motor imagery (imagining performing movements with the affected limb) also appears to facilitate recovery. The sEMG-VA brings all of these features together. It provides the patient opportunity for frequent exercise early after their stroke, calibrated to their current level of weakness. The virtual arm movements triggered by weak muscle contractions will provide visual imagery of full arm movements, similar to motor imagery techniques. Finally, the virtual reality interface can be adapted with games to boost interest and motivation.

How will your project contribute to the treatment, prevention or cure of a neurological disease(s)?

By creating a device by which patients profoundly weakened by stroke can control a virtual arm displayed on a virtual reality headset, we hope to create an system which will be usable in the acute setting, motivating/ rewarding, and easy to use. Ultimately we hope that this system will lead to better motor outcomes of stroke patients with severe arm weakness.

Project Budget

Total expense budget

An estimated total is acceptable.

64000

Value of existing funding or in-kind support

What portion of the above total expense has funding already received or promised?

0

Portion to be raised through crowdfunding

How much are you seeking from the crowdfunding platform?

64000

Attachments and Verifications

Please download, fill out, and upload the Financial Disclosures & Conflict of Interest form.

Financial Disclosures & Conflicts of Interest Form

CV of Principal Investigator

Busza_BioSketch_UFA_2017.pdf

I understand that the American Brain Foundation will not post approved projects for crowdfunding until documentation of IRB approval or exemption is provided.

Yes

Dear Applicant:

In the increasingly complex world of scientific publication, concerns about commercial influence and other possible conflicts make it important for authors to disclose all potential sources of bias. Our system of reviewing conflicts of interest aligns with the policies of the American Academy of Neurology and allows donors to judge whether conflicts exist. Please complete this form, referring to the definitions in the beginning regarding commercial entities, compensation, expert witness, and "immediate family member." At first glance, this task may seem onerous, but will likely take less than 10 minutes.

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DEFINITIONS

Personal compensation:
Serving on a scientific advisory board
Gifts worth more than $1000
Travel funded by a commercial entity
Serving as a journal editor, associate editor, or on an editorial advisory board
Patents held or pending
Royalties from publishing
Honoraria for speaking engagements
Corporate appointments or consultancies
Speakers' bureaus
Clinical, neurophysiology, or imaging studies in your practice and % effort devoted if the result of this paper will benefit your practice, affiliated unit, or a sponsor

Research support:
Commercial research support
Government research support (including funding organization, grant number, and role)
Academic research support not attributed in the manuscript
Support from a non-profit foundation or society
Stock options for serving on a Board of Directors
License fee payments
Royalty payments from technology or inventions

Stocks, stock options, and royalties
Stock options in a company in which you are (were) an investigator
Stock options in medical industry

Legal proceedings
Expert testimony for a legal proceeding on behalf of industry
Affidavit for a legal proceeding on behalf of industry
Witness or consultant for a legal proceeding on behalf of industry

Optional non-financial
Non-financial disclosures you wish to share

Definitions of Terms in Disclosure Agreement
Commercial entity: A for-profit business that manufactures, distributes, markets, sells, or advertises pharmaceutical or scientific products or medical devices.
Compensation: Anything of monetary value including a salary, honorarium, stipend, gift, or payment of travel-related expenses.
Expert witness: A person who has provided expert medical testimony during a trial or administrative hearing, in a deposition or an affidavit, or in any other type of legal proceeding.
"Immediate family member": Any person who would benefit financially from the publication of the manuscript because of their relationship to the author. This includes a member of an applicant's immediate family or anyone else who has a significant relationship with the applicant.

Please provide all financial relationships (and those of your "immediate family members") from the past two years regardless of whether these relationships are related to the project described in your application.

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All compensation received during the past two years regardless of the relationship to your project must be disclosed; for the period exceeding two years, only compensation relevant to the topic of the study needs to be disclosed.

1. Serving on a scientific advisory board or data safety monitoring board. List specific disclosures in the following format: (1) Commercial or non-profit entity (2) Commercial or non-profit entity... If none, please say "None":

None

2. Gifts (other than travel or compensation for consulting or for educational efforts) worth more than USD $1000. List specific disclosures in the following format: (1) Commercial or non-profit entity, brief description of gift, (2) Commercial or non-profit entity, brief description of gift... If none, please say "None":

None

3. Funding for travel or speaker honoraria to the individual from a commercial or non-profit entity not included in the study funding [Exclude CME activities and Grand Rounds]. List specific disclosures in the following format: (1) Commercial or non-profit entity, type of payment, (2) Commercial or non-profit entity, type of payment... If none, please say “None”:

None

4. Serving as a journal editor, an associate editor, or editorial advisory board member. This may include a journal published by your national medical/scientific organization. Please include regardless of whether you receive compensation. List specific disclosures in the following format: (1) Full journal name, role, year(s), (2) Full journal name... If none, please say “None”:

None

5. Patents issued or pending. List specific disclosures in the following format: (1) Brief description of invention/technology, (2) Brief description of invention/technology... If none, please say “None”:

None

6. Publishing Royalties (do not include honoraria for occasional writing). List specific disclosures in the following format: (1) Full title of work, full name of publisher, year(s) of publication (or receipt of royalties), (2) Full title of work... If none, please say “None”:

None

7. Employment. If you are currently employed by a commercial entity, please disclose below. In addition, if your past employment at a commercial entity is directly related to this manuscript, please disclose below. List specific disclosures in the following format: (1) Commercial entity, position, years (2) Commercial entity, position, years... If none, please say “None”:

None

8. Consultancies. List specific disclosures in the following format: (1) Commercial or non-profit entity, (2) Commercial or non-profit entity... If none, please say “None”:

None

9. Speakers' bureau. List specific disclosures in the following format: (1) Commercial or non-profit entity, (2) Commercial or non-profit entity... If none, please say “None”:

None

10. Other activities not covered in designations above (if in doubt, provide full disclosure). List specific disclosures in the following format: (1) Commercial or non-profit entity, brief description of activity, (2) Commercial or non-profit entity... If none, please say “None”:

None

11. Some studies have potential for financial gain for the project investigators or the sponsor. The following question seeks to provide transparency regarding any financial benefits to investigators or sponsors.

Do you perform clinical procedures or imaging studies in your practice or unit that overlap with the content of your proposed project, practice parameter, or clinical practice guideline and would your sponsor or this part of your practice or unit benefit if the conclusions were widely followed?
Note: This is the only item in this Agreement that applies to an interest that is related specifically to this particular study, practice parameter, or clinical practice guideline.

List specific disclosures in the following format: (1) Name of Practice or Research Unit, Clinical procedure/imaging study, % of effort (e.g. 35%), year(s), (2) Name of Practice or Research Unit, Clinical procedure/imaging study, % of effort (e.g., 35%)... If none, please say “None”:

None

RESEARCH SUPPORT
Within the past two years and during the course of the study under consideration if the study exceeded two years, I or one of my "immediate family members" received financial or material research support or compensation from the following:

All support received during the past two years regardless of the relationship to the study must be disclosed; for the period exceeding two years, only support relevant to the topic of the study needs to be disclosed.

12. Commercial entities. List specific disclosures in the following format: (1) Commercial entity, (2) Commercial entity... If none, please say “None”:

None

13. Government entities. List specific disclosures in the following format: (1) Sponsor/funding source, grant number(s), role, year(s), (2) Sponsor/funding source... If none, please say “None”:

NINDS-sponsored R25NS065743-05
Child Health Research Career Development Award 4K12HD027748-24

14. Academic entities other than those attributed in the manuscript. List specific disclosures in the following format: (1) Academic entity, (2) Academic entity... If none, please say “None”:

None

15. Foundations or societies (include grant number if required by funding agency). List specific disclosures in the following format: (1) Full name of Foundation or Society, (2) Full name of Foundation or Society... If none, please say “None”:

Aiming for a Cure Grant

STOCK, STOCK OPTIONS & ROYALTIES

In the past two years and during the course of the study under consideration if the study exceeded two years, I or one of my "immediate family members":

All revenues during the past two years regardless of the relationship to the study must be disclosed; for the period exceeding two years, only revenues relevant to the topic of the study needs to be disclosed.

16. Stock or stock options or expense compensation for serving on a board of directors. List disclosures in the following format: (1) Commercial entity, (2) Commercial entity... If none, please say “None”:

None

17. License fee payments. List specific disclosures in the following format: (1) Invention/technology, source of payment, (2) Invention/technology... If none, please say “None”:

None

18. Royalty payments or have contractual rights for receipt of future royalty payments from technology or inventions (this does not include royalties from publishing). List specific disclosures in the following format: (1) Technology/invention, source of payment, year(s), (2) Technology/invention... If none, please say “None”:

None

19. Stock or stock options in a commercial entity sponsoring research with which the author or "immediate family member" was involved as an investigator (Excludes investments in mutual funds held by the author or dependents). List specific disclosures in the following format: (1) Company, year(s), (2) Company, year... If none, please say “None”:

None

20. Stock or stock options in a commercial entity whose medical equipment or other materials related to the practice of medicine. (Exclude investments in mutual funds held by the author or dependents). List specific disclosures in the following format: (1) Company, year(s), (2) Company, year... If none, please say “None”:

None

LEGAL PROCEEDINGS

In the past two years and during the course of the study under consideration if the study exceeded two years, I or one of my "immediate family members" have (whether or not it pertains to the topic of the current study):

All compensation received during the past two years regardless of the relationship to the study must be disclosed; for the period exceeding two years, only compensation relevant to the topic of the study needs to be disclosed.

21. Given expert testimony, acted as a witness or consultant, or prepared an affidavit for any legal proceeding involving a commercial entity (do not include proceedings for individual patients). You may specify role, e.g., 'expert witness for plaintiff' if desired. (Include year only if activity is directly related to the present study.)

List specific disclosures in the following format: (1) Commercial entity, activity, year(s), (2) Commercial entity, activity, year(s)... If none, please say “None”:

None

OPTIONAL: NONFINANCIAL DISCLOSURE

22. I have chosen to declare one or more non-financial competing interests (e.g., special interest groups you represent or others that may be affected if your paper is published or that could be perceived as biasing the study; the corresponding author should be aware of conflicts of interest that Co-investigators or Contributors may have). Non-financial disclosures will not be published.

List specific disclosures, if none, please say “None”:

None

☑ I have completed this Disclosure Statement fully and to the best of my ability. I understand that all Applicants must complete this Disclosure Statement and that the information disclosed may be published if their project is accepted for crowdfunding.

By my electronic signature, I verify the completeness and accuracy of the contents of this form.

Click in the box above to add your electronic signature

03/18/2017

Date [MM/DD/YYYY]

ABF Full Application

Applicant Information

Prefix

First Name

Ania

Last Name

Busza

Suffix

Title

Dr.

Institution Name

University of Rochester Medical School

E-mail

Ania_Busza@urmc.rochester.edu

Office Phone

508-275-2530

Office Fax

Project Details

Project Title

A Surface EMG controlled Mixed Reality Smart glass for Motor Rehabilitation in Stroke Patients

Project Start Date

July 01, 2017

Project End Date

June 30, 2018

Disease focus

Stroke & Vascular Diseases
  Neurorehabilitation

Specific Disease Focus

neuro-rehabilitation post-stroke

Project Summary/Abstract

Every year over 795,000 people in the US suffer a stroke. Many are left with a permanent disability, such as weakness, vision loss, or language impairments. There is great need for developing more effective neurorehabilitation strategies. This project is a collaboration between a stroke neurologist and a computer scientist to develop a new system for motor rehabilitation in stroke patients with severe arm weakness.
We will build a system where patients with arm weakness from stroke will be able to control movements of a virtual arm. The virtual arm will

be displayed on a mixed reality interface (the Microsoft HoloLens -- a headset which presents holographic images over the user's field of view). The movement of the virtual arm will be controlled by electrical signals from arm muscles (measured by surface electromyography, or sEMG, which can detect weak muscle contractions even in patients who cannot lift their arm antigravity). We will develop the initial prototype using sEMG signals from healthy subjects, and then test and calibrate the system on stroke patients with arm weakness. An exercise paradigm will be developed in which patients repetitively activating their paretic arm muscles to move the virtual arm. We will then run a pilot study evaluating our system in patients with recent stroke, to obtain preliminary data for a future large-scale clinical trial. By creating a virtual arm interface with visual feedback, this device will encourage muscle activation, stimulate motor imagery, and potentially boost recovery in stroke patients with severe arm weakness.

Project Narrative

Our goal is to create a patient/virtual reality interface where muscle contractions performed by the subject/wearer are translated into movements of a virtual limb, which can be used for rehabilitation training. The system is personalized to the patient such that only muscle contraction intensities at the upper limit of their current ability activate movement of the virtual limb. It provides real-time feedback to the patient to indicate their progress, and has potential to being used in the context of a video game, to boost motivation and increase time spent in rehab exercises. Finally, it will be available to patients in the inpatient and rehabilitation settings to start an intensive rehabilitation regiment as early as possible.

Why our proposed system may be more effective than current rehabilitation techniques: Studies on neuroplasticity suggest that effective rehab strategies involve multiple repetitions of goal-directed movements. Patient recovery seems to improve when they practice more frequently, earlier, when the difficulty matches their level of weakness, and when they are more motivated. Motor imagery (imagining performing movements with the affected limb) also appears to facilitate recovery. Our surface EMG / HoloLens virtual arm system brings all of these features together. It provides the patient opportunity for frequent exercise early after their stroke, calibrated to their current level of weakness. The virtual arm movements triggered by weak muscle contractions will provide visual imagery of full arm movements, similar to motor imagery techniques. Finally, the virtual reality interface can be adapted with games to boost interest and motivation.

Facilities and Equipment

Facilities: The University of Rochester Medical Center is a large medical center with active stroke service (seeing approximately 900 acute patients each year), and in-house affiliated acute rehabilitation center with a large rehabilitation gym. There is ample space to provide inpatient and in-rehab assessments, as well as to provide locations to participate in therapy.

Equipment: We are seeking funding for the key components of the project, including the Microsoft Hololens and a surface EMG system.
Personnel: Dr Busza currently has funding for having 80% protected research time at least through December 2017 (the first 6 months of the grant) from support as an Experimental Therapeutics Fellow (NIH T32 NS 07388-11 Experimental Therapeutics of Neurological Disorders, R.C. Griggs, PI)

Specific Aims

SPECIFIC AIM 1: To develop a surface-EMG controlled Virtual Arm (sEMG-VA) in which movement of a virtual model arm is controlled by real-time surface EMG signals. We will focus on wrist flexion/extension of the model arm in our first prototype.
SPECIFIC AIM 2: To develop a method of rapidly calibrating the sEMG-VA system such that it can be adapted to sEMG signals from muscles of varying strength. This will be critical in making the system effective for patients with different levels weakness and through several phases of recovery.
SPECIFIC AIM 3: To assess the feasibility of using the sEMG-VA system on stroke patients in the inpatient and acute rehab setting. This preliminary study will provide information on tolerability, participation rates, and logistical challenges - all essential for proper design of a future larger clinical trial for efficacy.

Research Strategy

Significance, Innovation, Approach, Timeline

Over 75 % of stroke patients have arm or hand weakness at presentation. While many regain use of the extremity during the recovery period, 30-66% of patients have some persistent weakness, impairing their ability to do everyday activities. For patients with mild to moderate weakness, several rehabilitation strategies have been found to be effective, including Constraint Induced Motor Therapy (temporarily constraining the contralateral limb to force increased use of the paretic arm)(Wolf et al., 2006) and the MIT-Manus/InMotion robotic arm (a robotic device that facilitates repetitive practice while adapting to the patient's strength)(Volpe et al., 2000). For more severe weakness, i.e. when the patient cannot lift the limb antigravity, evidence-based therapies are limited. One reason for this may be because it is hard to motivate patients with little-to-no movement. A strategy to overcome the lack of positive feedback is Biofeedback, where patients receive information about the relative intensity of their muscle contractions. Another promising therapy is Motor Imagery, where patients spend time imagining the paretic limb performing specific movements (Reviewed in Carrasco et al., 2016). The goal of this project is to create a device that harnesses the positive effects of both biofeedback and motor imagery by providing real-time feedback to patients in the form of movement of a virtual arm. We hypothesize that such a device will be more effective than current rehabilitation standard of care treatments.
Approach:

AIM 1: For our initial device prototype, we will develop a sEMG-VA system where movement is limited to wrist flexion and extension. This is because (1) we want to focus on optimizing a simpler system for our initial proof-of-concept and because (2) small amounts of wrist flexion/ extension in patients with arm weakness can have significant impact on the patient's ability to function and on quality of life.
The sEMG-VA will be comprised of 3 components:
1. EMG machine -- a system with superficial skin electrodes, which feeds information about surface EMG signals into an amplifier and then to a PC for signal recording/analysis.
2. Computer -- On the PC, signals are processed by a data capture and analysis software. The raw EMG signals will be processed in real-time to produce a value corresponding to relative amount of muscle contraction for each muscle group. This value is then exported to the HoloLens.
3. Microsoft HoloLens -- The HoloLens is a head-mounted display device that consists of see-through holographic lenses that can display holograms over the view of the real world. By using the 3D modeling software, an image of an arm is projected in front of the user. The model's position will be continuously updated based on data received from the PC, and the wearer will see wrist flexion or extension in response to their efforts.
AIM 2: For the initial proof-of-concept (Aim 1), sEMG signals from healthy individuals will be used to develop the initial device. In the second phase, we will further develop the system so that it is optimized for a wide range of individual users. This is critical for developing a system that can be used for rehabilitation, as patients differ in their strength and relative amount of muscle contractions/sEMG signal. Tracking each patient's strength/muscle activation will help determine improvement during the first few weeks after the stroke. To enable this, we will develop a method by which the maximum contraction of each muscle group is measured for each patient each day. The system will be calibrated such that only contractions of 70% or more of the maximum intensity can cause movement of the virtual arm. We will evaluate our algorithm on patients with different amounts of weakness to make sure that we can rapidly calibrate the device before each rehabilitation session.
AIM 3: In this final phase, we will perform a preliminary study looking at the feasibility of using this system in the acute / subacute stroke period (i.e. the first month after the stroke). Patients with moderate to severe arm weakness due to a stroke within the past week will be enrolled, and will participate in 30 minutes of sEMG-VA rehab for each day while admitted to our inpatient service or acute rehabilitation facility (up to 3 weeks). The responsiveness of the system, ease of use, and tolerability of the HoloLens will be assessed, and the patients will give feedback about their experience. The information gained during this phase will be used to design larger trials to examine efficacy.
This project is a collaboration between a leading expert at understanding human factors when designing computer technologies (Professor M.

Ehsan Hoque) and a stroke neurologist with extensive training in clinical trial design/implementation (Dr. Ania Busza). The University of Rochester, with its cutting-edge engineering programs, and long history of leadership in clinical trials, is an ideal place for translating evolving technologies into the development of new rehabilitation therapeutics.

List up to 5 milestones you will reach within the first 6 months of your study.

1. Prototype development -- we will develop the first prototype of our device, where surface EMG (sEMG) signals from the forearms of healthy volunteers will be able to control the wrist flexion/extension of a virtual arm displayed by the HoloLens
2. Device calibration -- we will develop an algorithm by which the device can be calibrated to each individual user, based off of the relative strength of each muscle group (such as wrist-extensors or wrist-flexors) for each day.
3. Preliminary feasibility/tolerability assessments-- We will start our preliminary trial looking at the feasibility of using the sEMG-VA device on acute/subacute patients during the first 3 weeks after their stroke.

Age of Population Group(s) that will potentially benefit from this research

(check boxes that apply)

All Ages
Seniors (65+)

Scientific Literature References

Reference 1

García Carrasco, D. & Aboitiz Cantalapiedra, J. Effectiveness of motor imagery or mental practice in functional recovery after stroke: a systematic review. Neurol. (English Ed. 31, 43--52 (2016).

Reference 2

Jiang, N., Falla, D., d'Avella, A., Graimann, B. & Farina, D. Myoelectric control in neurorehabilitation. Crit. Rev. Biomed. Eng. 38, 381--391 (2010).

Reference 3

Volpe, B. T. et al. A novel approach to stroke rehabilitation: robot-aided sensorimotor stimulation. Neurology 54, 1938--1944 (2000).

Reference 4

Wolf, S. L. et al. Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: the EXCITE randomized clinical trial. JAMA 296, 2095--2104 (2006).

Reference 5

Reference 6

Reference 7

Reference 8

Reference 9

Reference 10

Budget, Attachments and Acknowledgements

Budget
We recognize that changes may have occurred since the time you submitted your Letter of Intent. Please share the most recent accurate numbers below:

Total Project Budget

52900

Total existing funding or in-kind support

0

Amount to be raised through crowdfunding campaign

52900

Evidence of institutional support (letter)

Full budget

Documentation of IRB/IUCAC approval or exemption, if applicable.

Completed conflict of interest & disclosure form

I understand that the ABF will not list approved projects for general public crowdfunding campaigns until documentation of IRB/IUCAC approval or exemption is provided.

Yes

I understand that approval of the project to be shared on the crowdfunding campaign site is dependent on providing and working with the ABF staff to create the requisite materials that present the project in an engaging, easy-to-understand website presentation. I am amenable to working with the ABF staff to create such materials.

Yes

I understand that approval once a project has been completed, I will be required to submit a summary of my findings to be posted online (one page), and will submit this in a reasonably timely fashion. I also agree to submit a financial report, and to co-sign a thank you letter with the ABF that will be sent to donors.

Yes

I understand and agree that the ABF may share the information that I provide (including but not limited to the project description and relevant biographical/background details) in conversations with other potential funders outside the website to bolster fundraising efforts.

Yes

American Brain Foundation Release Agreement

American Brain Foundation
Release Agreement – Research

1. **Grant**. For good and valuable consideration, the receipt and sufficiency of which is hereby acknowledged, I grant to the

   American Brain Foundation ("ABF") and to the ABF's affiliates (including the American Academy of Neurology), and their respective contractors, agents, assigns, licensees, and successors (collectively, the "ABF Group"), a worldwide, royalty-free, perpetual, irrevocable right to take and use my image, likeness, voice, verbal statements, written testimonials and name and all images, videos, sound recordings, and written and verbal materials that I provide to the ABF (collectively, the "Materials "), in all forms and media, including composite or modified representations, for the purpose of promoting and supporting the missions of the ABF. For the avoidance of doubt, the Materials include all research project proposal information, project reports and other research-related information submitted to the ABF. I understand and agree that the ABF may publish the Materials on any and all media, including printed matter, promotional materials, e-mail, websites and social media platforms.
2. **Acknowledgement of Use**. I understand that the ABF Group may use the Materials on any and all media, including printed matter, promotional materials, e-mail, websites and social media platforms. I understand that the ABF's use of the Materials may intentionally or unintentionally give rise to the impression that either I or a family member suffers from brain/neurologic disease, and I nevertheless consent to this use. The ABF is not obligated to utilize any of the rights granted in this agreement. I waive the right to inspect or approve any uses of the Materials in connection with this grant.
3. **Warranty**. I warrant that I have the full power to enter into this agreement and to grant the aforementioned rights.
4. **Release**. I release the ABF Group from all liability for any claims that may arise regarding the use of Materials, including any claims of defamation, invasion of privacy, or infringement of moral rights, rights of publicity, or copyright. The ABF is permitted, although not obligated, to include my name as a credit in connection with any use of the Materials.**I have read and understood this agreement, I understand that it contains a release of liability, and I am over the age of 18**. This agreement expresses the complete understanding of the parties and shall be binding on me and my heirs, legal representatives and assigns. I understand that I am entering into a legally binding agreement and that clicking "I Accept" below shall have the same legal effect as my signature on this Release Agreement.

I Accept

CURRICULUM VITAE

Ania Busza, M.D., Ph.D.

March 27, 2017

CURRENT APPOINTMENT

Instructor, Department of Neurology
Fellow, Experimental Therapeutics Program
University of Rochester School of Medicine and Dentistry
601 Elmwood Ave., Box 681
Rochester, New York 14642
Phone: (585) 275-2530
Fax: (585) 273-1026
Ania_Busza@urmc.rochester.edu

EDUCATION and POST-GRADUATE TRAINING

2016 - present University of Rochester Medical Center, Rochester, NY
Experimental Therapeutics Fellowship Program, Fellow

2015 University of Rochester Medical Center, Rochester, NY
Vascular Neurology (Stroke) Fellowship Program, Fellow

2011 - 2014 Boston Medical Center, Boston, MA
Neurology Residency Program, Resident

2010 - 2011 Boston Medical Center, Boston, MA
Internal Medicine Residency Program, Intern

2009 – 2010 University of Tübingen Medical School, Tübingen, Germany
Exchange student (clinical rotations) and part-time research associate (Experimental Magnetic Resonance of the CNS Laboratory)

2000 - 2009 University of Massachusetts Medical Center, Worcester, MA
MD/PhD program
PhD Thesis (May 2007): "Molecular and Behavioral Analysis of *Drosophila* Circadian Photoreception and Circadian Thermoreception"
Summer Schools (additional training during PhD):
VISU Summer School: History and Philosophy of the Biomedical Sciences (Vienna, Austria, 2008)
PENS Summer School: Advanced Course in Computational Neuroscience (Arcachon, France, 2013)

1995 - 1999 Massachusetts Institute of Technology, Cambridge, MA
Bachelor of Science in Biology
Bachelor of Science in Brain and Cognitive Sciences

RESEARCH ACTIVITIES

2016 - present Can Transcranial Electrical Stimulation improve Contrast Sensitivity in chronic Stroke Patients with partially recovered Visual Field Deficits?
Sponsor: University of Rochester Department of Neurology Pilot Grant
Funding period: 06/01/2016 – 05/31/2017
Role: Principal Investigator

2015 - present Fluoxetine for Visual Recovery after Ischemic Stroke (FLUORESCE)
Sponsor: The Schmitt Program on Integrative Brain Research
Funding period: 05/11/2015 – 12/31/2016
Principal Investigator: Bogachan Sahin, M.D., Ph.D.
Role: Sub-investigator. Also assisted with trial design and initial IRB submission

2015 - present Safety Evaluation of 3K3A-APC in Ischemic Stroke (RHAPSODY)
Identification number: NCT02222714
Sponsor: ZZ Biotech, LLC
Principal Investigator: Patrick D. Lyden, M.D.
Role: Co-investigator

2015 - present Platelet-oriented Inhibition in New TIA and Minor Ischemic Stroke Trial (POINT)
Identification number: NCT00991029
Sponsor: NINDS/NETT
Principal Investigator: S. Claiborne Johnston, M.D., Ph.D.
Role: Co-investigator

2009 Evaluation and Validation of a novel MRI Diffusion Tensor Imaging (DTI) protocol for automated Segmentation of the Thalamus
Visiting MD/PhD student, *medical student research project*
Mentor: Wolfgang Grodd, Ph.D., University of Tübingen, Germany.
Used Matlab algorithm to analyse MRI Diffusion Tensor Imaging (DTI) data from multiple healthy subjects, and then compared thalamus segmentation results with known thalamic substructures to help validate and improve the imaging algorithm.

2002 – 2007 Behavioral and Molecular analysis of Light and Temperature Input Pathways into the Drosophila Circadian Clock
Graduate student, *Doctoral dissertation*
Mentor: Patrick Emery, Ph.D., University of Massachusetts Medical Center
Used a wide range of techniques including circadian behavior assays and MATLAB analysis, genetic manipulations, insect cell culture techniques, immunoprecipitation, cytoimmunochemistry and biochemical analysis, to study photic and thermal input pathways into the *Drosophila* Circadian Clock.

2001 Calibration of a RT-PCR protocol for laboratory diagnosis of Dengue fever in Caracas, Venezuela
Visiting MD/PhD student, *medical student research project*
Mentor: Irene Bosch, Ph.D., University of Massachusetts Medical Center
Under the supervision of the Center of Disaese Control and Vaccine Research at UMass Medical School, set up a RT-PCR diagnostic protocol for Dengue fever at the Caracas National Blood Bank, Venezuela. Also tested a procedure for isolating circulating endothelial cells in Dengue patient's blood samples.

1997 - 1998 Evaluation of serum fluctuations of cyclic nucleotides and melatonin as potential outputs of the human circadian clock
Undergraduate student, *Senior thesis*
Mentor: Irina Zhdanova, Ph.D., Massachusetts Institute of Technology
Performed radioimmunoassays of circulating cyclic nucleotides and melatonin in an investigation of potential molecular outputs of the human circadian clock in serum.
Bachelor's thesis: The Effect of Posture on Circulating Cyclic Nucleotides in Humans

PUBLICATIONS

Peer-reviewed Original Research Articles

1. Tataroglu O, Zhao X, **Busza A**, Ling J, O'Neill JS, Emery P. Calcium and SOL Protease Mediate Temperature Resetting of Circadian Clocks. *Cell.* 2015; 163(5):1214-24
2. **Busza A**, Cervantes-Arslanian AM, Kase CS. Clinical Reasoning: A 32-year-old woman with right-sided numbness and word-finding difficulties. *Neurology.* 2014; 83:e98-e102
3. Mang SC, **Busza A**, Reiterer S, Grodd W, Klose AU. Thalamus segmentation based on the local diffusion direction: a group study. *Magn Reson Med.* 2012; 67(1):118-26
4. **Busza A**, Murad A, Emery P. Interactions between circadian neurons control temperature synchronization of *Drosophila* behavior. *Journal of Neuroscience* 2007; 27(40):10722-10733
5. **Busza A**, Emery-Le M, Rosbash M, Emery P. Roles of the two Drosophila CRYPTOCHROME structural domains in circadian photoreception. *Science.* 2004; 304(5676):1503-6
6. Zhdanova IV, Simmons M, Marcus JN, **Busza AC**, Leclair OU, Taylor JA. Nocturnal increase in plasma cGMP levels in humans. *Journal of Biological Rhythms.* 1999; 14 (4): 307-13.

Textbook Contributions

1. **Busza A**, Emery P. Circadian Timing Mechanisms in *Drosophila.* In: Fundamental Neuroscience. LR Squire *et al* editors. 3rd ed., Academic Press, 937-939, 2008.

Conferences/Abstract Presentations

1. **American Academy of Neurology 2014 Annual meeting:** co-author on poster presented at 2014 AAN Conference on "Implementing a Checklist into Stroke Patient Discharges: A Resident Driven Quality Improvement Project"
2. **Controversies in Neurology 2013 meeting:** poster and 5 minute oral presentation on "West Nile Virus Encephalitis presenting as acute onset headache with trunk and limb tremor in an urban construction worker"
3. **American Academy of Neurology 2012 Annual meeting**: presented a poster on "Thromboembolic Stroke in a Young Woman with Chagas Cardiomyopathy"
4. **Cold Spring Harbor Neurobiology of Drosophila Conference**: presented a poster on "Characterization of Temperature Entrainment of Circadian rhythms in *Drosophila*."
5. **Society for Research on Biological Rhythms 9th Annual Meeting**: Seminar oral presentation on "*Drosophila* CRYPTOCHROME: Photoreception Mechanisms and Unexpected Roles of Its Two Structural Domain."
6. **Cold Spring Harbor Neurobiology of Drosophila Conference:** presented a poster on "*Drosophila* CRYPTOCHROME: Light-Dependent Interactions and role of the C-terminal Domain in Circadian Photoreception."

EDUCATIONAL ACTIVITIES

Teaching

Classroom Instruction

2016 - present Lecturer, Psychiatry Resident Noon Conference
University of Rochester School of Medicine and Dentistry
"Stroke and Psychiatric Disorders"

2016 - present Lecturer, Neurology Resident Noon Conference
University of Rochester School of Medicine and Dentistry
"Cerebral Sinus Venous Thrombosis"
"Reversible Cerebral Vasoconstriction Syndrome"

2016 - present Lecturer, Internal Medicine Resident Noon Conference
Arnot Ogden Medical Center, Elmira, New York
"Secondary Stroke Prevention"

Clinical Instruction

2016 - present Instructor/ examiner, Neurology resident clinical skills evaluation
University of Rochester School of Medicine and Dentistry

2016 - present Instructor/ examiner, Medical student clinical skills evaluation
University of Rochester School of Medicine and Dentistry

CME Instruction

2016 Lecturer, University of Rochester Neuroscience CME, Batavia, New York
"Secondary Stroke Prevention"

2016 Lecturer, Cayuga Medical Center Grand Rounds, Cayuga, New York
"Secondary Stroke Prevention"

2016 Lecturer, University of Rochester Neuroscience CME, Auburn, New York
"Secondary Stroke Prevention"

2016 Lecturer, Stroke Treatment Alliance of Rochester
5th Annual Regional Stroke Management Symposium, Rochester, New York
"Secondary Stroke Prevention"

2015 Lecturer, Department of Neurology Grand Rounds, Rochester, New York
"Stroke Unit Update – Update on Endovascular Trials"

2014 Lecturer, Boston Medical Center Grand Rounds, Boston, MA
"Systems Engineering and how it can help us provide better care for our patients"

2013 Lecturer, Boston Medical Center Grand Rounds, Boston, MA
"Morbidity and Mortality"

Community Educational Outreach

2016 Lecturer, University of Rochester's Physical Plant employee health information noontime series, Rochester, New York
"Stroke: causes, symptoms, and what to do if someone you know may be having one"

2015 Lecturer, Patient education seminar series, Jones Memorial Hospital, Wellsville, New York
"Stroke: causes, symptoms, and what to do if someone you know may be having one"

COURSES

2015 Introduction to Biostatistics, University of Rochester School of Medicine and Dentistry
2016 Design of Clinical Trials, University of Rochester School of Medicine and Dentistry
2016 Ethics and Professional Integrity, University of Rochester School of Medicine and Dentistry
2016 Experimental Therapeutics, University of Rochester School of Medicine and Dentistry
2017 NeuroNEXT Principal Investigator Training Course (one-day course after the annual meeting of the NeuroNEXT clinical trial network, Dallas TX)

CLINICAL ACTIVITIES

Certification

Medical Licensure
New York State License
License number 276162

Board Certification
American Board of Psychiatry & Neurology, Diplomate in Neurology since 2014
Certificate number 58612
American Board of Psychiatry & Neurology, Diplomate in Vascular Neurology since 2016
Certificate number 1386

ADMINISTRATIVE ACTIVITIES

2016 - present Organizer, Working Group in Clinical Research bi-monthly seminar series
University of Rochester School of Medicine and Dentistry

2016 - present Organizer, Mellow Fellows in Experimental Therapeutics bi-monthly seminar series
University of Rochester School of Medicine and Dentistry

2015 Revised institutional guidelines for clinical approach to Intracerebral Hemorrhage, University of Rochester Medical Center

AWARDS and HONORS

2016-present: Experimental Therapeutics in Neurological Disease Fellow (NIH NRSA 2T32NS007338-16, Robert Griggs, PI), University of Rochester
2005-2009 NIH Kirschstein-NRSA Fellowship award (NINDS F30 NS054421-04, role: Principal Investigator), University of Massachusetts Medical School
2003-2005 NIH Cellular and Molecular Neurobiology training grant for Department of Neuroscience (recipient student), University of Massachusetts Medical School

AWARDS and HONORS (cont.)

2002 Pathways International Program Scholarship (full funding for summer research program), University of Massachusetts Medical School)
2002 Student Leadership Award, University of Massachusetts Medical School
1998 MIT Burchard Humanities Scholar, Massachusetts Institute of Technology
1997 MIT Art Scholar, Massachusetts Institute of Technology
1995 Society of Women Engineers Award

PROFESSIONAL SOCIETIES

American Academy of Neurology
American Stroke Association/American Heart Association

LEADERSHIP POSITIONS

2013-2014: Resident Committee for Quality Improvement member, Boston Medical Center
2003-2005: Graduate School/Medical School Student Liaison, UMass Medical School
2001-2002: President of International Medicine student interest group, UMass Medical School
2001-2002: President of Physicians for Human Rights student group, UMass Medical School
2001-2002: President of QMass student group, UMass Medical School
1995-1999: Shakespeare Ensemble (university theater group), M.I.T.
1998: President of the Woman's Independent Living Group, M.I.T.

LANGUAGES/VOLUNTEERING/EXTRACURRICULAR INTERESTS

Languages	English (native), Polish (fluent), French (conversational), German (conversational), Spanish (sufficient for basic medical history and exam)
Volunteering	2000: 9 months teaching English in an orphanage for children 5-18 years old, Krakow, Poland 1995-1999: Weekly volunteering and co-director (1998-1999) of a student telephone mental health/counselling hotline at M.I.T. 1998: Weekly volunteering in a hospital hospice.

Review - (415) Full Application Review	
Review	
Acceptance Due Date	
Due Date	
Visible From	
Visible To	
Request	
Name (Full)	Dr. Adam Mecca
Organization Name	Yale Unversity
Type	Other Research Projects
Project Budget	$145,080.00
Exisiting Funding / In-Kind Support	$76,080.00
Requested Amount	$69,000.00
Project Title	Investigation of molecular changes in mGluR5 and SV2A to study synaptic alteration in Alzheimer's disease using PET
General focus	Alzheimer’s & Dementia
Specific Disease Focus	Alzheimer's Disease Neurobiology
Project Description	Project Description Alzheimer's disease (AD) is a common and progressive illness that leads to impaired memory and thinking, impaired ability to function independently, and profound societal costs. This proposal seeks to expand the understanding of AD pathophysiology with the ultimate goals of enhancing care by ensuring timely/accurate diagnosis, as well as preventing and effectively treating this disease. AD afflicts over 5 million people in the US and no current therapy modifies its course. Positron Emission Tomography (PET) imaging has been successfully employed to investigate changes in living humans at the molecular level, aiding in the diagnosis and understanding of AD. Therefore, the neurobiology of AD can be studied in vivo with multi-tracer neuroimaging and neuropsychological characterization. Molecular changes at the synaptic level have been shown to be associated with AD, but the majority of molecular and synaptic investigations are performed in humans after death or in animal models. Metabotropic glutamate receptor subtype 5 (mGluR5) is present at synapses throughout the cortex and is a mediator of amyloid beta induced AD pathology. Therefore, mGluR5 is a candidate biomarker for AD and a target for therapeutic intervention, making its detection an important goal. Furthermore, synaptic vesicle glycoprotein 2A (SV2A) is a pre-synaptic protein with potential as the first in vivo marker of synaptic density. Since synaptic loss is observed in the earliest stages of AD, SV2A binding stands to be a robust marker of disease progression. The objective of this proposal is to apply PET methods to understand the neurobiological changes associated with AD using [18F]FPEB, a specific ligand for mGluR5, and [11C]UCB-J, a specific ligand for SV2A (synaptic density). This is likely to have a significant impact by (i) determining the changes in

	mGluR5 receptor availability that occur during AD, (ii) determining the changes in synaptic density that are detectible during AD, and (iii) understanding the relationship between changes in mGluR5 receptor availability and synaptic density. These investigations will provide valuable understanding of the AD disease process and lead to the development of both novel treatments and therapeutic biomarkers.
Specific Aims	To address the existing gaps in current knowledge of the pathophysiology of synaptic- and receptor-level changes in AD, the following aims are proposed: AIM 1. Investigate mGluR5 binding as a biomarker of AD. Utilizing PET and the radiotracers [18F]FPEB for mGluR5 and [11C]PiB for amyloid, mGluR5 binding will be quantified in a group of amyloid-positive individuals with clinical AD (MCI or dementia) compared to a healthy control (HC) group of amyloid-negative individuals with normal cognition (n = 20 per group). AIM 2. Investigate SV2A binding as a biomarker of synaptic density in AD. Utilizing PET and the radiotracers [11C]UCB-J and [11C]PiB, synaptic density will be quantified in a group of individuals with clinical AD (MCI or dementia) compared to a HC group of individuals with normal cognition (n = 20 per group). AIM 3. Investigate group and individual differences in mGluR5 binding in relation to synaptic density. Utilizing the data from the above aims, mGluR5 binding and SV2A density will be quantified and compared in a group of AD (n =20) and HC (n = 20) participants. The central hypothesis is that mGluR5 and SV2A density will be reduced in AD with differing deficits in regional distribution and density between markers. This study is innovative because it explores the neurochemistry of AD in vivo in humans using two novel PET radiotracers. These investigations will provide valuable information that will contribute to the understanding of an ongoing disease process and lead to the development of both novel treatments and therapeutic biomarkers.
Milestones	1. Enroll 10 participants (5 HC and 5 AD) and complete the screening visit. 2. Complete [11C]PiB scan for 6 participants (3 HC and 3 AD). 3. Complete [18F]FPEB scan for 6 participants (3 HC and 3 AD). 4. Complete [11C]UCB-J scan for 6 participants (3 HC and 3 AD). 5. Complete neuropsychiatric testing visit for 6 participants (3 HC and 3 AD). 6. Refine analysis stream for regional and voxel-based analyses.
Feedback	
Yes/No	Undecided
Review Long Notes	

Dear Applicant:

In the increasingly complex world of scientific publication, concerns about commercial influence and other possible conflicts make it important for authors to disclose all potential sources of bias. Our system of reviewing conflicts of interest aligns with the policies of the American Academy of Neurology and allows donors to judge whether conflicts exist. Please complete this form, referring to the definitions in the beginning regarding commercial entities, compensation, expert witness, and "immediate family member." At first glance, this task may seem onerous, but will likely take less than 10 minutes.

What to expect: You will be asked whether you have disclosures relating to each question (check yes or no) and will be provided a field in which to list the disclosures. Filling out the forms on the next few screens will be easiest if you have a list of the following items regarding your activity (either commercial or non-profit) and that of any immediate family members during the period of your project. Disclosures are required for any dollar amount, except for gifts valued under $1000. Names of commercial and non-profit entities are required along with specific roles, grant numbers for grants, and specific years. No dollar amounts need to be included. Please indicate complete names of sponsors or companies.

DEFINITIONS

Personal compensation:
Serving on a scientific advisory board
Gifts worth more than $1000
Travel funded by a commercial entity
Serving as a journal editor, associate editor, or on an editorial advisory board
Patents held or pending
Royalties from publishing
Honoraria for speaking engagements
Corporate appointments or consultancies
Speakers' bureaus
Clinical, neurophysiology, or imaging studies in your practice and % effort devoted if the result of this paper will benefit your practice, affiliated unit, or a sponsor

Research support:
Commercial research support
Government research support (including funding organization, grant number, and role)
Academic research support not attributed in the manuscript
Support from a non-profit foundation or society
Stock options for serving on a Board of Directors
License fee payments
Royalty payments from technology or inventions

Stocks, stock options, and royalties
Stock options in a company in which you are (were) an investigator
Stock options in medical industry

Legal proceedings
Expert testimony for a legal proceeding on behalf of industry
Affidavit for a legal proceeding on behalf of industry
Witness or consultant for a legal proceeding on behalf of industry

Optional non-financial
Non-financial disclosures you wish to share

Definitions of Terms in Disclosure Agreement
Commercial entity: A for-profit business that manufactures, distributes, markets, sells, or advertises pharmaceutical or scientific products or medical devices.
Compensation: Anything of monetary value including a salary, honorarium, stipend, gift, or payment of travel-related expenses.
Expert witness: A person who has provided expert medical testimony during a trial or administrative hearing, in a deposition or an affidavit, or in any other type of legal proceeding.
"Immediate family member": Any person who would benefit financially from the publication of the manuscript because of their relationship to the author. This includes a member of an applicant's immediate family or anyone else who has a significant relationship with the applicant.

Please provide all financial relationships (and those of your "immediate family members") from the past two years regardless of whether these relationships are related to the project described in your application.

FINANCIAL DISCLOSURE
Personal Compensation from Commercial and Non-Profit Entities that benefits you directly or indirectly. Within the past two years (and during the course of the study under consideration if the study exceeded two years), I or one of my "immediate family members" received personal compensation for the following:

All compensation received during the past two years regardless of the relationship to your project must be disclosed; for the period exceeding two years, only compensation relevant to the topic of the study needs to be disclosed.

1. Serving on a scientific advisory board or data safety monitoring board. List specific disclosures in the following format: (1) Commercial or non-profit entity (2) Commercial or non-profit entity... If none, please say "None":

None

2. Gifts (other than travel or compensation for consulting or for educational efforts) worth more than USD $1000. List specific disclosures in the following format: (1) Commercial or non-profit entity, brief description of gift, (2) Commercial or non-profit entity, brief description of gift... If none, please say "None":

None

3. Funding for travel or speaker honoraria to the individual from a commercial or non-profit entity not included in the study funding [Exclude CME activities and Grand Rounds]. List specific disclosures in the following format: (1) Commercial or non-profit entity, type of payment, (2) Commercial or non-profit entity, type of payment... If none, please say “None”:

None

4. Serving as a journal editor, an associate editor, or editorial advisory board member. This may include a journal published by your national medical/scientific organization. Please include regardless of whether you receive compensation. List specific disclosures in the following format: (1) Full journal name, role, year(s), (2) Full journal name... If none, please say “None”:

None

5. Patents issued or pending. List specific disclosures in the following format: (1) Brief description of invention/technology, (2) Brief description of invention/technology... If none, please say “None”:

None

6. Publishing Royalties (do not include honoraria for occasional writing). List specific disclosures in the following format: (1) Full title of work, full name of publisher, year(s) of publication (or receipt of royalties), (2) Full title of work... If none, please say “None”:

None

7. Employment. If you are currently employed by a commercial entity, please disclose below. In addition, if your past employment at a commercial entity is directly related to this manuscript, please disclose below. List specific disclosures in the following format: (1) Commercial entity, position, years (2) Commercial entity, position, years... If none, please say “None”:

None

8. Consultancies. List specific disclosures in the following format: (1) Commercial or non-profit entity, (2) Commercial or non-profit entity... If none, please say “None”:

None

9. Speakers' bureau. List specific disclosures in the following format: (1) Commercial or non-profit entity, (2) Commercial or non-profit entity... If none, please say “None”:

None

10. Other activities not covered in designations above (if in doubt, provide full disclosure). List specific disclosures in the following format: (1) Commercial or non-profit entity, brief description of activity, (2) Commercial or non-profit entity... If none, please say “None”:

None

11. Some studies have potential for financial gain for the project investigators or the sponsor. The following question seeks to provide transparency regarding any financial benefits to investigators or sponsors.

Do you perform clinical procedures or imaging studies in your practice or unit that overlap with the content of your proposed project, practice parameter, or clinical practice guideline and would your sponsor or this part of your practice or unit benefit if the conclusions were widely followed?
Note: This is the only item in this Agreement that applies to an interest that is related specifically to this particular study, practice parameter, or clinical practice guideline.

List specific disclosures in the following format: (1) Name of Practice or Research Unit, Clinical procedure/imaging study, % of effort (e.g. 35%), year(s), (2) Name of Practice or Research Unit, Clinical procedure/imaging study, % of effort (e.g., 35%)... If none, please say “None”:

None

RESEARCH SUPPORT
Within the past two years and during the course of the study under consideration if the study exceeded two years, I or one of my "immediate family members" received financial or material research support or compensation from the following:

All support received during the past two years regardless of the relationship to the study must be disclosed; for the period exceeding two years, only support relevant to the topic of the study needs to be disclosed.

12. Commercial entities. List specific disclosures in the following format: (1) Commercial entity, (2) Commercial entity... If none, please say “None”:

None

13. Government entities. List specific disclosures in the following format: (1) Sponsor/funding source, grant number(s), role, year(s), (2) Sponsor/funding source... If none, please say “None”:

NINDS-sponsored R25NS065743-05
Child Health Research Career Development Award 4K12HD027748-24

14. Academic entities other than those attributed in the manuscript. List specific disclosures in the following format: (1) Academic entity, (2) Academic entity... If none, please say “None”:

None

15. Foundations or societies (include grant number if required by funding agency). List specific disclosures in the following format: (1) Full name of Foundation or Society, (2) Full name of Foundation or Society... If none, please say “None”:

Aiming for a Cure Grant

STOCK, STOCK OPTIONS & ROYALTIES

In the past two years and during the course of the study under consideration if the study exceeded two years, I or one of my "immediate family members":

All revenues during the past two years regardless of the relationship to the study must be disclosed; for the period exceeding two years, only revenues relevant to the topic of the study needs to be disclosed.

16. Stock or stock options or expense compensation for serving on a board of directors. List disclosures in the following format: (1) Commercial entity, (2) Commercial entity... If none, please say “None”:

None

17. License fee payments. List specific disclosures in the following format: (1) Invention/technology, source of payment, (2) Invention/technology... If none, please say “None”:

None

18. Royalty payments or have contractual rights for receipt of future royalty payments from technology or inventions (this does not include royalties from publishing). List specific disclosures in the following format: (1) Technology/invention, source of payment, year(s), (2) Technology/invention... If none, please say “None”:

None

19. Stock or stock options in a commercial entity sponsoring research with which the author or "immediate family member" was involved as an investigator (Excludes investments in mutual funds held by the author or dependents). List specific disclosures in the following format: (1) Company, year(s), (2) Company, year... If none, please say “None”:

None

20. Stock or stock options in a commercial entity whose medical equipment or other materials related to the practice of medicine. (Exclude investments in mutual funds held by the author or dependents). List specific disclosures in the following format: (1) Company, year(s), (2) Company, year... If none, please say “None”:

None

LEGAL PROCEEDINGS

In the past two years and during the course of the study under consideration if the study exceeded two years, I or one of my "immediate family members" have (whether or not it pertains to the topic of the current study):

All compensation received during the past two years regardless of the relationship to the study must be disclosed; for the period exceeding two years, only compensation relevant to the topic of the study needs to be disclosed.

21. Given expert testimony, acted as a witness or consultant, or prepared an affidavit for any legal proceeding involving a commercial entity (do not include proceedings for individual patients). You may specify role, e.g., 'expert witness for plaintiff' if desired. (Include year only if activity is directly related to the present study.)

List specific disclosures in the following format: (1) Commercial entity, activity, year(s), (2) Commercial entity, activity, year(s)... If none, please say “None”:

None

OPTIONAL: NONFINANCIAL DISCLOSURE

22. I have chosen to declare one or more non-financial competing interests (e.g., special interest groups you represent or others that may be affected if your paper is published or that could be perceived as biasing the study; the corresponding author should be aware of conflicts of interest that Co-investigators or Contributors may have). Non-financial disclosures will not be published.

List specific disclosures, if none, please say “None”:

None

☑ I have completed this Disclosure Statement fully and to the best of my ability. I understand that all Applicants must complete this Disclosure Statement and that the information disclosed may be published if their project is accepted for crowdfunding.

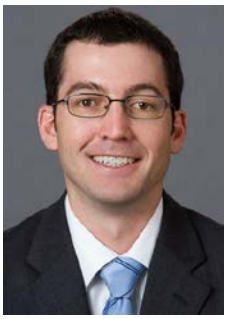
By my electronic signature, I verify the completeness and accuracy of the contents of this form.

Click in the box above to add your electronic signature

03/18/2017

Date [MM/DD/YYYY]

CURRICULUM VITAE



Adam P. Mecca, M.D., Ph.D.

Contact Information

Yale School of Medicine
Alzheimer's Disease Research Unit
One Church Street, 8th Floor
New Haven, CT 06510
Phone: (203)764-8100
E-Mail: adam.mecca@yale.edu

Education/Training

2016 – Present Yale School of Medicine Department of Psychiatry
Geriatric Psychiatry Fellow
Alzheimer's Disease Research Unit, Clinical Research Fellow

2012 – 2016 Yale School of Medicine, Department of Psychiatry
Adult Psychiatry Resident
Neuroscience Research Training Program (2012-2016)
Alzheimer's Disease Research Unit, Chief Resident (2016)

2005 – 2012 University of Florida College of Medicine, M.D. - Ph.D. Program
Graduation with honors in Academic Excellence, Research, and Special Achievement
Dissertation Research: Targeting the ACE2/Ang-(1-7)/Mas Axis for Cerebroprotection during Ischemic Stroke
Mentors: Colin Sumners Ph.D. and Michael J. Katovich, Ph.D.

2001 – 2005 University of Florida – B.S., Highest Honors
Double Major: Chemistry, Microbiology and Cell Science

Honors

2015 American Association for Geriatric Psychiatry Honors Scholar
2014 NIMH Outstanding Resident Award
2014 American Psychiatric Association - Janssen Research Scholars Award
2014 AGS Annual Meeting – Case Studies Poster Presentation Honorable Mention
2012 Dr. Peter Regan Award in Psychiatry – University of Florida
2011 Experimental Physiology Early Career Author Prize
2011 Hazel Donegan Scholarship Award
2010 UF Medical Guild Graduate Student Research Competition, Silver Medal
2010 Florida American Legion Medical Scholarship, Runner-up
2009 Florida Medical Association Foundation Medical Student Scholarship
2009 American Medical Association Foundation Seed Grant

2009	Bryan Robinson Neuroscience Endowment Grant
2009	The Gareth Kerr Memorial Scholarship Award
2009	HHMI – Science for Life Graduate Student Mentor Award
2008	Bryan Robinson Neuroscience Endowment, Honorable Mention
2008	Clinical Translational Science Institute Graduate Student Grant
2008	HHMI – Science for Life Graduate Student Mentor Award
2008	McKnight Brain Institute Graduate Student Investigators Research Grant
2008	UF College of Medicine, Equal Access Clinic Service Award
2007	UF Medical Guild Research Incentive Award
2007	University of Florida College of Medicine Distinguished Service Award
2006	Aurther K. Woodman Scholarship Recipient
2005	Endocrine Society Summer Research Fellowship
2004	Alachua County Fire Rescue Reserves Distinguished Service Award
2004	McLaughlin Scholarship Recipient
2004	Anderson Scholar
2004	President's Honor Roll
2003	Hazen E. Nutter Scholarship Recipient
2002	Golden Key National Honor Society Inductee

Professional Organizations and Activities

2015 - Present	**Member, American Association for Geriatric Psychiatry**
2014 – Present	**Psychiatry Clerkship Interview Tutor (Yale School of Medicine, New Haven, CT)**
2014 - Present	**Member, American Psychiatric Association**
2011	**Member, Professionalism Curriculum Implementation Group (UF, College of Medicine, Gainesville, FL)**
2011 - Present	**Alpha Omega Alpha Honor Society**
2011	**Inductee, Gold Humanism Honor Society, Chapman Chapter**
2002 – 2012	**Equal Access Clinic (UF, College of Medicine, Gainesville, FL) – Equal Access Clinic is a network of multidisciplinary student-run free clinics that provides healthcare to the medically underserved.** 2011/2012, 2009/2010, 2008/2009, 2006/2007 Co-Director 2010/2011 Public Relations Officer 2005/2006 MS1 Representative, Equal Access Clinic 2004/2005 Co-Director, Equal Access Support Committee (UF, Pre-med AMSA) 2003/2004 Associate Director, Equal Access Support Committee 2002/2003 Undergraduate Volunteer, Equal Access Support Committee
2008 – 2016	**Society of Student-Run Free Clinics (SSRFC) – SSRFC is an international organization made up of students participating in student-run free clinics. Our mission is to facilitate collaboration between student-run free clinics.** 2012 - 2016 Resident Advisor 2011/2012 Conference Committee Chair 2010/2011, 2011/2012 Information Technology Officer

2009/2010 Conference Coordinator
2008/2009 Co-founder and member

2008 – 2012 **American Physician Scientist Association (APSA)**
2008/2009, 2009/2010 President, APSA University of Florida Chapter
2008/2009, 2009/2010 University of Florida Institutional Representative
2008/2009, 2009/2010 Membership Committee Member

2008 – 2012 **Medical Student Selection Committee, University of Florida**
2008-Present Member, MD-PhD Program Student Selection Committee
2011/2012 Member, Medical Student Selection Committee

2009, 2011 **Teaching Assistant, Medical Neuroscience**
Spring neurobiology/neuroanatomy course for first year medical students

2008 – 2009 **Citizens for Social Justice (Gainesville, FL)**
Co-Director, Medical Affairs, Citizens for Social Justice

2003 – 2005 **Alachua County Fire Rescue – Reserves (Gainesville, Florida)**
2004/2005 Bike Team Leader, Alachua County Fire Rescue Reserves
2003/2004 Volunteer, Alachua County Fire Rescue Reserves

Research Experience

2012 – 2016	Neuroscience Research Training Program (Department of Psychiatry, Yale University School of Medicine)
2008 – 2012	NIH/NINDS Predoctoral Fellow (Department of Physiology and Functional Genomics, University of Florida) – F30 Recipient
2007	Graduate Research Assistant (Department of Physiology and Functional Genomics, University of Florida)
2006	NIH Medical Science Research Program Fellow (Department of Pharmacodynamics, University of Florida)
2005	Endocrine Society Summer Research Fellow (Department of Pharmacodynamics, University of Florida)
2003 – 2005	Laboratory Technician (Department of Pharmacodynamics, University of Florida)
2002 – 2003	Undergraduate Research Student (Department of Pharmacodynamics, University of Florida)

Grant Support

VISN1 Innovation Grant. “Screening Program for Identifying Needs due to Geriatric Syndromes in Homeless Veterans (SPRING). 2014-2015 Co-Author: Adam Mecca, Co-PIs: Marcia Mecca, Theddeus Iheanacho.

Hartford Change AGEnts Action Award. “SPRING: Screening Program for Identifying Needs due to Geriatric Syndromes in Homeless Veterans. 11/2014 – 4/2016 Co-Author: Adam Mecca, Co-PIs: Marcia Mecca, Theddeus Iheanacho.

Thomas P. Detre Fellowship Award in Translational Neuroscience Research in Psychiatry. "Functional Connectivity Alterations and Related Changes in Glutamate Receptor Subtype 5 in Individuals with and at risk Alzheimer's Disease." 2014. PI: Adam Mecca

NIH/NINDS, F30 060335-01A1. "Cerebroprotection via viral-mediated gene delivery of angiotensin AT2 receptors." MD-PhD student individual Fellowship. PI: Adam Mecca; Sponsors: Colin Sumners and Michael Katovich. 7/01/2008 – 06/30/2012.

American Heart Association, Greater Southeast Affiliate 09GRNT2060421. "Angiotensin (1-7) induced cerebroprotection." Co-Author: Adam Mecca; PI: Colin Sumners. 7/01/2009 - 6/30/2011.

AAMC Caring for the Community Grant. "Equal Access Clinic." Author and Project Manager. 7/2008-7/2012.

AMA Foundation Fund for Better Health Grant. "Equal Access Clinic." Author and Project Manager. 7/2008 – 7/2009.

Publications and Presentations:

Mecca AP, Wang S, Barcelos NM, Planeta-Wilson, B, Gelernter J, Van Ness, P, Carson R, van Dyck CH,. Amyloid-Beta Burden is Inversely Associated with Gray Matter Volume but not Episodic Memory Performance in Cognitively Normal First-Degree Relatives at Risk for Alzheimer's Disease. (Under Review)

Mecca AP, Michalak H, McDonald J, Pugh E, Becker M, Kemp E, Zhao H, van Dyck CH. Sleep Disturbance and Risk of Cognitive Decline in the ADNI Cohort. (in preparation)

Thomas JM, Mecca MC, Niehoff K, **Mecca AP**, Van Ness PH, Hyson A, Brienza R, Jeffery S. Development and Validation of a Polypharmacy Knowledge Assessment for Post-Graduate Primary Care Trainees. (in preparation)

Mecca MC, **Mecca AP**. "Principles of Care for the Hospitalized Geriatric Patient." *The Hospital Neurology Book.* Ed. Arash S, Ed. Biller J. New York: McGraw-Hill Education, 2016. Print.

Fineberg SK, **Mecca A**, Lerner Ab BA, Hills OF, Corlett PR, Viron M. Idiom use in a young man with schizophrenia and prominent sexual delusions. Harv Rev Psychiatry. 2014 Sep-Oct;22(5):306-15.

Bennion DM, Regenhardt RW, **Mecca AP**, Sumners C. "Mas and Neuroprotection in Stroke." *The Protective Arm of the Renin-Angiotensin System: Functional Aspects and Therapeutic Implications.* Ed. Unger T, Ed. Steckelings UM, Ed. Santos R. Elsevier, Academic Press, 2015. Print.

Joseph JP, **Mecca AP**, Regenhardt RW, Bennion DM, Rodriguez V, Desland F, Patel NA, Pioquinto DJ, Unger T, Katovich MJ, Steckelings UM, Sumners C. The angiotensin type 2 receptor agonist Compound 21 elicits cerebroprotection in endothelin-1 induced ischemic stroke. *Neuropharmacology*. 2014 Jun;81:134-41.

Regenhardt RW, **Mecca AP**, Desland F, Ritucci-chinni PF, Ludin JA, Greenstein D, Banuelos C, Bizon JL, Reinhard MK, Sumners C. Centrally administered angiotensin-(1-7) increases the survival of stroke prone spontaneously hypertensive rats. *Exp Physiol.* 2014 Feb;99(2):442-53.

Regenhardt RW, Desland F, **Mecca AP**, Pioquinto DJ, Afzal A, Mocco J, Sumners C. Anti-inflammatory effects of angiotensin-(1-7) in ischemic stroke. *Neuropharmacology*. 2013 Aug;71:154-63.

Regenhardt RW, Ansari S, Azari H, Caldwell KJ, **Mecca AP**. Utilizing a cranial window to visualize the middle cerebral artery during endothelin-1 induced middle cerebral artery occlusion. *J Vis Exp*. 2013 Feb 22;(72):e50015.

Ansari S, Azari H, Caldwell KJ, Regenhardt RW, Hedna VS, Waters MF, Hoh BL, **Mecca AP**. Endothelin-1 induced middle cerebral artery occlusion model for ischemic stroke with laser Doppler flowmetry guidance in rat. *J Vis Exp*. 2013 Feb 16;(72).

Mecca AP, Regenhardt, RW, O'Connor TE, Joseph JP, Raizada MK, Katovich MJ, Sumners C. Angiotensin-(1-7) is cerebroprotective in a rat model of ischemic stroke. *Exp Physiol*. 2011 Oct;96(10):1084-96. (Cover Image)

Cao W, Glushakov A, Shah HP, **Mecca AP**, Sumners C, Shi P, Seubert CN, Martynyuk AE. Halogenated aromatic amino acid 3,5-dibromo-D-tyrosine produces beneficial effects in experimental stroke and seizures. *Amino Acids*. 2011 Apr;40(4):1151-8.

Ferreira AJ, Santos RA, Bradford CN, **Mecca AP**, Sumners C, Katovich MJ, Raizada MK. Therapeutic implications of the vasoprotective axis of the renin-angiotensin system in cardiovascular diseases. *Hypertension*. 2010 Feb;55(2):207-13.

Cao W, Shah HP, Glushakov AV, **Mecca AP**, Shi P, Sumners C, Seubert CN, Martynyuk AE. Efficacy of 3,5-dibromo-L-phenylalanine in rat models of stroke, seizures and sensorimotor gating deficit. *Br J Pharmacol*. 2009 Dec;158(8):2005-13.

Mecca AP, O'Connor TE, Katovich MJ, Sumners C. Candesartan pretreatment is cerebroprotective in a rat model of endothelin-1-induced middle cerebral artery occlusion. *Exp Physiol*. 2009 Aug;94(8):937-46. (Cover Image)

Grobe JL, **Mecca AP**, Lingis M, Shenoy V, Bolton T, Machado J, Speth RC, Raizada MK, and Katovich MJ. Prevention of angiotensin II-induced cardiac remodeling by angiotensin-(1-7). *Am J Physiol Heart Circ Physiol*. 2007 Feb; 292(2):H736-42.

Mitra A, Katovich MJ, **Mecca A**, Rowland NE. Effects of central and peripheral injections of apelin on fluid intake and cardiovascular parameters in rats. *Physiol Behav*. 2006 Sep 30; 89(2):221-5.

Grobe JL, **Mecca AP**, Mao H, Katovich MJ. Chronic angiotensin 1-7 prevents cardiac fibrosis in DOCA-salt model of hypertension. *Am J Physiol Heart Circ Physiol*. 2006 Jun; 290(6):H2417-23.

Huentelman MJ, Grobe JL, Vazquez J, Stewart JM, **Mecca AP**, Katovich MJ, Ferrario CM, Raizada MK. Protection from the angiotensin II – induced cardiac hypertrophy and fibrosis by systemic lentiviral delivery of ACE2 in rats. *Exp Physiol*. 2005 Sep; 90(5):783-90.

Abstracts:

Mecca MC, Maiaroto M, DeWorsop D, Rodriguez-Guzman J, Hassell C, **Mecca AP**, Iheanacho T. Screening Program to Identify Needs due to Geriatric Syndromes (SPRING): Improving Healthcare for Homeless Adults. *American Association for Geriatric Psychiatry – Annual Meeting*. 2016.

Rodriquez-Guzman J, Maiaroto M, DeWorsop D, Hassell C, Iheanacho T, **Mecca AP,** Mecca MC**.** Utilizing a Direct Assessment to Identify Functional Impairments in Homeless Adults. *American Association for Geriatric Psychiatry – Annual Meeting.* 2016.

Hassell C, Mecca MC, DeWorsop D, Rodriquez-Guzman J, Maiaroto M, Iheanacho T, **Mecca AP.** Characterizing Trajectories of Homelessness in Older Adults. *American Association for Geriatric Psychiatry – Annual Meeting.* 2016.

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Presentations:

Mecca AP. Brain Amyloid Imaging in Healthy Individuals at Risk of Alzheimer's Disease. *American Association of Geriatric Psychiatry – Annual Meeting.* 2016. (Oral Paper Presentation).

Mecca AP. The SPRING Project: Screening Program to Identify Needs due to Geriatric Syndromes in Homeless Veterans. *American Association of Geriatric Psychiatry – Annual Meeting.* 2016. (Oral Presentation).

Mecca AP, Lynn PJ, Bennett A, Kari M, Ewigman N, Timpane S. Process improvement through analysis of work flow at a student-run free clinic. *2012 Society for Student Run Free Clinics Conference.* Long Beach, California. (*Oral Presentation)*

Mecca AP, Mecca MC. New onset bleeding diathesis in an alcoholic patient: Evaluation and treatment at a student-run free clinic. *American College of Physicians, Florida Chapter, 42nd Scientific Meeting.* 2010. (*Poster Presentation)*

Mecca AP, Targeting the ACE2/Ang-(1-7)/Mas Axis for Cerebroprotection during Ischemic Stroke. *12th Annual Bryan W. Robinson Endowment Awards and Dinner.* 2010. Tallahassee, FL. (*Oral Presentation*)

Mecca AP, CNS activation of the ACE2/Ang-(1-7)/Mas axis and cerebroprotection during ischemic stroke. *2010 UF Medical Guild Graduate Student Research Competition. (Oral Presentation)*

Mecca AP. Brain angiotensin system and cerebroprotection during focal cerebral ischemia. *11th Annual Bryan W. Robinson Endowment Awards and Dinner*. 2009. Tallahassee, FL. (*Oral Presentation*)

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Slone M, **Mecca A**, Jaworek A, Esmail F, Woodard L. Student-run free clinics: Inspiring students to improve the quality of healthcare and medical education. 2009 *Society of Teachers of Family Medicine Predoctoral Education Conference.* Savannah, Georgia. (*Oral Presentation)*

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Mecca AP. Funding a Student Run Free Clinic. *2008 Society for Student Run Free Clinics Conference.* Washington, D.C. (*Oral Presentation)*

ABF Letter of Intent

Letter of Intent Form

Prefix

First Name

Adam

Last Name

Mecca

Suffix

Title

Institution

Yale Unversity

Office Address

One Church Street
8th Floor

City

New Haven

State

CT

Postal Code

06510

E-mail

adam.mecca@yale.edu

Office Phone

203.764.8100

Office Fax

203.764.8111

Project Details

Project Title

Investigation of molecular changes in mGluR5 and SV2A to study synaptic alteration in Alzheimer's disease using PET

General focus

Alzheimer’s & Dementia

Specific Disease Focus

Alzheimer's Disease Neurobiology

Project Description

Alzheimer's disease (AD) is a common and progressive illness that leads to impaired memory and thinking, impaired ability to function independently, and profound societal costs. This proposal seeks to expand the understanding of AD pathophysiology with the ultimate goals of

enhancing care by ensuring timely/accurate diagnosis, as well as preventing and effectively treating this disease. AD afflicts over 5 million people in the US and no current therapy modifies its course. Positron Emission Tomography (PET) imaging has been successfully employed to investigate changes in living humans at the molecular level, aiding in the diagnosis and understanding of AD. Therefore, the neurobiology of AD can be studied in vivo with multi-tracer neuroimaging and neuropsychological characterization.
Molecular changes at the synaptic level have been shown to be associated with AD, but the majority of molecular and synaptic investigations are performed in humans after death or in animal models. Metabotropic glutamate receptor subtype 5 (mGluR5) is present at synapses throughout the cortex and is a mediator of amyloid beta induced AD pathology. Therefore, mGluR5 is a candidate biomarker for AD and a target for therapeutic intervention, making its detection an important goal. Furthermore, synaptic vesicle glycoprotein 2A (SV2A) is a pre-synaptic protein with potential as the first in vivo marker of synaptic density. Since synaptic loss is observed in the earliest stages of AD, SV2A binding stands to be a robust marker of disease progression.
The objective of this proposal is to apply PET methods to understand the neurobiological changes associated with AD using [18F]FPEB, a specific ligand for mGluR5, and [11C]UCB-J, a specific ligand for SV2A (synaptic density). This is likely to have a significant impact by (i) determining the changes in mGluR5 receptor availability that occur during AD, (ii) determining the changes in synaptic density that are detectible during AD, and (iii) understanding the relationship between changes in mGluR5 receptor availability and synaptic density. These investigations will provide valuable understanding of the AD disease process and lead to the development of both novel treatments and therapeutic biomarkers.

How will your project contribute to the treatment, prevention or cure of a neurological disease(s)?

In summary, both synaptic and receptor level changes that occur with AD may be valuable biomarkers used in clinical trials to track therapeutic response and disease progression. Therefore, understanding of the receptor and synaptic level changes that occur due to Alzheimer's disease (AD) will provide valuable insights into the disease process and lead to the development of novel treatments.

Project Budget

Total expense budget

An estimated total is acceptable.

$140,000

Value of existing funding or in-kind support

What portion of the above total expense has funding already received or promised?

$71,000

Portion to be raised through crowdfunding

How much are you seeking from the crowdfunding platform?

$69,000

Attachments and Verifications

Please download, fill out, and upload the Financial Disclosures & Conflict of Interest form.

Financial Disclosures & Conflicts of Interest Form

Mecca_AP_Financial-Disclosure-Conflict-of-Interest-Form.pdf

CV of Principal Investigator

Mecca_CV_full_14March2017.pdf

I understand that the American Brain Foundation will not post approved projects for crowdfunding until documentation of IRB approval or exemption is provided.

Yes

YALE UNIVERSITY
SCHOOL OF MEDICINE
DEPARTMENT OF PSYCHIATRY

JOHN H. KRYSTAL, M.D.
Chair, Department of Psychiatry
Chief of Psychiatry, Yale-New Haven Hospital

OFFICE OF THE CHAIR
Department of Psychiatry
300 George St., Suite 901.
New Haven, Connecticut 06511
Tel: 203-785-6396
Fax: 203-785-6196
Email: john.krystal@yale.edu

March 28, 2017

Re: Letter of Institutional Committee: Adam Mecca, M.D., Ph.D.

Dear Review Committee Members,

As Chair of the Yale Department of Psychiatry, I enthusiastically confirm the Institutional and Department commitment for Dr. Mecca's American Brain Foundation crowdfunding campaign application entitled, "Investigation of molecular changes in mGluR5 and SV2A to study synaptic alteration in Alzheimer's disease using PET."

Dr. Mecca is a Geriatric Psychiatry Fellow and Research Fellow at the Yale Alzheimer's Disease Research Unit (ADRU). He is an extremely talented psychiatrist and an invaluable member of the ADRU Team. Upon completion of his training in June 2017, he will begin a tenure-track Assistant Professor position that would include the studies outlined in this proposal.

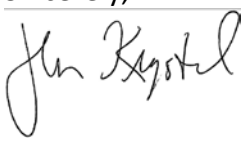
Prior to his fellowship, Dr. Mecca was a member of the Yale Psychiatry Residency Neuroscience Research Training Program (NRTP). This is a highly competitive program (1300 applicants for 16 positions) that we have developed to provide integrated clinical and research training during residency. I have personally followed Dr. Mecca's progress and invested in Dr. Mecca's career development through the NRTP. I will continue to do so as he moves to the next stage of his career.

Our Department is committed to Dr. Mecca's career. I will ensure that he has the necessary protected time, support, and assistance to complete the next critical phase of his career development development. We will provide the needed space, equipment, and other resources and facilities necessary to allow Dr. Mecca to complete this proposal. Dr. Mecca will devote ≥75% of his effort to the proposed research and career development activities. Our commitment to Dr. Mecca's career development is not contingent upon the receipt of a career development award.

Dr. Mecca is an integral part of our Department's research program, where he is mentored by Dr. Christopher van Dyck (Co-Director of our NIA ADRC and Director of the ADRU). Dr. Mecca's has two additional on-site mentors: Richard Carson, Ph.D. (PET), and Peter Van Ness, Ph.D. (biostatistics). Dr. Mecca will have extensive opportunities for formal and informal training in these areas through seminars, courses, and conferences. In addition, he will receive support and encouragement to seek additional funding opportunities, both extramural and intramural, which will promote collaborative work across departments and at other institutions.

We are extremely pleased that Dr. Mecca has chosen to begin his career at Yale. I believe that Dr. Mecca holds great promise of attaining an independent research career. We look forward to nurturing his growth and development.

Sincerely,



John H. Krystal, M.D.
Robert L. McNeil, Jr. Professor of Translational Research
Professor of Neuroscience

BUDGET

PET/MRI scanning costs. This protocol will utilize PET and MRI data from 40 individuals each for Aim 1 and Aim 2 that are being collected during ongoing projects. It is expected that at least 75% of participants will complete the PET scans for both aims. In order to complete Aim 3, it is expected that approximately 30 subjects will co-enroll in the protocols for Aim 1 and 2. Therefore, an additional 10 subjects will be recruited to complete Aim 3 and funding for their PET scans and MRIs are being requested.

Therefore, funds are requested for 10 individuals will co-enroll and complete a screening visit, MRI, [^{11}C]PiB PET scan, [^{18}F]FPEB PET scan, [^{11}C]UCB-J PET scan, and neuropsychological testing visit. The cost of scans is currently $525 for each MRI, $5078 for each [^{11}C]UCB-J batch production plus scan and metabolite measurement, $4244 for [^{11}C]PiB synthesis and scan, and $4661 for each [^{18}F]FPEB batch production plus scan and metabolite measurement.

Participant payments. Funds are requested to compensate subjects for time and participation. Payments are $50 for screening visit assessments, $250 for each PET scan (3 scans), $50 for MRI, and $50 for neuropsychological testing assessments visit.

Item	Cost per subject	Subjects	Total
[11C]UCB-J	$5078	10	$50,780
[11C]PiB	$4244	10	$42,440
[18F]FPEB	$4661	10	$46,610
MRI	$525	10	$5,250
Total			$145,080
Funds Requested			**$69,000**

Yale University

Institutional Review Board
150 Munson St 3rd Floor
P.O. Box 208327
New Haven CT, 06520-8327

Telephone: 203-785-4688
Fax: 203-785-2847
http://info.med.yale.edu/hic

To:	Christopher Van Dyck, M.D.
From:	**Yale University Institutional Review Board**
Date:	09/15/2016
HIC/HSC Protocol#:	1608018300
Study Title:	PET Imaging of Synaptic Density in Alzheimer's Disease
Submission Type:	Initial Application
Committee Action:	**Approval**
Committee Action Date:	09/14/2016
Expiration Date:	09/13/2017

Your request regarding the above-referenced protocol has been APPROVED following a review by the convened Institutional Review Board (IRB) at a meeting held on the Committee Action Date noted above. This review meets approval criteria set forth in 45 CFR 46.111. **It is the investigator's responsibility to apply for reapproval prior to the Expiration Date noted above.**

Please note the Review Comments listed below that relate to the review of this study.

Review Comments:

- The Committee has determined that this protocol presents greater than minimal risk to subjects. The protocol attempts to minimize risks to subjects, and the foreseeable risks are reasonable in relation to the potential benefits.

- This protocol was reviewed in accordance with 45 CFR 46.111(b), and appropriate safeguards are in place to protect the welfare of this population considered to be decisionally impaired.

- The Committee acknowledges that this study involves the use of an investigational radiotracers, [11C]APP311 and [11C]PIB, that will be reviewed and approved under the purview of the RDRC, per 21 CFR 361.1. It is the Principal Investigator's responsibility to promptly inform the HIC if the RDRC requires changes to the protocol, and to submit a protocol amendment request accordingly. A copy of the letter from the RDRC approving this protocol must be submitted to the HIC Office. The PI is advised that the HIC will not release the consent documents until receipt of the RDRC approval letter.

- The Principal Investigator is reminded that this study must be submitted to the Yale University Radiation Safety Committee (YURSC) for review and approval of the research-related PET scans described in the study procedures. YURSC approval should be submitted to the HIC for acknowledgment prior to commencing with these procedures. Investigators are advised that if there will be a change in approved radiation use (e.g., an increase in the dose or number of research-related scans per subject), a modification needs to be submitted to the HIC and approved by both the HIC and the RSC prior to implementation.

- The IRB has reviewed the NIA grant #1R01AG052560 (IRES 16-004476) and found it to be consistent with research activities described in the protocol.

- The HIC recognizes that protected health information (PHI) will be collected from potential subjects via telephone screen, and approves a waiver of HIPAA Authorization for Research to allow for verbal authorization for the use of this PHI to determine subject eligibility. The HIC finds that this activity meets the criteria for waiver of documentation of HIPAA research authorization and for waiver of documentation of informed consent, pursuant to 45 CFR §164.512(i)(2) and 45 CFR §46.117(c)(2), respectively.

- All additional recruitment materials should be submitted to the HIC for review and approval prior to use.

- The HIC acknowledges receipt and review of study main points, study blurb, and patient and next of kin assessments.

- The HIC application and compound authorization forms (3) are approved with this submission. The compound authorization forms will be released once RDRC approval has been received.

Amendments: If you wish to change any aspect of this study, such as the study procedures or processes, the informed consent document(s), recruitment activities, or wish to add or remove investigators or key study personnel, you must communicate your requested changes to the HIC using the appropriate form located at http://www.yale.edu/hrpp. Any changes must be approved by the HIC prior to implementation.

Request for Reapproval: It is the investigator's responsibility to obtain reapproval of ongoing research prior to the Expiration Date. Please submit the request for reapproval form 100FR5R at least two months prior to the expiration date to allow for reapproval processing and review.

*Should the research activities no longer involve human participants and you are only conducting data analysis of anonymous de-identified data (with no link to identifiers), IRB approval is no longer required but the IRB does require notification via submission of a closure form 100FR5C.

Request to Close: When the study procedures and the data analysis are fully complete, the Form100FR5C must be completed and sent to the HIC requesting that the study be closed. Investigators should attach a copy of the study findings. Abstracts or publications satisfy this findings requirement.

Adverse Events/UPIRSOs: Serious, unanticipated, and related adverse events, and unanticipated problems involving risk to subjects or others must be reported generally within 5 days of the PI becoming aware of the event (see **Policy 710: Reporting Unanticipated Problems Involving Risks to Subjects or Others, including Adverse Events**).

Please keep this memo with your copy of the approved protocol documents.

Yale University

Human Investigation Committee
Human Subjects Committee
25 Science Park – 3rd Fl., 150 Munson St.
New Haven CT 06520-8327

Telephone: 203-785-4688
http://www.yale.edu/hrpp

APPROVAL OF SUBMISSION VIA FULL BOARD REVIEW

February 20, 2017

Christopher Van Dyck
203-764-8100
christopher.vandyck@yale.edu

Dear Christopher Van Dyck:

On 2/8/2017, the Yale Institutional Review Board (IRB) reviewed the following submission:

Type of Review:	Modification/Update
Title of Study:	PET Imaging of Metabotropic Glutamate Receptor Subtype 5 in Individuals With and at Risk for Alzheimer's Disease
Investigator:	Christopher Van Dyck
Protocol ID:	1410014799
Submission ID:	MOD00000832
Documents:	• HIC Protocol 30Jan17, Category: IRB Protocol; • RDRC Application 1.23.17, Category: Drug Attachment; • Hyacinth_Human Subject Protection Training, Category: Training certificates; • RDRC Letter 1.2.17, Category: Drug Attachment; • RDRC Response Letter 1.23.17, Category: Drug Attachment; • YU RSC Approval 7.9.16, Category: Drug Attachment;

The Yale IRB approved this submission following a full board review. This approval is valid from 2/8/2017 to 1/7/2018 inclusive.

Review Comments:

The approved amendment revises the repeat scanning protocol in this study to a possibility for one repeat scan (instead of two) and moves information regarding unknown allergies from the radiation risk section, giving it its own section per the request of RDRC. The approved amendment also adds the following non-consenting personnel: Nabeel Nabulsi, Henry Huang, Kelly Rogers, and Ting Xiao.

The Committee has determined that the amendment does not change the assessment of greater than minimal risk for this protocol. The benefits continue to outweigh the risks.

The Committee acknowledges that this study involves the use of investigational radiotracers, [18F]-FPEB and [11C]-PiB, reviewed under the purview of the RDRC, per 21 CFR 361 and that final approval of this modification is needed. A copy of the letter from the RDRC approving this protocol must be submitted to the HIC Office. The PI is advised that the HIC will not release the revised consent documents until receipt of the RDRC approval letter.

The Principal Investigator is reminded to contact Yale University Radiation Safety Committee (YURSC) to identify if they need to review radiation changes that occur with this amendment. YURSC approval should be submitted to the HIC for acknowledgment prior to commencing with these procedures. Investigators are advised that if there will be a change in approved radiation use (e.g., an increase in the dose or number of research-related scans per subject), a modification needs to be submitted to the HIC and approved by both the HIC and the RSC prior to implementation.

The Committee understands that subjects are currently active on study intervention. The Committee requires that the currently enrolled subjects be re-consented at the next study visit, after release of the revised consent, with the newest version of the Compound Authorization and Consent Form with changes clearly identified.

This protocol was reviewed in accordance with 45 CFR 46.111(b), and appropriate safeguards are in place to protect the welfare of this population considered to be decisionally-impaired.

The HIC protocol is approved and validated.

By 11/8/2017, you are to submit documentation for a continuing review. You can request a continuing review by navigating to the active study and clicking Create Modification / CR. Alternatively, you can close the study when the study procedures and the data analysis of identifiable data are fully complete. You can submit a closure request by navigating to the active study and clicking Create Modification /CR.

If you wish to change any aspect of this study, such as the study procedures or processes, the informed consent document(s), recruitment activities, or wish to add or remove investigators or study personnel, you must submit a modification to the study. Any changes must be approved by the IRB prior to implementation.

Serious, unanticipated, and related adverse events, and unanticipated problems involving risk to subjects or others must be reported generally within 5 days of the PI becoming aware of the event (see Policy 710: Reporting Unanticipated Problems Involving Risks to Subjects or Others, including Adverse Events).

In conducting this study, you should refer to and follow the Investigator Manual (HRP-103), which can be found in the IRB Library within the IRB system.

Please keep this letter with your copy of the approved protocol documents.

Sincerely,

Sandra Alfano, Human Investigation Committee II

Dear Applicant:

In the increasingly complex world of scientific publication, concerns about commercial influence and other possible conflicts make it important for authors to disclose all potential sources of bias. Our system of reviewing conflicts of interest aligns with the policies of the American Academy of Neurology and allows donors to judge whether conflicts exist. Please complete this form, referring to the definitions in the beginning regarding commercial entities, compensation, expert witness, and "immediate family member." At first glance, this task may seem onerous, but will likely take less than 10 minutes.

What to expect: You will be asked whether you have disclosures relating to each question (check yes or no) and will be provided a field in which to list the disclosures. Filling out the forms on the next few screens will be easiest if you have a list of the following items regarding your activity (either commercial or non-profit) and that of any immediate family members during the period of your project. Disclosures are required for any dollar amount, except for gifts valued under $1000. Names of commercial and non-profit entities are required along with specific roles, grant numbers for grants, and specific years. No dollar amounts need to be included. Please indicate complete names of sponsors or companies.

DEFINITIONS

Personal compensation:
Serving on a scientific advisory board
Gifts worth more than $1000
Travel funded by a commercial entity
Serving as a journal editor, associate editor, or on an editorial advisory board
Patents held or pending
Royalties from publishing
Honoraria for speaking engagements
Corporate appointments or consultancies
Speakers' bureaus
Clinical, neurophysiology, or imaging studies in your practice and % effort devoted if the result of this paper will benefit your practice, affiliated unit, or a sponsor

Research support:
Commercial research support
Government research support (including funding organization, grant number, and role)
Academic research support not attributed in the manuscript
Support from a non-profit foundation or society
Stock options for serving on a Board of Directors
License fee payments
Royalty payments from technology or inventions

Stocks, stock options, and royalties
Stock options in a company in which you are (were) an investigator
Stock options in medical industry

Legal proceedings
Expert testimony for a legal proceeding on behalf of industry
Affidavit for a legal proceeding on behalf of industry
Witness or consultant for a legal proceeding on behalf of industry

Optional non-financial
Non-financial disclosures you wish to share

Definitions of Terms in Disclosure Agreement
Commercial entity: A for-profit business that manufactures, distributes, markets, sells, or advertises pharmaceutical or scientific products or medical devices.
Compensation: Anything of monetary value including a salary, honorarium, stipend, gift, or payment of travel-related expenses.
Expert witness: A person who has provided expert medical testimony during a trial or administrative hearing, in a deposition or an affidavit, or in any other type of legal proceeding.
"Immediate family member": Any person who would benefit financially from the publication of the manuscript because of their relationship to the author. This includes a member of an applicant's immediate family or anyone else who has a significant relationship with the applicant.

Please provide all financial relationships (and those of your "immediate family members") from the past two years regardless of whether these relationships are related to the project described in your application.

FINANCIAL DISCLOSURE
Personal Compensation from Commercial and Non-Profit Entities that benefits you directly or indirectly. Within the past two years (and during the course of the study under consideration if the study exceeded two years), I or one of my "immediate family members" received personal compensation for the following:

All compensation received during the past two years regardless of the relationship to your project must be disclosed; for the period exceeding two years, only compensation relevant to the topic of the study needs to be disclosed.

1. Serving on a scientific advisory board or data safety monitoring board. List specific disclosures in the following format: (1) Commercial or non-profit entity (2) Commercial or non-profit entity... If none, please say "None":

None

2. Gifts (other than travel or compensation for consulting or for educational efforts) worth more than USD $1000. List specific disclosures in the following format: (1) Commercial or non-profit entity, brief description of gift, (2) Commercial or non-profit entity, brief description of gift... If none, please say "None":

None

3. Funding for travel or speaker honoraria to the individual from a commercial or non-profit entity not included in the study funding [Exclude CME activities and Grand Rounds]. List specific disclosures in the following format: (1) Commercial or non-profit entity, type of payment, (2) Commercial or non-profit entity, type of payment... If none, please say “None”:

None

4. Serving as a journal editor, an associate editor, or editorial advisory board member. This may include a journal published by your national medical/scientific organization. Please include regardless of whether you receive compensation. List specific disclosures in the following format: (1) Full journal name, role, year(s), (2) Full journal name... If none, please say “None”:

None

5. Patents issued or pending. List specific disclosures in the following format: (1) Brief description of invention/technology, (2) Brief description of invention/technology... If none, please say “None”:

None

6. Publishing Royalties (do not include honoraria for occasional writing). List specific disclosures in the following format: (1) Full title of work, full name of publisher, year(s) of publication (or receipt of royalties), (2) Full title of work... If none, please say “None”:

None

7. Employment. If you are currently employed by a commercial entity, please disclose below. In addition, if your past employment at a commercial entity is directly related to this manuscript, please disclose below. List specific disclosures in the following format: (1) Commercial entity, position, years (2) Commercial entity, position, years... If none, please say “None”:

None

8. Consultancies. List specific disclosures in the following format: (1) Commercial or non-profit entity, (2) Commercial or non-profit entity... If none, please say “None”:

None

9. Speakers' bureau. List specific disclosures in the following format: (1) Commercial or non-profit entity, (2) Commercial or non-profit entity... If none, please say “None”:

None

10. Other activities not covered in designations above (if in doubt, provide full disclosure). List specific disclosures in the following format: (1) Commercial or non-profit entity, brief description of activity, (2) Commercial or non-profit entity... If none, please say “None”:

None

11. Some studies have potential for financial gain for the project investigators or the sponsor. The following question seeks to provide transparency regarding any financial benefits to investigators or sponsors.

Do you perform clinical procedures or imaging studies in your practice or unit that overlap with the content of your proposed project, practice parameter, or clinical practice guideline and would your sponsor or this part of your practice or unit benefit if the conclusions were widely followed?
Note: This is the only item in this Agreement that applies to an interest that is related specifically to this particular study, practice parameter, or clinical practice guideline.

List specific disclosures in the following format: (1) Name of Practice or Research Unit, Clinical procedure/imaging study, % of effort (e.g. 35%), year(s), (2) Name of Practice or Research Unit, Clinical procedure/imaging study, % of effort (e.g., 35%)... If none, please say “None”:

None

RESEARCH SUPPORT
Within the past two years and during the course of the study under consideration if the study exceeded two years, I or one of my "immediate family members" received financial or material research support or compensation from the following:

All support received during the past two years regardless of the relationship to the study must be disclosed; for the period exceeding two years, only support relevant to the topic of the study needs to be disclosed.

12. Commercial entities. List specific disclosures in the following format: (1) Commercial entity, (2) Commercial entity... If none, please say “None”:

None

13. Government entities. List specific disclosures in the following format: (1) Sponsor/funding source, grant number(s), role, year(s), (2) Sponsor/funding source... If none, please say “None”:

1. Department of Veteran's Affairs, VISN1 Innovations Grant, Project Director/Junior PI, 12/1/2014 - 6/1/2016
2. NIH/NIMH, R25 5R25MH071584, Fellow, 7/1/2014-6/30/2016

14. Academic entities other than those attributed in the manuscript. List specific disclosures in the following format: (1) Academic entity, (2) Academic entity... If none, please say “None”:

Yale University, Department of Psychiatry

15. Foundations or societies (include grant number if required by funding agency). List specific disclosures in the following format: (1) Full name of Foundation or Society, (2) Full name of Foundation or Society... If none, please say “None”:

1. John A. Hartford Foundation (Hartfor Change AGEnts Action Award)

STOCK, STOCK OPTIONS & ROYALTIES

In the past two years and during the course of the study under consideration if the study exceeded two years, I or one of my "immediate family members":

All revenues during the past two years regardless of the relationship to the study must be disclosed; for the period exceeding two years, only revenues relevant to the topic of the study needs to be disclosed.

16. Stock or stock options or expense compensation for serving on a board of directors. List disclosures in the following format: (1) Commercial entity, (2) Commercial entity... If none, please say “None”:

None

17. License fee payments. List specific disclosures in the following format: (1) Invention/technology, source of payment, (2) Invention/technology... If none, please say “None”:

None

18. Royalty payments or have contractual rights for receipt of future royalty payments from technology or inventions (this does not include royalties from publishing). List specific disclosures in the following format: (1) Technology/invention, source of payment, year(s), (2) Technology/invention... If none, please say “None”:

None

19. Stock or stock options in a commercial entity sponsoring research with which the author or "immediate family member" was involved as an investigator (Excludes investments in mutual funds held by the author or dependents). List specific disclosures in the following format: (1) Company, year(s), (2) Company, year... If none, please say “None”:

None

20. Stock or stock options in a commercial entity whose medical equipment or other materials related to the practice of medicine. (Exclude investments in mutual funds held by the author or dependents). List specific disclosures in the following format: (1) Company, year(s), (2) Company, year... If none, please say “None”:

None

LEGAL PROCEEDINGS

In the past two years and during the course of the study under consideration if the study exceeded two years, I or one of my "immediate family members" have (whether or not it pertains to the topic of the current study):

All compensation received during the past two years regardless of the relationship to the study must be disclosed; for the period exceeding two years, only compensation relevant to the topic of the study needs to be disclosed.

21. Given expert testimony, acted as a witness or consultant, or prepared an affidavit for any legal proceeding involving a commercial entity (do not include proceedings for individual patients). You may specify role, e.g., 'expert witness for plaintiff' if desired. (Include year only if activity is directly related to the present study.)

List specific disclosures in the following format: (1) Commercial entity, activity, year(s), (2) Commercial entity, activity, year(s)... If none, please say “None”:

None

OPTIONAL: NONFINANCIAL DISCLOSURE

22. I have chosen to declare one or more non-financial competing interests (e.g., special interest groups you represent or others that may be affected if your paper is published or that could be perceived as biasing the study; the corresponding author should be aware of conflicts of interest that Co-investigators or Contributors may have). Non-financial disclosures will not be published.

List specific disclosures, if none, please say “None”:

None

☑ I have completed this Disclosure Statement fully and to the best of my ability. I understand that all Applicants must complete this Disclosure Statement and that the information disclosed may be published if their project is accepted for crowdfunding.

By my electronic signature, I verify the completeness and accuracy of the contents of this form.

Click in the box above to add your electronic signature

03/23/2017

Date [MM/DD/YYYY]

ABF Full Application

Applicant Information

Prefix

First Name

Adam

Last Name

Mecca

Suffix

Title

Geriatric Psychiatry Fellow, Assistant Professor of Psychiatry (July 1, 2017)

Institution Name

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Project Details

Project Title

Investigation of molecular changes in mGluR5 and SV2A to study synaptic alteration in Alzheimer's disease using PET

Project Start Date

July 01, 2017

Project End Date

July 01, 2019

Disease focus

Alzheimer’s & Dementia

Specific Disease Focus

Alzheimer's Disease Neurobiology

Project Summary/Abstract

This proposal seeks to expand the understanding of Alzheimer's disease (AD) pathophysiology with the ultimate goals of enhancing care by ensuring timely/accurate diagnosis, as well as preventing and effectively treating AD. AD afflicts over 5 million people in the US and no current therapy modifies its course. Using Positron Emission Tomography (PET), the neurobiology of AD can be studied in vivo with multi-tracer neuroimaging.

Molecular changes at the synaptic level are associated with AD. Metabotropic glutamate receptor subtype 5 (mGluR5) is present at synapses throughout the cortex and is a mediator of amyloid □ induced AD pathology. Therefore, mGluR5 is a candidate biomarker for AD and a target for therapeutic intervention. Furthermore, synaptic vesicle glycoprotein 2A (SV2A) is a pre-synaptic protein with potential as the first in vivo marker of synaptic density. Since synaptic loss is observed in the earliest stages of AD, SV2A binding stands to be a robust marker of disease progression.

This proposal will apply PET methods to understand the neurobiological changes of AD using [18F]FPEB, a ligand for mGluR5, and [11C]UCB-J, a ligand for SV2A. This is likely to have a significant impact by (i) determining the changes in mGluR5 availability in AD (Aim 1), (ii) determining the changes in synaptic density in AD (Aim 2), and (iii) understanding the relationship between changes in mGluR5 availability and synaptic density (Aim 3). These investigations will provide valuable understanding of the AD disease process and lead to the development of both novel treatments and therapeutic biomarkers.

Project Narrative

Alzheimer's disease is a common and progressive illness that leads to impaired memory and thinking, impaired ability to function independently, and profound societal costs (loss of productivity, utilization of health care services, and a significant need of support from caregivers). To expand the basic understanding of Alzheimer's disease pathophysiology, this proposal aims to utilize two novel radioligands and Positron Emission Tomography imaging to characterize synaptic and receptor level changes that occur in disease. A clearer understanding of synapse and receptor level changes will provide valuable insights into the Alzheimer's disease process that lead to the development of both novel treatments and therapeutic biomarkers.

Facilities and Equipment

The Yale Alzheimer's Disease Research Unit (ADRU) is an established clinical research unit that has specialized in cognitive disorders and aging research for the past 21 years (~60 multicenter clinical trials). The ADRU is staffed by a geriatric psychiatrist (van Dyck, Director), a behavioral neurologist (Dr. Salardini), a neuropsychologist, a clinical research fellow (Dr. Mecca), four geriatric psychiatry fellows, a research psychologist, a nurse practitioner, and nine research assistants. The ADRU is an ADCS member site and houses the clinical core of the Yale Alzheimer's Disease Research Center, both funded by the NIA. The ADRU is a robust infrastructure for subject recruitment, as well as expertise in clinical research methodology.

The Yale PET Center is a state-of-the-art 16,000 sq. ft. facility that opened in July 2005. The PET Center has a GE PETtrace cyclotron, with targetry for producing C-11, F-18, N-13 and O-15 radioisotopes. Chemistry modules are available for the production of radiotracers. The Center has 6 scanners including the Siemens High Resolution Research Tomography (HRRT) scanner that will be used in this study (world's

highest-resolution human PET imaging camera). Two laboratories for blood and metabolite analyses are available. The Center also has an image analysis laboratory. Over 8,000 administrations of PET radiopharmaceuticals as part of quantitative in vivo PET studies have been performed with over 100 radiopharmaceuticals.
The Yale Magnetic Resonance Research Center operates two identically equipped, research-dedicated 3.0T Siemens Trio TIM systems, one of which will be used to perform MRI for this study.

Specific Aims

To address the existing gaps in current knowledge of the pathophysiology of synaptic- and receptor-level changes in AD, the following aims are proposed:
AIM 1. Investigate mGluR5 binding as a biomarker of AD. Utilizing PET and the radiotracers [18F]FPEB for mGluR5 and [11C]PiB for amyloid, mGluR5 binding will be quantified in a group of amyloid-positive individuals with clinical AD (MCI or dementia) compared to a healthy control (HC) group of amyloid-negative individuals with normal cognition (n = 20 per group).
AIM 2. Investigate SV2A binding as a biomarker of synaptic density in AD. Utilizing PET and the radiotracers [11C]UCB-J and [11C]PiB, synaptic density will be quantified in a group of individuals with clinical AD (MCI or dementia) compared to a HC group of individuals with normal cognition (n = 20 per group).
AIM 3. Investigate group and individual differences in mGluR5 binding in relation to synaptic density. Utilizing the data from the above aims, mGluR5 binding and SV2A density will be quantified and compared in a group of AD (n =20) and HC (n = 20) participants.
The central hypothesis is that mGluR5 and SV2A density will be reduced in AD with differing deficits in regional distribution and density between markers. This study is innovative because it explores the neurochemistry of AD in vivo in humans using two novel PET radiotracers. These investigations will provide valuable information that will contribute to the understanding of an ongoing disease process and lead to the development of both novel treatments and therapeutic biomarkers.

Research Strategy

Significance, Innovation, Approach, Timeline

1. Significance

The progression of AD is increasingly understood to occur along a continuum from pre-clinical AD, to mild cognitive impairment (MCI), and finally AD dementia(1). At all stages, the progression is coupled to a distinct pathology, with plaques of Amyloid-β (Aβ), neurofibrillary tangles of hyperphosphorylated Tau protein, and synaptic loss(2). Positron emission tomography (PET) has aided in the diagnosis and understanding of AD, by revealing molecular-level metabolic changes and Aβ in humans(3). Therefore, the neurobiology of AD can be investigated in vivo with the advantages of multi-tracer neuroimaging and robust neuropsychological characterization.

Synaptic loss is linked with AD progression and provides a novel target for exploration with PET(4). Synaptic changes are important biological markers of disease and potential therapeutic targets. For example, metabotropic glutamate receptor subtype 5 (mGluR5) is present post-synaptically, is a modulator of synaptic transmission(5-7), and mediates the synaptotoxic action of Aβ(8). Therefore, mGluR5 is a candidate biomarker for AD and a therapeutic target. Additionally, synaptic vesicle glycoprotein 2A (SV2A) binding measured with [11C]UCB-J PET is the first in vivo marker of synaptic density(9). Since mGluR5 links Aβ toxicity to synaptic loss that is observed in the earliest stages of AD, SV2A binding stands to be a robust marker of disease(10).

2. Innovation

• First-in-human AD studies of mGluR5 and SV2A in vivo.

• Comparison of [18F]FPEB and [11C]UCB-J allows us to test whether the loss of mGluR5 at the post synaptic density differs from decline in synaptic density.

• High-resolution brain PET with state-of-the-art methodology.

3. Approach

Imaging mGluR5 with [18F]FPEB. Parametric images of [18F]FPEB VT are of an excellent quality suitable for regional and whole-brain analysis methods(7). Preliminary experiments support the hypotheses that mGluR5 density is lower in individuals with AD. Cortical regions commonly affected by AD pathology had decreased binding in the AD participants (n=6) compared to HC participants (n=7), with the largest difference in the hippocampus (p=0.04) and a slightly reduced effect after PVC (p=0.06).

SV2A human imaging with [11C]UCB-J. Initial test-retest studies with [11C]UCB-J showed fairly homogenous uptake across GM regions, much lower white matter uptake, tissue activity curves well described by the 1 tissue compartment model, and specific SV2A binding(9). We have scanned one amyloid negative, cognitively normal older adult, as well as two amyloid positive amnestic MCI participants and one amyloid positive AD-dementia participant with [11C]UCB-J. Binding of [11C]UCB-J in the older adults was most distinctly reduced in hippocampus (compared to young controls), with a VT reduction of 29% in the older control, and more robust reductions of 27% and 54% in the 2 MCI participants, and 57% in the AD-dementia participant. Cortical VT values were also reduced. These data suggest that hippocampal SV2A binding is dramatically altered by aging and the AD-spectrum.

Screening Evaluation. Participant (age 55-90) will have a screening visit including informed consent, the Mini-Mental State Examination, Logical Memory Test, Clinical Dementia Rating Scale, and the Geriatric Depression Scale. A physical examination and screening laboratory tests will be performed.

Neuropsychological Assessment. Participants will have a neuro¬psychological evaluation.

MRI Methods. MRI will be obtained using a 3T Trio (Siemens Medical Systems, Erlangen, Germany).

PET Scan Methods. PET scans will be performed on the HRRT, the highest resolution human PET scanner. The [18F]FPEB scan will be acquired using administration of up to 5 mCi of tracer using a bolus/ infusion method. The [11C]UCB J scan will be acquired following administration of up to 20 mCi using bolus/infusion delivery.
AIM 1. Investigate mGluR5 binding as a biomarker of AD. A total of 20 AD participants and 20 age- and sex-matched HC participants will be scanned with [18F]FPEB. Our primary hypothesis is that compared to HC, [18F]FPEB will reveal decreased mGluR5 binding (VT) in AD using a composite cortical region and hippocampus. For Aim 1 and Aim 2, analyses will be performed using linear mixed models with diagnostic group as the main explanatory factor, sex as a fixed factor, age as a covariate, and matching group as a random factor.
AIM 2. Investigate SV2A binding as a biomarker of synaptic density in AD. A total of 20 AD participants and matched HC participants will be scanned with [11C]UCB-J. Our primary hypothesis is that compared to HC, [11C]UCB-J will reveal decreased synaptic density in AD.
AIM 3. Investigate group and individual differences in mGluR5 binding in relation to synaptic density. mGluR5 binding and SV2A density will be quantified and compared in a group of AD and HC participants (20 per group). Our primary hypothesis is that compared to HC participants, AD participants will have greater reductions in mGluR5 binding than SV2A binding using regional analysis, reflecting that mGluR5 is a more direct marker of Aβ mediated toxicity.
4. Timeline.
10-12 participants will complete the research protocol per year. This is feasible based on recruitment rates of the Yale ADRU and PET Center.

List up to 5 milestones you will reach within the first 6 months of your study.

1. Enroll 10 participants (5 HC and 5 AD) and complete the screening visit.
2. Complete [11C]PiB scan for 6 participants (3 HC and 3 AD).
3. Complete [18F]FPEB scan for 6 participants (3 HC and 3 AD).
4. Complete [11C]UCB-J scan for 6 participants (3 HC and 3 AD).
5. Complete neuropsychiatric testing visit for 6 participants (3 HC and 3 AD).
6. Refine analysis stream for regional and voxel-based analyses.

Age of Population Group(s) that will potentially benefit from this research

(check boxes that apply)

Seniors (65+)

Scientific Literature References

Reference 1

Sperling RA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the NIA-AA workgroups on diagnostic

guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7(3):280-92. PMC3220946.

Reference 2

Jack CR, Jr., et al. Introduction to the recommendations from the NIA-AA workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7(3):257-62. PMC3096735.

Reference 3

Klunk WE, et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. Annals of neurology. 2004;55(3):306-19. PMID: 14991808.

Reference 4

Selkoe DJ. Alzheimer's disease is a synaptic failure. Science (New York, NY). 2002;298(5594):789-91. PMID: 12399581

Reference 5

Daggett LP, et al. Molecular and functional characterization of recombinant human metabotropic glutamate receptor subtype 5. Neuropharmacology. 1995;34(8):871-86. PMID: 8532169

Reference 6

Ohnuma T, et al. Expression of the human excitatory amino acid transporter 2 and mGluRs 3 and 5 in the prefrontal cortex from normal individuals and patients with schizophrenia. Brain Res Mol Brain Res. PMID: 9602129

Reference 7

Sullivan JM, et al. Kinetic analysis of the metabotropic glutamate subtype 5 tracer [(18)F]FPEB in bolus and bolus-plus-constant-infusion studies in humans. J Cereb Blood Flow Metab. 2013;33(4):532-41. PMC3618388

Reference 8

Kaufman AC, et al. Fyn inhibition rescues established memory and synapse loss in Alzheimer mice. Annals of neurology. 2015. PMID: 25707991

Reference 9

Finnema SJ, et al. Imaging synaptic density in the living human brain. Sci Transl Med. 2016;8(348):348ra96. PMID: 27440727

Reference 10

Pham E, et al. Progressive accumulation of amyloid-beta oligomers in AD and in amyloid precursor protein transgenic mice is accompanied by selective alterations in synaptic scaffold proteins. FEBS J. PMCID: 2933033

Budget, Attachments and Acknowledgements

Budget

We recognize that changes may have occurred since the time you submitted your Letter of Intent. Please share the most recent accurate numbers below:

Total Project Budget

$145,080

Total existing funding or in-kind support

$76,080

Amount to be raised through crowdfunding campaign

$69,000

Evidence of institutional support (letter)

Mecca Institution Letter.pdf

Full budget

budget.docx

Documentation of IRB/IUCAC approval or exemption, if applicable.

hic_approval.pdf

Completed conflict of interest & disclosure form

Mecca_AP_Financial-Disclosure-Conflict-of-Interest-Form.pdf

I understand that the ABF will not list approved projects for general public crowdfunding campaigns until documentation of IRB/IUCAC approval or exemption is provided.

Yes

I understand that approval of the project to be shared on the crowdfunding campaign site is dependent on providing and working with the ABF staff to create the requisite materials that present the project in an engaging, easy-to-understand website presentation. I am amenable to working with the ABF staff to create such materials.

Yes

I understand that approval once a project has been completed, I will be required to submit a summary of my findings to be posted online (one page), and will submit this in a reasonably timely fashion. I also agree to submit a financial report, and to co-sign a thank you letter with the ABF that will be sent to donors.

Yes

I understand and agree that the ABF may share the information that I provide (including but not limited to the project description and relevant biographical/background details) in conversations with other potential funders outside the website to bolster fundraising efforts.

Yes

American Brain Foundation Release Agreement

American Brain Foundation
Release Agreement – Research

1. **Grant**. For good and valuable consideration, the receipt and sufficiency of which is hereby acknowledged, I grant to the American Brain Foundation ("ABF") and to the ABF's affiliates (including the American Academy of Neurology), and their respective contractors, agents, assigns, licensees, and successors (collectively, the "ABF Group"), a worldwide, royalty-free, perpetual, irrevocable right to take and use my image, likeness, voice, verbal statements, written testimonials and name and all images, videos, sound recordings, and written and verbal materials that I provide to the ABF (collectively, the "Materials "), in all forms

and media, including composite or modified representations, for the purpose of promoting and supporting the missions of the ABF. For the avoidance of doubt, the Materials include all research project proposal information, project reports and other research-related information submitted to the ABF. I understand and agree that the ABF may publish the Materials on any and all media, including printed matter, promotional materials, e-mail, websites and social media platforms.

2. **Acknowledgement of Use**. I understand that the ABF Group may use the Materials on any and all media, including printed matter, promotional materials, e-mail, websites and social media platforms. I understand that the ABF's use of the Materials may intentionally or unintentionally give rise to the impression that either I or a family member suffers from brain/neurologic disease, and I nevertheless consent to this use. The ABF is not obligated to utilize any of the rights granted in this agreement. I waive the right to inspect or approve any uses of the Materials in connection with this grant.
3. **Warranty**. I warrant that I have the full power to enter into this agreement and to grant the aforementioned rights.
4. **Release**. I release the ABF Group from all liability for any claims that may arise regarding the use of Materials, including any claims of defamation, invasion of privacy, or infringement of moral rights, rights of publicity, or copyright. The ABF is permitted, although not obligated, to include my name as a credit in connection with any use of the Materials.**I have read and understood this agreement, I understand that it contains a release of liability, and I am over the age of 18**. This agreement expresses the complete understanding of the parties and shall be binding on me and my heirs, legal representatives and assigns. I understand that I am entering into a legally binding agreement and that clicking "I Accept" below shall have the same legal effect as my signature on this Release Agreement.

I Accept

AMERICAN BRAIN FOUNDATION®

April 7, 2017

Adam Mecca, MD
One Church Street
8th Floor
New Haven, CT 06510

Dear Dr. Mecca,

Congratulations! On behalf of the American Brain Foundation, I am pleased to inform you that your project has been selected to post on the Foundation's crowdfunding site.

An email was sent requesting several documents. It is critical that you provide all of the requested documents in order for your project to be posted on the crowdfunding site.

As a reminder, you will have 90 days from when your project goes live on the site to raise the funds needed to complete your proposed project. Once the funds are raised, a gift agreement will be sent to you and your institution to review and sign. As soon as the American Brain Foundation receives the signed gift agreement, the first payment for your project will be sent to your institution. The final payment for your project will be sent after your progress report has been reviewed and approved by the Foundation.

Please respond to this letter with the name of and contact information for the contact at your institution that the Foundation should work with to process payments. Please send your response to grants@americanbrainfoundation.org.

Again, congratulations on being selected for this opportunity.

Sincerely,

Suzi Sherman
Program Officer, Research & Digital Grants

CC: John H. Krystal, MD

Review - (391) Full Application Review	
Review	
Acceptance Due Date	3/31/2017
Due Date	3/31/2017
Visible From	3/29/2017
Visible To	12/31/2017
Request	
Name (Full)	Dr. A. Gordon Smith
Organization Name	University of Utah
Type	Other Research Projects
Project Budget	$150,145.00
Exisiting Funding / In-Kind Support	$75,145.00
Requested Amount	$75,000.00
Project Title	Axonal mitochondrial failure precedes chemotherapy induced neurotoxicity in breast cancer patients
General focus	ALS & Neuromuscular Technology & Innovation
Specific Disease Focus	Chemotherapy Induced Peripheral Neuropathy
Project Description	Project Description Chemotherapy-induced peripheral neuropathy (CIPN) is the most common dose-limiting side effect of first line chemotherapeutic agents including the microtubule inhibitor paclitaxel, a common agent in the treatment of breast cancer. Paclitaxel infusion frequently causes acute widespread pain that is thought to be neuropathic in origin (paclitaxel acute pain syndrome, P-APS). Our preliminary data suggest patients with P-APS have a higher risk of subsequent CIPN. The mechanisms by which paclitaxel causes P-APS and CIPN are unknown, and there are no effective preventative or treatment strategies. Data from animal models of CIPN suggest paclitaxel and other neurotoxic chemotherapy agents impair microtubular dynamics and mitochondrial calcium signaling leading to increased mitochondrial permeability, swelling, and toxicity. Mitochondrial injury is a well recognized contributor to axonal degeneration in other forms of neuropathy, including diabetes (which is itself a CIPN risk factor). We hypothesize that paclitaxel leads to acute mitochondrial stress in small unmyelinated nociceptive axons resulting in P-APS. Continued exposure leads to length dependent mitochondrial toxicity and, ultimately axonal degeneration manifested as clinical CIPN. Preliminary data indicate that 70% of paclitaxel patients develop P-APS and 42% CIPN. Among those with clinically defined CIPN, nerve conduction studies (NCS) are normal in 46%, and 86% of these have normal intraepidermal nerve fiber density (IENFD). These findings are consistent with functional axonal failure preceding axonal degeneration. We propose to address our hypothesis by fulfilling the following two specific aims: Specific Aim #1: Determine if mitochondrial injury leads to

	functional axonal failure prior to degeneration. 20 breast cancer patients with planned paclitaxel therapy will undergo a baseline evaluation including validated neuropathy scales, NCS and distal leg skin biopsy for IENFD determination. Immunohistochemistry with quantitative image analysis will be used to evaluate axonal mitochondrial numbers and distribution. Electron microscopy (EM) will be used to directly visualize and analyze the size and structure of mitochondria in axons and keratinocytes for comparison. These procedures will be repeated 2 weeks after the final paclitaxel dose. We anticipate that patients with functional axonal failure (CIPN with normal NCS and IENFD) will have greater axonal mitochondrial injury compared to keratinocytes, and that the severity will be intermediate between those without CIPN and those with evidence of axonal degeneration based on NCS and IENFD. Specific Aim #2: Determine if PAP-S is associated with abnormalities of mitochondrial structure. The first 5 patients who develop PAP-S will undergo a distal leg skin biopsy, which will be processed and analyzed as outlined in SA#1. We anticipate that mitochondria from both axons and keratinocytes will have abnormal structure and distribution, suggesting generalized mitochondrial injury. If mitochondrial or other structural axonal abnormalities are observed, skin biopsies will be obtained from 5 patients without P-APS at the same time point for comparison.
Specific Aims	Chemotherapy-induced peripheral neuropathy (CIPN) is the dose-limiting side effect of paclitaxel, a commonly used agent for breast adenocarcinoma. Paclitaxel causes acute widespread neuropathic pain in 45% of patients (paclitaxel acute pain syndrome, P-APS); over 40% develop CIPN. Animal models suggest paclitaxel is mitotoxic(1). We hypothesize paclitaxel causes acute mitochondrial stress in small unmyelinated axons resulting in P-APS; continued exposure causes length-dependent mitochondrial toxicity and axonal degeneration. SA#1: Determine if mitochondrial injury is associated with predegenerative functional axonal failure. CIPN scales, nerve conduction studies (NCS) and calf skin biopsy for intraepidermal nerve fiber density (IENFD) determination will be performed on 20 patients prior to paclitaxel. Immunohistochemistry with quantitative image analysis will evaluate axonal mitochondrial number and distribution(2). Electron microscopy will measure mitochondrial size and structure. These procedures will be repeated 2 weeks after the final dose. We anticipate patients with functional axonal failure (CIPN with normal NCS and IENFD) will have greater axonal mitochondrial injury (e.g. swelling, vacuolization, reduced size and increased numbers) compared to keratinocytes, and that the severity will be greater in those with evidence of axonal degeneration. SA#2: Determine if PAP-S is associated with mitochondrial structural changes. The first 5 patients who develop PAP-S will undergo a repeat biopsy and clinical scales at that time. We anticipate that axonal, but not keratinocyte, mitochondria will

	have abnormal structure, size and distribution, but that IENFD and NCS will remain normal. If mitochondrial axonal abnormalities are observed, 5 age-matched patients without P-APS will be evaluated at the same time.
Milestones	We anticipate the full project to take approximately 12 months to complete. During the first 6 months we will complete the following 5 milestones. 1. Month 1: We will enroll the first participants by the end of the first month. 2. Month 2: During the first two months we will refine the immunohistochemistry and electron microscopy protocols using banked tissue from a normal control, a patient with CIPN and normal IENFD, and a CIPN patient with reduced IENFD. This will allow us to identify and resolve any unanticipated technical issues. 3. Month 3: By the end of the third month we anticipate having enrolled 5 P-APS patients. 4. Month 4: By the end of the fourth month we project recruitment will be 50% completed 5. Month 5: By the end of month 5 we will have determined if there are mitochondrial changes in P-APS patients and if so will have enrolled 5 non P-APS patients. If there is uncertainty regarding the extent of mitochondrial abnormalities we will enroll non P-APS patients for comparison.
Feedback	
Yes/No	Undecided
Review Long Notes	

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Last Updated: 01/26/2017

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PERSONAL DATA

Birth Place: Richmond, Virginia
Citizenship: United States
Languages: English

EDUCATION

Years	Degree	Institution (Area of Study)
1984 - 1988	B.A.	University of Virginia (Archeology) Charlottesville, VA
1988 - 1992	M.D.	Mayo Medical School (Medicine) Rochester, MN
1992 - 1993	Intern	University of Michigan (Internal Medicine) Ann Arbor, MI
1993 - 1996	Resident	University of Michigan (Neurology) Ann Arbor, MI
1996 - 1997	Fellow	University of Michigan (Neuromuscular Fellowship) Ann Arbor, MI
1997		Johns Hopkins University (Cutaneous Innervation) Baltimore, MD
2004		University of Utah Hospital School of Medicine (Physician Executive Course) Salt Lake City, UT

BOARD CERTIFICATIONS

05/05/1997 - 12/31/2017	American Board of Psychiatry & Neurology (Neurology), Certified [Recertified 04/16/2007]
04/04/1998 - 12/31/2018	American Board of Electrodiagnostic Medicine, Certified [Recertified 12/31/2008]
04/13/1999 - 12/31/2009	American Board of Psychiatry & Neurology (Sub: Clinical Neurophysiology), Certified
08/17/2011 -	American Board of Psychiatry & Neurology (Sub: Neuromuscular

Present Medicine), Certified

LICENSES/CERTIFICATIONS

1999 - 2018 Controlled Substance (UT) - Physician (MD)
1999 - 2018 State License (UT) - Physician (MD)
2006 - 2018 DEA Certificate (UT) - Physician (MD)

CLINICAL AREAS OF SPECIALIZATION

ALS, Botulinum Toxins, EMG, Neurology, Neuromuscular Diseases, Neuropathy, Hemifacial Spasm, Neuromuscular Pathology, Spinal Muscular Atrophy, Botulism

RESEARCH INTERESTS

Peripheral Nervous System Diseases, Obesity, Diabetes, Cutaneous Innervation, Clinical Neurophysiology (EMG), Lambert-Eaton Myasthenic Syndrome

PROFESSIONAL EXPERIENCE

Full-Time Positions

1997 - Present Staff Neurologist, VA Hospital, Salt Lake City, UT
1997 - 2003 Assistant Professor (Clinical) of Neurology, University of Utah School of Medicine, Salt Lake City, UT
Responsibilities: Subspecialty in neuromuscular disease and EMG
1998 - Present Director, University of Utah Department of Neurology, Peripheral Neuropathy Clinic, Salt Lake City, UT
1998 - Present Director, University of Utah, Cutaneous Innervation Laboratory, Salt Lake City, UT
2000 - Present Director, Therapeutic Botulinum Toxin Clinic,
2000 - Present Adjunct Assistant Professor of Pathology, University of Utah, Salt Lake City, UT
2004 - 2012 Associate Professor (Clinical) of Neurology, University of Utah School of Medicine, Salt Lake City, UT
Responsibilities: Subspecialty in neuromuscular disease and EMG
2008 - 2012 Associate Professor, University of Utah School of Medicine, Salt Lake City, UT
2010 - Present Associate Professor of Anesthesiology (Clinical), University of Utah, Salt Lake City, UT
2012 - Present Professor of Neurology (Tenure), University of Utah, Salt Lake City, UT
2013 - Present Vice Chair for Research, University of Utah, Salt Lake City, UT

Editorial Experience

2005 Editor for The Handbook of Peripheral Neuropathy. Taylor and Francis, New York.
2006 Editor for Journal of the Neurological Sciences, Special Issue 2006; 242 (1)

2007 - 2011	Editorial Board for Journal of the Peripheral Nervous System (Advisory)
2010 - 2012	Associate Editor for Education, AAN.com
2011 - Present	Editorial Board for Journal of the Peripheral Nervous System
2012	Editor for Seminars of Neurology, Neuromuscular Medicine from Bench to Bedside
2014 - Present	Editor in Chief for NeuroLearn (AAN Online Learning Program)
2014 - Present	Editorial Board for Annals of Clinical and Translational Science
2016	Editor for Journal of Delivery Science and Innovation

Reviewer Experience

Reviewer for Journal of Delivery Science and Innovation
Abstract Reviewer for American Neurological Association
Experimental Neurology
Expert Opinion on Drug Metabolism and Toxicology
Journal of Neuroscience Methods
Reviewer for Acta Diabetologica
Reviewer for Archives of Internal Medicine
Reviewer for BMJ Open
Reviewer for Brain and Behavior
Reviewer for British Medical Journal
Reviewer for Clinical Endocrinology and Metabolics
Reviewer for Clinical Therapeutics
Reviewer for Clinical Therapeutics
Reviewer for Cytokine
Reviewer for Diabetic Medicine
Reviewer for Expert Opinion on Investigational Drugs
Reviewer for Gerontology
Reviewer for International Journal for Vitamin and Nutrition Research
Reviewer for International Journal of Endocrinology
Reviewer for International Journal of Obesity
Reviewer for Journal of Applied Physiology, Nutrition, and Metabolism
Reviewer for Journal of Biomedical Materials Research: Part A
Reviewer for Journal of Diabetes
Reviewer for Journal of Diabetes Metabolism Research and Reviews
Reviewer for Journal of Diabetes Research
Reviewer for Journal of Diabetes and its Complications
Reviewer for Journal of Immunology Research
Reviewer for Journal of Neuroinflammation
Reviewer for Journal of Pain & Palliative Care Pharmacotherapy
Reviewer for Journal of Pain
Reviewer for Journal of the Peripheral Nervous System
Reviewer for Lipids in Health and Disease
Reviewer for Neuro-oncology
Reviewer for Neuroscience Letters

Reviewer for PLOS 1
Reviewer for Physical Medicine and Rehab
Reviewer for Therapeutic Advances in Endocrinology and Metabolism
Reviewer for American Journal of Managed Care
Reviewer for Annals of Neurology
Reviewer for British Journal of Nutrition
Reviewer for Clinical Journal of Pain
Reviewer for Cochrane Collaboration
Reviewer for Experimental Neurology
Reviewer for Journal of Neurology Neurosurgery and Psychiatry
Reviewer for Journal of the American Medical Association
Reviewer for Journal of the Neurological Sciences
Reviewer for Journal of the Royal Society Interface
Reviewer for Muscle and Nerve
Reviewer for Neurobiology of Disease
Reviewer for Neurology
Reviewer for New England Journal of Medicine
Reviewer for Sleep

SCHOLASTIC HONORS

1985 - 1988	Echols Scholar, University of Virginia
1988	Phi Beta Kappa, University of Virginia
1988	Dean of Faculty Alumni Scholarship, University of Virginia
1988	Magna Cum Laude, University of Virginia
1988 - 1992	Ruth A. Masson Scholar and Dean's Grant recipient, Mayo Medical School
2005	American Academy of Neuromuscular Disease and Electrodiagnostic Medicine Presidential Award

ADMINISTRATIVE EXPERIENCE

Administrative Duties

1998 - Present	Director, Cutaneous Innervation Laboratory.
1998 - Present	Director, University of Utah Peripheral Neuropathy Clinic.
2000 - Present	Director, Therapeutic Botulinum Toxin Clinic.
2006 - Present	Director, Peripheral Neuropathy Association Center of Excellence
2011 - Present	Director, Division of Neuromuscular Medicine
2011 - Present	Director, University of Utah Electrodiagnostic Laboratory
2011 - 2014	Co-Director, Neurology Clinical Trials Unit
2013 - Present	Neurology Department Academic Advisory Committee
2013 - Present	Vice-Chair for Research, Department of Neurology
2014 - Present	Chair, Neurodegeneration Pillar Steering Committee, University of Utah Neurosciences Initiative
2014 - Present	Member, Episodic Brain Dysfunction Pillar Steering Committee
2014 - Present	University of Utah Neuroscience Initiative Scientific Advisory Board

Professional Organization & Scientific Activities

1990 - 1991	Member, American Medical Association, State Governing Council
1990 - 1991	Member, Minnesota Medical Association, Legislation Committee
1990 - 1991	Delegate, American Medical Association, National Convention
1990 - 1991	Treasurer, American Medical Association, local chapter
2000 - 2003	Member, American Association of Electrodiagnostic Medicine, Young Physician Task Force
2003 - 2007	Member, American Association of Electrodiagnostic Medicine, Alternative Media Committee
2005 - 2009	Member, American Academy of Neurology, Annual Meeting Subcommittee with the Education Committee
2006 - Present	Abstract Reviewer, American Neurological Association, Abstract Reviewer
2006 - 2010	Oral Board Examiner, American Board of Electrodiagnostic Medicine
2006 - 2008	Chair, American Academy of Neurology, Topic Work Group for Cognitive Disorders
2006	Member, National Institutes of Health, Consensus Conference on Peripheral Neuropathy
2007 - 2011	Elected Board Member, Peripheral Nerve Society
2007 - 2011	Member, Peripheral Nerve Society, Finance Committee
2008 - 2011	Chair, American Academy of Neurology, Topic Work Group on Neuromuscular Disease and Clinical Neurophysiology
2009 - Present	Committee Member, American Academy of Neurology, Education Committee
2009 - 2011	Member, American Academy of Neurology, Learning Across the Lifetime Taskforce
2009	Member, European Association for the Study of Diabetes, ISDN/Neurodiab, Consensus Conference on Diagnosis of Peripheral Neuropathy, Marker Structure Subgroup
2010 - 2011	Member, American Academy of Neurology, Web Work Group
2011 - Present	Abstract Reviewer, American Academy of Neurology, Annual Meeting-Peripheral Nerve
2011 - 2015	Chair, American Academy of Neurology, Distance Learning Subcommittee
2011 - 2014	Chair, American Academy of Neurology - Neuromuscular Section, Education Work Group
2011 - Present	Member, American Neurological Association, Finance Committee
2012 - 2014	Member, American Academy of Neurology, Web Redesign Work Group (WRWG)
2012	Member, National Institute of Neurological Disorders and Stroke, Neuro NEXT Protocol Working Group 02012012
2012	Member, American Academy of Neurology, Topic Work Group on Child Neurology
2012 - Present	Member, American Academy of Neurology, Topic Work Group on Neuromuscular Disease and Neurophysiology
2012 - Present	Chair, American Academy of Neurology, Topic Work Group on Neuro-

	ophthalmology and Neuro-otology
2012 - 2014	Member, American Academy of Neurology, Navigating Health Care Reform Task Force
2013 - Present	Member, American Academy of Neurology, Membership Subcommittee
2014 - Present	Member, American Diabetes Association, Program Committee
2015 - Present	Member, American Academy of Neurology, Conference Subcommittee (ex officio)
2015 - Present	Board of Directors, American Academy of Neurology
2015 - Present	Chair, American Academy of Neurology, Education Committee
2015 - Present	Member, American Academy of Neurology, Meeting Management Committee
2016 - Present	Member, American Academy of Neurology, Nominations Committee

Grant Review Committee/Study Section

2004	Neuroscience Foundation of New Zealand (Ad Hoc)
2006 - 2014	American Diabetes Association
2008	Juvenile Diabetes Research Foundation
2009	Diabetes UK (Ad Hoc)
2009	NIH ETTN (Ad Hoc)
2009	External Reviewer, University of Michigan MDRTC Pilot and Feasibility Grants
2011	ARG1 MOSS-D12 (SBIR)
2011	ZDK1 GRB-2 (O3) Epidemiology of Diabetes
2011	NSD-K (NINDS Clinical Trials)
2012	Rehabilitation Research and Development (RR&D)
2012	ZDK1 GRB-2 (O4) 1
2014	ZNS1 SRB-G (78) NINDS Clinical Trials
2014	ZDK1 GRB-9(J2) NIDDK Small grants to support diversity (R03)
2014	Reviewer, Michigan Diabetes Interdisciplinary Study Program, Pilot and Feasibility Grants.
2015	Neuroscience Initiative Seed Grant Review Committee
2015	Princess Beatrix Muscle Fund (Netherlands)
2016	Longer Life Foundation Pilot Feasibility Study
2016	ZNSI-SRB G (07) - Clinical Trial Readiness for Rare Neurological Disease

Symposium/Meeting Chair/Coordinator

2006	Session Co-Chair, Genetic Neuropathies, 2006 American Academy of Neurology
2007	Chair, Local Organization Committee. Peripheral Nerve Society Meeting
2009	Session Co-Chair, Diabetic and Metabolic Neuropathies. Peripheral Nerve Society Meeting, Wurzburg Germany
2009	Moderator, Diabetic Neuropathy Case Conference, Peripheral Nerve Society Meeting, Wurzburg Germany

2010	Small vs. Large Fiber Debate, Neurodiab, Stockholm Sweden
2011	Session Moderator, Peripheral Nerve: Clinical and Basic Science Poster Session, American Academy of Neurology, Honolulu Hawaii
2011	Moderator, Diabetic Neuropathy Clinical Poster Tour. Peripheral Nerve Society. Washington D.C.
2012	Session co-chair, Neuropathy Posters, American Academy of Neurology Annual Meeting, New Orleans, LA
2012	Session co-chair, Poster walking tour. Muscle Study Group. Beaver Hollow New York
2013	Session Chair, Plenary Lecture, Peripheral Nerve Society, St. Malo France
2014	Session co-chair, Peripheral Neuropathy Poster Walking Tour, American Academy of Neurology Annual Meeting, Philadelphia PA
2014	Session Chair: The Conundrum of Diabetic Neuropathy. American Diabetes Association Annual Meeting. San Francisco, CA
2015	Session Chair, American Diabetes Association Peripheral Neuropathy Session, Boston Massachusetts

PROFESSIONAL COMMUNITY ACTIVITIES

2011 - 2013	Chair, Baxter, Bioscience Data Monitoring Committee, Protocol 160604
2013 - Present	Board of Trustees, American Brain Foundation, Scientific Advisory Board
2013 - Present	Member, American Brain Foundation, Board of Trustees
2015 - Present	Chair, Celgene Corporation, Celgene CCT-PDA-001-DPN-001 Data Monitoring Board
2015 - Present	Secretary, American Brain Foundation
2015 - Present	Member, American Brain Foundation, Strategic Planning Committee
2015 - Present	Member, Foundation for Peripheral Neuropathy
2015 - Present	Member, Foundation for Peripheral Neuropathy, Scientific Advisory Board

UNIVERSITY COMMUNITY ACTIVITIES

University Level

2008	Member, Search Committee, Physical Therapy Department Search Committee

Health Sciences Level

2010 - 2013	Active Member, University of Utah Medical Group, Finance Committee
2010	Ad Hoc Reviewer, Center for Clinical Translational Science, CCTS K12 Grant
2014 - Present	Member, Health Sciences Center, Neuroscience Initiative, Scientific Advisory Board

University Hospitals & Clinics

2009 - Present Active Member, Pharmacy and Therapeutics Committee
2013 - Present Member, University of Utah Hospitals and Clinics, Academic Advisory Committee
2015 - Present Chair, University of Utah Hospitals and Clinics, Epilepsy Center Director Search Committee

Department Level

1997 - 2004 Member, Neurology, Resident Education Committee
1997 - Present Member, Neurology, Resident Selection Committee
2008 Member, Neurology, Workgroup on Bridge Funding Policy

Programs, Centers & Institutes

2012 - Present Member, Clinical Neurosciences Center, Leadership Team
2013 - Present Executive Committee Member, Clinical Neurosciences Center

SERVICE AT AFFILIATED INSTITUTIONS

1997 - 2011 Medical Staff, Veterans Administration Medical Center, Neurology

CONSULTING

2011 Chair, Pfizer Inc., Advisory board on Tafamadis
2012 Advisory Board Member, Pfizer Inc., Mock FDA Advisory Board for Tafamadis
2012 Consultant, ViroMed Laboratories, Diagnosis of diabetic neuropathy: the MNSI in VM202
2012 - 2014 Consultant, ViroMed Laboratories, Skin biopsy as an endpoint measure in diabetic neuropathy trials and in VM202

MEMBERSHIPS IN PROFESSIONAL SOCIETIES

1993 - Present Member, American Academy of Neurology
1996 - Present Member, American Association of Electrodiagnostic Medicine
1997 - Present Member, Peripheral Nerve Society
2006 - Present Member, American Neurological Association

FUNDING

Active Grants

12/01/16 - 11/30/20 Topiramate as a disease altering therapy for cryptogenic sensory peripheral neuropathy (CSPN): The TopCSPN Study
1U01NS095388-01
Principal Investigator: A. Gordon Smith
Direct Costs: $5,811,767 Total Costs: $7,630,254
National Institute of Neurological Disorders and Stroke
Role: Principal Investigator

09/01/11 - The Utah Regional Center for Excellence in Neuroscience Clinical

06/30/18 Trails (The UR-NEXT) 5U10NS077305-03
Principal Investigator: A. Gordon Smith
Direct Costs: $1,400,000 Total Costs: $2,107,000
National Institute of Neurological Disorders and Stroke
Role: Principal Investigator

10/25/12 - 02/28/16 International Guillain Barré Outcome Study
Principal Investigator(s): Noah Kolb; A. Gordon Smith
Direct Costs: $20,347 Total Costs: $27,000
GBS/CIDP Foundation International
Role: Principal Investigator

09/30/13 - 08/31/18 UT StrokeNet 1U10NS086606-01
Direct Costs: $1,250,000 Total Costs: $1,833,100
National Institute of Neurological Disorders and Stroke
Role: Co-Investigator

02/25/14 - 12/31/16 Sudoscan as a Biomarker for Chemotherapy Induced Peripheral Neuropathy
Principal Investigator: A. Gordon Smith
Direct Costs: $365,760 Total Costs: $485,364
Impeto Medical Sas
Role: Principal Investigator

07/01/14 - 03/31/17 Patient Centered Outcomes Research Institute (PCORI) Pain-Controls
Direct Costs: $35,500 Total Costs: $39,050
University of Kansas
Role: Site Investigator

09/01/14 - 08/31/17 Developing Corneal Confocal Microscopy as a Screening Tool and Biomarker for Diabetic Neuropathy 1DP3DK104394-01
Principal Investigator(s): J. Robinson Singleton; A. Gordon Smith
Direct Costs: $987,594 Total Costs: $1,442,115
NIH National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
Role: Principal Investigator

10/01/14 - 09/30/18 NN103-Rituximab In MG
Direct Costs: $68,677 Total Costs: $99,841
National Institute of Neurological Disorders and Stroke (NINDS)
Role: Site Investigator

01/01/15 - 12/31/20 Peripheral Neuropathy Research Registry (PNRR)
Principal Investigator: A. Gordon Smith
Direct Costs: $77,500 Total Costs: $83,700
Foundation for Peripheral Neuropathy
Role: Principal Investigator

04/01/15 - 03/31/20 Activity for Diabetic Polyneuropathy: The ADAPT Study 2R01DK064814-09A1
Principal Investigator(s): J. Robinson Singleton; A. Gordon Smith
Direct Costs: $2,388,109 Total Costs: $3,208,760
NIH National Institute of Diabetes and Digestive and Kidney

Diseases (NIDDK)
Role: Principal Investigator

08/07/15 - 11/30/19
ADAPT-Sudoscan
Principal Investigator: A. Gordon Smith
Direct Costs: $14,580 Total Costs: $19,348
Impeto Medical Sas
Role: Principal Investigator

05/01/16 - 06/30/18
Vmdn-003
Principal Investigator(s): J. Robinson Singleton; A. Gordon Smith
Direct Costs: $214,800 Total Costs: $285,040
Viromed Co Ltd Dba Vm Biopharma
Role: Principal Investigator

07/01/16 - 06/30/17
The Utah Regional Network Of Excellence Cl
Principal Investigator: A. Gordon Smith
Direct Costs: $100,000 Total Costs: $149,000
National Institute of Neurological Disorders and Stroke (NINDS)
Role: Principal Investigator

Pending Grants

09/01/16 - 08/31/18
Nn105 Huntington's Disease
Principal Investigator: A. Gordon Smith
Massachusetts General Hospital
Role: Principal Investigator

09/01/17 - 08/31/21
A Phase 1/2 Trial of Gene Transfer to Prevent CIPN
R01CA203848
Principal Investigator: David Fink
National Cancer Institute
Role: Co-Investigator

Past Grants

01/01/99 - 01/01/00
Fellowship Award, Clinical Mentor for Dr. Victoria Lawson, MD.
Principal Investigator: A. Gordon Smith
Charcot-Marie-Tooth Association
Role: Co-Principal Investigator

08/01/01 - 07/31/04
The Electrophysiology of Motor Neuron Diseases.
Principal Investigator: Mark B. Bromberg
Direct Costs: $200,000 Total Costs: $283,500
National Institute of Neurological Disorders and Stroke
Role: Co-Investigator

09/01/01 - 07/31/02
The Use of Intraepidermal Nerve Fiber Density Measurement as a Research Tool in Peripheral Neuropathy.
Principal Investigator: A. Gordon Smith
Direct Costs: $31,988 Total Costs: $31,988
University of Utah Research Foundation
Role: Principal Investigator

08/01/02 - 07/30/06
Impaired Glucose Tolerance Causing Neuropathy. R01 NS40458
Principal Investigator: J. Robinson Singleton
Direct Costs: $1,076,525 Total Costs: $1,311,550
National Institute of Neurological Disorders and Stroke
Role: Co-Investigator

04/01/04 - 02/28/08
Cutaneous Measures of Diabetic Neuropathy R01DK064814
Principal Investigator: A. Gordon Smith
Direct Costs: $942,112 Total Costs: $1,401,831
National Institute of Diabetes and Digestive and Kidney Diseases
Role: Principal Investigator

01/01/07 - 12/31/08
Metabolic Syndrome and Reinnervation
Principal Investigator: A. Gordon Smith
Direct Costs: $35,000 Total Costs: $35,000
University of Utah Research Foundation
Role: Principal Investigator

04/15/07 - 03/31/08
2007 International Peripheral Nerve Society Meeting at Snowbird, Utah 1R13NS059289-01
Principal Investigator: A. Gordon Smith
Direct Costs: $28,000 Total Costs: $28,000
National Institute of Neurological Disorders and Stroke
Role: Principal Investigator

09/16/08 - 07/31/13
The Utah Diabetic Neuropathy Study 2R01DK064814-05
Principal Investigator: A. Gordon Smith
Direct Costs: $1,274,059 Total Costs: $2,108,701
National Institute of Diabetes and Digestive and Kidney Diseases
Role: Principal Investigator

01/01/09 - 12/31/11
Peripheral Neuropathy and Metabolic Syndrome: A Lifestyle Intervention Study
Principal Investigator: A. Gordon Smith
Direct Costs: $511,983 Total Costs: $588,780
American Diabetes Association
Role: Principal Investigator

09/01/09 - 08/31/11
Chemotherapy Induced Peripheral Neuropathy in Multiple Myeloma Patients Receiving Total Therapy 3
Principal Investigator(s): J. Robinson Singleton; A. Gordon Smith
University of Utah Neurodegenerative Disease Center
Role: Principal Investigator

05/04/10 - 04/30/11
ARRA Administrative Supplement to Fund Additional Recruitment and Retention Efforts for the UDNS
Principal Investigator(s): J. Robinson Singleton; A. Gordon Smith
National Institute of Diabetes and Digestive and Kidney Diseases
Role: Principal Investigator

03/01/11 - 09/22/11
Corneal Confocal Microscopy as a Research Tool in Peripheral Neuropathy (Research Instrumentation Fund)
Principal Investigator: A. Gordon Smith
Direct Costs: $45,000 Total Costs: $45,000

University of Utah Vice President for Research
Role: Principal Investigator

07/01/11 - 06/30/14 The effect of bariatric surgery on peripheral nerve and axonal regeneration (7-11-AEC-23)
Principal Investigator: A. Gordon Smith
Direct Costs: $521,123 Total Costs: $599,292
American Diabetes Association
Role: Principal Investigator

09/01/11 - 01/31/12 Neurogesx, Inc.
Principal Investigator: A. Gordon Smith
Direct Costs: $19,894 Total Costs: $26,399
NeurogesX, Inc.
Role: Principal Investigator

09/01/11 - 08/31/12 Corneal Confocal Microscopy as a Clinical and Research Tool in Peripheral Neuropathy (Funding Incentive Seed Grant)
Principal Investigator: A. Gordon Smith
Direct Costs: $35,000 Total Costs: $35,000
University of Utah Funding Incentive Seed Grant
Role: Principal Investigator

01/01/12 - 06/30/15 Sudoscan As a Diagnostic and Research Tool for Peripheral Neuropathy
Principal Investigator: A. Gordon Smith
Direct Costs: $204,490 Total Costs: $271,358
Inflexion Point Strategy, LLC
Role: Principal Investigator

05/01/13 - 04/30/14 Personalized Medicine in Peripheral Neuropathy
Principal Investigator: A. Gordon Smith
Direct Costs: $30,000 Total Costs: $30,000
R Harold Burton Foundation
Role: Principal Investigator

Active Contracts

09/01/11 - 06/30/14 3,4 DAPPER: randomized placebo controlled trial of 3,4 diaminopyridine for Lambert Eaton myasthenic syndrome
Principal Investigator: A. Gordon Smith
Direct Costs: $167,527 Total Costs: $222,308
Jacobus Pharmaceutical Company, Inc.
Role: Principal Investigator

08/01/13 - 07/01/15 MYSTICOL - Myobloc for Sialorrhea Treatment with Intraglandular Injection - Controlled and Open Label: A Phase 3, Multicenter, Double-Blind, Placebo-Controlled, Single-Treatment Efficacy and Safety Study of MYOBLOC (SN-SIAL-301)
Principal Investigator: A. Gordon Smith
Direct Costs: $242,100 Total Costs: $321,267
US World Med

Role: Principal Investigator

Past Contracts

07/30/98 - 04/15/01
A 24-Month, Double-Blinded, Randomized, Placebo-Controlled, Fixed-Dose, Parallel-Group, Multicenter Study of Zenarestat (CI-1014) in the Treatment of diabetic Neuropathy.
Principal Investigator: Mark B. Bromberg
Direct Costs: $250,980 Total Costs: $320,000
Warner-Lambert/Parke-Davis
Role: Co-Investigator

10/08/99 - 05/31/01
Magnetic Biostimulation in Painful Diabetic Peripheral Neuropathy.
Principal Investigator: Mark B. Bromberg
Direct Costs: $35,000 Total Costs: $35,000
Michael I. Weintraub, MD
Role: Co-Investigator

04/12/00 - 09/30/02
Safety & Efficacy of ABT-594 to Placebo for Patients with Painful Diabetic Polyneuropathy.
Principal Investigator: Mark B. Bromberg
Direct Costs: $70,736 Total Costs: $87,936
Abbott Laboratories
Role: Co-Investigator

07/01/03 - 06/30/05
A Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study to Determine the Safety & Efficacy of Avonex When Used in Subjects With Chronic Inflammatory Demyelinating polyradiculoneuropathy (CIDP).
Principal Investigator: Mark B. Bromberg
Direct Costs: $33,006 Total Costs: $42,000
Biogen Idec Inc
Role: Co-Investigator

07/01/03 - 12/31/06
A Randomized, Double-Blind, Placebo-Controlled, Stratified, Parallel-Group, Multi-Center, Dose-Ranging Study Evaluating Four Oral Doses of TCH346 Administered Once Daily in Patients With Amyotrophic Lateral Sclerosis.
Principal Investigator: Mark B. Bromberg
Direct Costs: $151,670 Total Costs: $191,612
Novartis Pharmaceuticals Corporation
Role: Co-Investigator

06/12/06 - 03/01/08
Bi-axial rotating magnetic field therapy in diabetic peripheral neuropathy
Principal Investigator: A. Gordon Smith
Direct Costs: $45,000 Total Costs: $45,000
New York University
Role: Principal Investigator

05/15/07 - 03/31/08
Double Blind Placebo Controlled Study of Myobloc for Troublesome Siallorhea Due to Parkinson's Disease

Principal Investigator(s): A. Gordon Smith; John D. Steffens
Direct Costs: $26,667 Total Costs: $34,000
Solstice Neurosciences Inc
Role: Principal Investigator

06/01/12 - 05/31/15 A PHASE II, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, MULTICENTER STUDY TO ASSESS THE SAFETY AND EFFICACY OF VM202 IN SUBJECTS WITH PAINFUL DIABETIC PERIPHERAL NEUROPATHY
Principal Investigator: A. Gordon Smith
Direct Costs: $187,498 Total Costs: $248,810
ViroMed
Role: Principal Investigator

07/01/12 - 05/31/14 VM202 Central Laboratory Contract for Processing Skin Biopsies for IENFD
Principal Investigator: A. Gordon Smith
Direct Costs: $216,100 Total Costs: $286,765
ViroMed
Role: Principal Investigator

Clinical Studies

2008 - Present Clinical versus Neurophysiology Study I and II (Rochester Diabetic Neuropathy Study, Mayo Clinic, Rochester, MN).

TEACHING RESPONSIBILITIES/ASSIGNMENTS

Course and Curriculum Development

1997 - 2004 Director, Clinical Neurology Lecture Series, University of Utah Department of Neurology.

2007 - Present Botox Cervical Dystonia Injection Center (Director)

2009 Organizer & Speaker, Peripheral Neuropathy Society, Peripheral Neuropathy Conference: Neuropathy and You

2010 Planning Committee, Neuropathy Association's Peripheral Neuropathy Summit, Washington D.C.

2011 - Present American Academy of Neurology : On-line Assessment Design Framework Curriculum Design Course Development

Courses Directed

2005 Skin Biopsy for Peripheral Neuropathy, American Academy of Electrodiagnostic Medicine, Monterey California

2006 Neuromuscular Therapy: The Top Ten, The American Academy of Neurology Annual Meeting, San Diego California

2009 Diabetic Neuropathy Case Conference, Peripheral Nerve Society, Wurzburg Germany

2010 Neuromuscular Skills Pavilion: Neuromuscular Bedside Rounds, American Academy of Neurology Annual Meeting, Toronto Canada

2011 Neuromuscular Skills Pavilion, Neuromuscular Bedside Rounds.

	American Academy of Neurology Annual Meeting. Honolulu Hawaii.
2012	Neuromuscular Skills Pavilion, Neuromuscular Bedside Rounds. American Academy of Neurology Annual Meeting. New Orleans LA.
2013	Neuromuscular Skills Pavilion, Neuromuscular Bedside Rounds, American Academy of Neurology Annual Meeting, San Diego California

Course Lectures

1988 - 1992	Lecturer, University of Michigan Medical School. medical student physical examination course
2004	Instructor, NEURO 7020 (1): Neurology OS - Small Groups, University of Utah, Neurology
2004	Instructor, NEURO 7020 (1): Neurology OS - Small Groups 3, University of Utah, Neurology
2004	Instructor, NEURO 7020 (1): Neurology OS - Small Groups 4 - Dementia New cases MID, AD, PD, Depression, University of Utah, Neurology
2004	Instructor, NEURO 7020 (1): Neurology OS - Small Groups, University of Utah, Neurology
2006	Instructor, NEURO 7020 (1): Neurology OS - Small Groups: Cases 2 - 6, University of Utah, Neurology
2006	Instructor, NEURO 7020 (1): Neurology OS - Small Groups, University of Utah, Neurology
2007	Instructor, NEURO 7020(1): Neurology OS - Small Groups, University of Utah, Neurology
2008	Instructor, NEURO 7020(1): Neurology OS - Small Groups, University of Utah, Neurology
2009	Instructor, NEURO 7020(1): Neurology OS - Small Groups, University of Utah, Neurology
2009	Instructor, NEURO 7020 (1): Neurology - Cases Set 1 - 6, University of Utah, Neurology
2009	Instructor, NEURO 7020 (1): Neurology - Small Groups - Cases 2 - 6 - Quiz 1%, University of Utah, Neurology
2009	Instructor, NEURO 7020 (1): Neurology - Cases 4-6 Small Group Dementias, University of Utah, Neurology
2010	Instructor, NEURO 7020 (1): Cases, Small Group Discussions, University of Utah, Neurology

Clinical Teaching

1997 - Present	Clinical teaching for residents and students on the inpatient Neurology service at University of Utah Hospital and the Salt Lake City VA 6-12 weeks/year.
1997 - Present	Clinical teaching for all residents and fellows and selected students rotating on the Neuromuscular Service (neuromuscular clinic and EMG laboratory).
1997 - 2003	General Neurology Resident Continuity Clinic

2000 - Present Clinical teaching in Botulinum Toxin Clinic for all rotating residents, fellows and selected medical students.

Small Group Teaching

1997 - Present Small group leader in second year medical school neuroscience course, University of Utah School of Medicine.
2000 - 2001 Small group leader, Introduction to Medicine course.
2005 - 2007 Clinical Small Group for Graduate Bioengineering Students

Trainee Supervision

Fellow

1997 - 1998 Supervisor, Rob McLaughlin, University of Utah. Neuromuscular Fellow
Trainee's Current Career Activities: Private Practice

1997 - 1998 Supervisor, John Steffens, University of Utah. Neuromuscular Fellow
Trainee's Current Career Activities: Faculty, University of Utah

1998 - 1999 Supervisor, Greg Meekins, University of Utah. Neuromuscular Fellow
Trainee's Current Career Activities: Faculty University of Washington

1998 - 1999 Supervisor, Dennis Obrien, University of Utah. Neuromuscular Fellow
Trainee's Current Career Activities: Private Practice

2000 - 2001 Supervisor, Jun Li, University of Utah. Neuromuscular Fellow
Trainee's Current Career Activities: Faculty, Vanderbilt University

2000 - 2001 Supervisor, Ross Lipton, University of Utah. Neuromuscular Fellow
Trainee's Current Career Activities: Private Practice

2000 - 2002 Supervisor, Victoria Lawson, University of Utah. Neuromuscular Fellow, Special Interest in CMT
Trainee's Current Career Activities: Faculty, Ohio State University

2001 - 2002 Supervisor, David Renner, University of Utah. Neuromuscular Fellow
Trainee's Current Career Activities: Faculty, University of Utah

2002 - 2003 Supervisor, Mouaz Sbei, University of Utah. Neuromuscular Fellow
Trainee's Current Career Activities: Private Practice

2004 - 2005 Supervisor, Elizabeth Sunderman, University of Utah. Neuromuscular Fellow
Trainee's Current Career Activities: Private Practice

2006 - 2007 Supervisor, Jeffrey Wagner, University of Utah. Neuromuscular Fellow
Trainee's Current Career Activities: Faculty, University of Utah

2007 - 2008 Supervisor, Mohammed Shoari, University of Utah. Neuromuscular Fellow
Trainee's Current Career Activities: Private Practice Salt Lake City

2008 - 2009 Supervisor, Jackie Whitesell, University of Utah. Neuromuscular Fellow
Trainee's Current Career Activities: Faculty, University of Utah Department of Neurology

2008 - 2009 Supervisor, Nicole Clark, University of Utah
Trainee's Current Career Activities: Practice, Helena Montana
2009 - 2010 Supervisor, Mengjing Huan, University of Utah
Trainee's Current Career Activities: Private Practice, Salt Lake City, Utah
2009 - 2010 Supervisor, Peter Masny, University of Utah
Trainee's Current Career Activities: Practice, California
2011 - 2012 Supervisor, Lia Chebeleu, University of Utah. Neuromuscular Fellow
Trainee's Current Career Activities: Private Practice
2011 - 2012 Supervisor, Emma Burbank, University of Utah. Neuromuscular Fellow
Trainee's Current Career Activities: Private Practice, Oregon
2012 - 2013 Supervisor, Summer Gibson, University of Utah. Neuromuscular Fellow
Trainee's Current Career Activities: Assistant Professor of Neurology University of Utah
2012 - 2013 Supervisor, Noah Kolb, University of Utah. Neuromuscular Fellow
Trainee's Current Career Activities: Assistant Professor of Neurology University of Utah
2013 - 2014 Supervisor, Payam Soltanzadeh, University of Utah. Neuromuscular Fellow
Trainee's Current Career Activities: Staff Cleveland Clinic
2014 - 2015 Supervisor, Christopher Muth, University of Utah. Neuromuscular Fellow
2014 - 2015 Supervisor, Ligia Onofrei, University of Utah. Neuromuscular Fellow
2015 - 2016 Supervisor, Kelsey Juster-Switlyk, University of Utah. Neuromuscular Fellow
2015 - 2016 Supervisor, Yoonhee Hong-Choi, University of Utah. Neuromuscular Fellow
2016 Supervisor, Patrick Nicholson, University of Utah. Neuromuscular

MD, PhD
2001 - 2003 Supervisor, Shawn Smith, University of Utah.
2005 - 2008 Supervisor, Kristi Rose, University of Utah

Medical Student
2012 Supervisor, Ryan Brinn, University of Utah
2016 Supervisor, Joshua Winegar, University of Utah
2016 Supervisor, Melanie Torres, University of Puerto Rico

High School
2011 Supervisor, Grace Hunt, University of Utah. Neuroscience Summer Student

Educational Lectures

Didactic Lectures

1997 - Present	Lecturer in the Clinical Neurophysiology Lecture Series, University of Utah, Department of Neurology.
2004 - Present	Peripheral Neuropathy, PMR Resident Lecture Series

Continuing Education

CE Courses Developed

2010	Spasticity Pain and Dystonia, University of Utah Departments of PMR, Neurology and Anesthesiology

CE Courses Taught

2004	Peripheral Neuropathy Update, Update in Internal Medicine, Park City Utah
2007	Update on Peripheral Neuropathy, Internal Medicine Update, Park City Utah
2009	Peripheral Neuropathy, Diabetes Educators of Utah, Snowbird, Utah

Other Educational Activities

2007	Director Cervical Dystonia Injection Center
2009	Residents and Fellows Career Forum Fellowship Panel Member, American Academy of Neurology Annual Meeting, Seattle Washington
2009	Dystonia Injection Workshop Faculty Member
2010	Residents and Fellows Career Forum Fellowship Panel Member, American Academy of Neurology Annual Meeting, Toronto Canada
2010	Dystonia Injection Workshop Faculty Member
2011	Moderator, Residents and Fellows Career Forum Fellowship Panel, American Academy of Neurology Annual Meeting, Honolulu Hawaii
2011	American Academy of Neurology Assessment Design Framework Model (ADFM) Workshop for NeuroLearn Faculty
2012	American Academy of Neurology Assessment Design Framework Model (ADFM) Workshop for NeuroLearn Faculty

PEER-REVIEWED JOURNAL ARTICLES

1. Windebank AJ, **Smith AG**, Russell JW (1994). The effect of nerve growth factor, ciliary neurotrophic factor, and ACTH analogs on cisplatin neurotoxicity in vitro. *Neurology*, *44*(3 Pt 1), 488-94.
2. **Smith AG**, Wald J (1996). Acute ventilatory failure in Lambert-Eaton myasthenic syndrome and its response to 3,4-diaminopyridine. *Neurology*, *46*(4), 1143-5.
3. **Smith AG**, Albers JW (1997). n-Hexane neuropathy due to rubber cement sniffing. *Muscle Nerve*, *20*, 1445-50.
4. **Smith AG**, Cornblath WT, Deveikis JP (1997). Local thrombolytic therapy in deep cerebral venous thrombosis. *Neurology*, *48*, 1613-9.
5. **Smith AG**, Bromberg MB, Singleton JR, Forshew DA (1999). The use of "clinic

room" presentation as an educational tool in the ambulatory care setting. *Neurology*, *52*(2), 317-20.
6. Bromberg MB, **Smith AG**, Bauerle J (1999). A comparison of two commercial quantitative electromyographic algorithms with manual analysis. *Muscle Nerve*, *22*(9), 1244-8.
7. Entezari-Taher M, Singleton JR, Jones CR, Meekins G, Petajan JH, **Smith AG** (1999). Changes in excitability of motor cortical circuitry in primary restless legs syndrome. *Neurology*, *53*(6), 1201-5.
8. Carey MJ, **Smith AG**, Townsend JJ (2000). Pathologic quiz case: progressive diffuse weakness after chemotherapy for large cell lymphoma in a middle age woman. Lymphomatous meningitis with neurolymphomatosis. *Arch Pathol Lab Med*, *124*, 645-6.
9. **Smith AG**, Urbanits S, Blaivas M, Grisold W, Russell JW (2000). Clinical and pathologic features of focal myositis. *Muscle Nerve*, *23*(10), 1569-75.
10. **Smith AG** (2001). Charcot-Marie-tooth disease. *Arch Neurol*, *58*(6), 1014-6.
11. Singleton JR, **Smith AG**, Bromberg MB (2001). Increased prevalence of impaired glucose tolerance in patients with painful sensory neuropathy. *Diabetes Care*, *24*(8), 1448-53.
12. Moore KR, Blumenthal DT, **Smith AG**, Ward JH (2001). Neurolymphomatosis of the lumbar plexus: high-resolution MR neurography findings. *Neurology*, *57*(4), 740-2.
13. Singleton JR, **Smith AG**, Bromberg MB (2001). Painful sensory polyneuropathy associated with impaired glucose tolerance. *Muscle Nerve*, *24*(9), 1225-8.
14. **Smith AG**, Ramachandran P, Tripp S, Singleton JR (2001). Epidermal nerve innervation in impaired glucose tolerance and diabetes-associated neuropathy. *Neurology*, *57*(9), 1701-4.
15. Li J, Petajan J, Smith G, Bromberg M (2002). Electromyography of sternocleidomastoid muscle in ALS: a prospective study. *Muscle Nerve*, *25*(5), 725-8.
16. Lawson VL, **Smith AG**, Bromberg MB (2003). Assessment of axonal loss in Charcot Marie Tooth neuropathies. *Exp Neurol*, *184*(2), 753-7.
17. Bonkowsky JL, Johnson J, Carey JC, **Smith AG**, Swoboda KJ (2003). An infant with primary tooth loss and palmar hyperkeratosis: a novel mutation in the NTRK1 gene causing congenital insensitivity to pain with anhidrosis. *Pediatrics*, *112*(3 Pt 1), e237-41.
18. **Smith AG**, Singleton JR (2004). The diagnostic yield of a standardized approach to idiopathic sensory-predominant neuropathy. *Arch Intern Med*, *164*(9), 1021-5.
19. **Smith AG**, Howard JR, Kroll R, Ramachandran P, Hauer P, Singleton JR, McArthur J (2005). The reliability of skin biopsy with measurement of intraepidermal nerve fiber density. *J Neurol Sci*, *228*(1), 65-9.
20. **Smith AG**, Singleton JR (2006). Idiopathic neuropathy, prediabetes and the metabolic syndrome. *Journal of Neurological Sciences*, (242), 9-14.
21. Singleton JR, **Smith AG** (2006). Therapy insight: neurological complications of prediabetes. *Nat Clin Pract Neurol*, *2*(5), 276-82.
22. **Smith AG**, Russell J, Feldman EL, Goldstein J, Peltier A, Smith S, Hamwi J, Pollari D, Bixby B, Howard J, Singleton JR (2006). Lifestyle intervention for pre-diabetic

neuropathy. *Diabetes Care*, *29*(6), 1294-9.
23. Sampson JB, Smith SM, **Smith AG**, Singleton JR, Chin S, Pestronk A, Flanigan KM (2007). Paraneoplastic myopathy: response to intravenous immunoglobulin. *Neuromuscul Disord*, *17*(5), 404-8.
24. Orme HT, **Smith AG**, Nagel MA, Bert RJ, Mickelson TS, Gilden DH (2007). VZV spinal cord infarction identified by diffusion-weighted MRI (DWI). *Neurology*, *69*(4), 398-400.
25. Singleton JR, **Smith AG** (2007). Neuropathy associated with prediabetes: what is new in 2007? *Curr Diab Rep*, *7*(6), 420-4.
26. **Smith AG**, Singleton JR (2008). Impaired glucose tolerance and neuropathy. *Neurologist*, *14*(1), 23-9.
27. Feldman EL, Cornblath DR, Porter J, Dworkin R, Scherer S, Attendees of the NIH Peripheral Neuropathy Conference (2008). National Institute of Neurological Disorders and Stroke (NINDS): advances in understanding and treating neuropathy, 24-25 October 2006; Bethesda, Maryland. *J Peripher Nerv Syst*, *13*(1), 1-6.
28. Singleton JR, Bixby B, Russell JW, Feldman EL, Peltier A, Goldstein J, Howard J, **Smith AG** (2008). The Utah Early Neuropathy Scale: a sensitive clinical scale for early sensory predominant neuropathy. *J Peripher Nerv Syst*, *13*(3), 218-27.
29. Shprecher DR, Flanigan KM, **Smith AG**, Smith SM, Schenkenberg T, Steffens J (2008). Clinical and diagnostic features of delayed hypoxic leukoencephalopathy. (PMID: 19196933). *J Neuropsychiatry Clin Neurosci*, *20*(4), 473-7.
30. **Smith AG**, Rose K, Singleton JR (2008). Idiopathic neuropathy patients are at high risk for metabolic syndrome. *J Neurol Sci*, *273*(1-2), 25-8.
31. Peltier A, **Smith AG**, Russell JW, Sheikh K, Bixby B, Howard J, Goldstein J, Song Y, Wang L, Feldman EL, Singleton JR (2009). Reliability of quantitative sudomotor axon reflex testing and quantitative sensory testing in neuropathy of impaired glucose regulation. *Muscle Nerve*, *39*(4), 529-35.
32. Blackburn MK, Lamb RD, Digre KB, **Smith AG**, Warner JE, McClane RW, Nandedkar SD, Langeberg WJ, Holubkov R, Katz BJ (2009). FL-41 tint improves blink frequency, light sensitivity, and functional limitations in patients with benign essential blepharospasm. *Ophthalmology*, *116*(5), 997-1001.
33. Weintraub MI, Herrmann DN, **Smith AG**, Backonja MM, Cole SP (2009). Pulsed electromagnetic fields to reduce diabetic neuropathic pain and stimulate neuronal repair: a randomized controlled trial. *Arch Phys Med Rehabil*, *90*(7), 1102-9.
34. Lauria G, Hsieh ST, Johansson O, Kennedy WR, Leger JM, Mellgren SI, Nolano M, Merkies IS, Polydefkis M, **Smith AG**, Sommer C, Valls-Sole J (2010). European Federation of Neurological Societies/Peripheral Nerve Society Guideline on the use of skin biopsy in the diagnosis of small fiber neuropathy. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society. *Eur J Neurol*, *17*(7), 903-12, e44-9.
35. Dyck PJ, Overland CJ, Low PA, Litchy WJ, Davies JL, Dyck PJ, O'Brien PC, Albers JW, Andersen H, Bolton CF, England JD, Klein CJ, Llewelyn JG, Mauermann ML, Russell JW, Singer W, **Smith AG**, Tesfaye S, Vella A (2010). Signs and symptoms versus nerve conduction studies to diagnose diabetic sensorimotor polyneuropathy: CI vs. NPhys trial. *Muscle Nerve*, *42*(2), 157-64.

36. Lauria G, Bakkers M, Schmitz C, Lombardi R, Penza P, Devigili G, **Smith AG**, Hsieh ST, Mellgren SI, Umapathi T, Ziegler D, Faber CG, Merkies IS (2010). Intraepidermal nerve fiber density at the distal leg: a worldwide normative reference study. *J Peripher Nerv Syst*, *15*(3), 202-7.
37. Tesfaye S, Boulton AJ, Dyck PJ, Freeman R, and the Toronto Consensus Conference (2010). Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. *Diabetes Care*, *33*(10), 2285-2293.
38. Joint Task Force of the EFNS and the PNS (2010). European Federation of Neurological societies/Peripheral Nerve Society Guideline on the use of skin biopsy in the diagnosis of small fiber neuropathy. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society. *J Peripher Nerv Syst*, *15*, 79-92.
39. Zilliox L, Peltier AC, Wren PA, Anderson A, **Smith AG**, Singleton JR, Feldman EL, Alexander NB, Russell JW (2011). Assessing autonomic dysfunction in early diabetic neuropathy: the Survey of Autonomic Symptoms. *Neurology*, *76*(12), 1099-105.
40. Dyck PJ, Albers JW, Andersen H and the Toronto Consensus Group (2011). Diabetic polyneuropathies (DPNs): update on research definition, diagnositc criteria and estimation of severity. *Diabetes Metab Res Rev*, *27*(7), 620-628.
41. Malik R, Veves A, Tesfaye S, **Smith AG**, CameronN, Zochodne D, Lauria G. on behalf of The Toronto Consensus Panel on Diabetic Neuropathy (2011). Small fiber neuropathy role in the diagnosis of DSPN. *Diabetes Metab Res Rev*, *27*(7), 674-684.
42. Tesfaye S, Vileikyte L, Rayman G, Sindrup SH, Perkins, BA, Baconja J, Vinik AI, Boulton AJM, on behalf of The Toronto Expert Panel on Diabetic Neuropathy (2011). Painful diabetic peripheral neuropathy: consensus recommendations on diagnosis, assessment and management. *Diabetes Metab Res Rev*, *27*(7), 629-638.
43. French KF, Hoesch RE, Allred J, Wilder M, **Smith AG**, Digre KB, La Barge DV 3rd (2012). Repetitive use of intra-arterial verapamil in the treatment of reversible cerebral vasoconstriction syndrome. *J Clin Neurosci*, *19*(1), 174-6.
44. **Smith AG** (2012). Diagnosis of neuropathy: comment on "tests and expenditures in the initial evaluation of peripheral neuropathy". *Arch Intern Med*, *172*(2), 132-3.
45. **Smith AG** (2012). Neuromuscular therapy from bench to bedside. *Semin Neurol*, *32*(3), 171-2.
46. Singleton JR, **Smith AG** (2012). The diabetic neuropathies: practical and rational therapy. *Semin Neurol*, *32*(3), 196-203.
47. Boger MS, Hulgan T, Haas DW, Mitchell V, **Smith AG**, Singleton JR, Peltier AC (2012). Measures of small-fiber neuropathy in HIV infection. *Auton Neurosci*, *169*(1), 56-61.
48. **Smith AG**, Marcus R (2012). Exercise for diabetic neuropathy: A toe in the therapeutic door. *J Diabetes Complications*, *26*(5), 361-2.
49. Burns TM, **Smith AG** (2012). "Measure twice, cut once": improving diagnostic accuracy of skin biopsy. (PMID: 23100394). *Neurology*, *79*(22), 2164-5.
50. **Smith AG**, Marcus R (2012). Exercise for diabetic neuropathy: a toe in the therapeutic door. *Neurology*, *26*(5), 2104-5.

51. **Smith AG** (2012). Impaired glucose tolerance and metabolic syndrome in idiopathic neuropathy. *J Peripher Nerv Syst*, *17*(2), 15-21.
52. Dyck PJ, Overland CJ, Low PA, Litchy WJ, Davies JL, Dyck PJ, Carter RE, Melton LJ, Andersen H, Albers JW, Bolton CF, England JD, Klein CJ, Llewelyn G, Mauermann ML, Russell JW, Selvarajah D, Singer W, **Smith AG**, Tesfaye S, Vella A (2012). "Unequivocally Abnormal" vs "Usual" Signs and Symptoms for Proficient Diagnosis of Diabetic Polyneuropathy: Cl vs N Phys Trial. *Arch Neurol*, *69*(12), 1609-14.
53. Gibson SB, Majersik JJ, **Smith AG**, Bromberg MB (2013). Three cases of acute myositis in adults following influenza-like illness during the H1N1 pandemic. *J Neurosci Rural Pract*, *4*(1), 51-4.
54. **Smith AG**, Kim G, Porzio M, Allen B, Koach M, Mifflin M, Digre K, Keung BM, Singleton JR (2013). Corneal confocal microscopy is efficient, well-tolerated, and reproducible. *Journal of the Peripheral Nervous System Online*, *18*(1), 54-8.
55. Frech TM, **Smith AG**, Reily M, Chamberlain J, Murtaugh MA, Penrod J, Battistone MJ, Stults BM (2013). Peripheral neuropathy: a complication of systemic sclerosis. *Clin Rheumatol*, *32*(6), 885-8.
56. Cheng HT, Dauch JR, Porzio MT, Yanik BM, Hsieh W, **Smith AG**, Singleton JR, Feldman EL (2013). Increased axonal regeneration and swellings in intraepidermal nerve fibers characterize painful phenotypes of diabetic neuropathy. *J Pain*, *14*(9), 941-7.
57. Dyck PJ, Albers JW, Wolfe J, Bolton CF, Walsh N, Klein CJ, Zafft AJ, Russell JW, Thomas K, Davies JL, Carter RE, Melton LJ 3rd, Litchy WJ (2013). A trial of proficiency of nerve conduction: greater standardization still needed. *Muscle Nerve*, *48*(3), 369-74.
58. **Smith AG**, Singleton JR (2013). Obesity and hyperlipidemia are risk factors for early diabetic neuropathy. *J Diabetes Complications*, *27*(5), 436-42.
59. Kim G, Singleton JR, Mifflin MD, Digre KB, Porzio MT, **Smith AG** (2013). Assessing the Reproducibility of Quantitative In Vivo Confocal Microscopy of Corneal Nerves in Different Corneal Locations. *Cornea*, *32*(10), 1331-8.
60. Cortez M, Singleton JR, **Smith AG** (2014). Glucose intolerance, metabolic syndrome, and neuropathy. *Handb Clin Neurol*, *126*, 109-22.
61. **Smith AG**, Lessard M, Reyna S, Doudova M, Singleton JR (2014). The diagnostic utility of Sudoscan for distal symmetric peripheral neuropathy. *J Diabetes Complications*, *Jul-Aug*(4), 511-516.
62. **Smith AG** (2014). Do all neuropathy patients need an EMG at least once? *Continuum (Minneap Minn)*, *20*(5 Peripheral Nervous System Disorders), 1430-4.
63. Hamid HS, Mervak CM, Munch AE, Robell NJ, Hayes JM, Porzio MT, Singleton JR, **Smith AG**, Feldman EL, Lentz SI (2014). Hyperglycemia- and neuropathy-induced changes in mitochondria within sensory nerves. *Ann Clin Transl Neurol*, *1*(10), 799-812.
64. Singleton JR, Marcus RL, Jackson JE, K Lessard M, Graham TE, **Smith AG** (2014). Exercise increases cutaneous nerve density in diabetic patients without neuropathy. *Ann Clin Transl Neurol*, *1*(10), 844-9.
65. **Smith AG**, Burns TM (2014). Re-evaluating clinical measurement tools in therapeutic trials: time to make a Rasch decision? *Neurology*, *Dec 2;83*(23), 2014-

5.
66. Singleton JR, Marcus RL, Lessard MK, Jackson JE, **Smith AG** (2015). Supervised exercise improves cutaneous reinnervation capacity in metabolic syndrome patients. *Ann Neurol*, *77*(1), 146-53.
67. Kessler JA, Vinik A, **Smith AG**, Choi SH, Wymer J, Shaibani A, Ajroud-Driss S, Cha BS, VM202 DPN-II Study Group (2015). Double-blind, placebo-controlled study of HGF gene therapy in diabetic neuropathy. *Ann Clin Transl Neurol*, *2015 May;2*(5), 465-78.
68. Kinard KI, **Smith AG**, Singleton JR, Lessard M, Katz BJ, Warner JEA, Crum AV, Mifflin MD, Brennan KC, Digre KB (03/31/2015). Chronic migraine is associated with reduced corneal nerve fiber density and symptoms of dry eye. *Headache*, *2015Apr;55*(4), 543-9.
69. Baets J, Duan X, Wu Y, Smith G, Seeley WW, Mademan I, McGrath NM, Beadell NC, Khoury J, Botuyan MV, Mer G, Worrell GA, Hojo K, DeLeon J, Laura M, Liu YT, Senderek J, Weis J, Van den Bergh P, Merrill SL, Reilly MM, Houlden H, Grossman M, Scherer SS, De Jonghe P, Dyck PJ, Klein CJ (2015). Defects of mutant DNMT1 are linked to a spectrum of neurological disorders. *Brain*, *138*(Pt 4), 845-61.
70. Tavakoli M, Ferdousi M, Petropoulos IN, Morris J, Pritchard N, Zhivov A, Ziegler D, Pacaud D, Romanchuk K, Perkins BA, Lovblom LE, Bril V, Singleton JR, Smith G, Boulton AJ, Efron N, Malik RA (2015). Normative values for corneal nerve morphology assessed using corneal confocal microscopy: a multinational normative data set. *Diabetes Care*, *38*(5), 838-43.
71. Singleton JR, **Smith AG**, Marcus RL (2015). Exercise as Therapy for Diabetic and Prediabetic Neuropathy. *Curr Diab Rep*, *Dec;15*(12), 120.
72. Burns TM, **Smith AG**, et al (2016). Editorial by concerned physicians: Unintended effect of the Orphan Drug Act on the potential cost of 3,4-diaminopyridine. *Muscle Nerve*, *Feb; 53*(2), 165-8.
73. Kissel J, **Smith AG** (2016). Understanding Small Fiber Neuropathy: The Long and Short of It. *JAMA Neurol*, *73*(6), 635-7.
74. Juster-Switlyk K, **Smith AG** (2016). Updates in diabetic peripheral neuropathy. *F1000Res*, *2016 Apr*, 25;5 Rev-738.
75. **Smith AG** (2016). Price Gouging and the Dangerous New Breed of Pharma Companies. *Harv Bus Rev*.
76. Vinik AI, **Smith AG**, Singleton JR, Callaghan B, Freedman BI, Tuomilehto J, Bordier L, Baudeceau B, Roche F (2016). Normative values for Electrochemical Skin Conductances and Impact of Ethnicity on Quantitative Assessment of Sudomotor Function. *Diabetes Technol Ther*, *18*(6), 391-8.
77. Pucillo EM, Christensen-Mayer N, Poole SD, Whitten DM, Freeman D, Bohe BR, Swensen BR, **Smith AG**, Johnson NE (2016). Same-day physical therapy consults in an outpatient neuromuscular disease physician clinic. *J Multidiscip Healthc*, *2016 Oct 3*(9), 493-497.
78. Kolb NA, **Smith AG**, Singleton JR, Beck SL, Stoddard GJ, Brown S, Mooney K (2016). The Association of Chemotherapy-Induced Peripheral Neuropathy Symptoms and the Risk of Falling. *JAMA Neurol*, *73*(7), 860-6.
79. de Havenon A, Haynor D, Tirschwell D, Majersik J, **Smith AG**, Cohen W, Andre J

(2016). Collateral Blood Vessels Detected by Arterial Spin Labeling MRI Predict Better Neurological Outcome After Ischemic Stroke. *JAMA Neurol*.

80. Kluding PM, Singleton JR, Pasnoor M, Dimachkie MM, **Smith AG**, Marcus RL (2016). Activity in People With Diabetic Polyneuropathy (ADAPT): Study Design and Protocol for a Two-Site Randomized Controlled Trial. *Phys Ther*, *Epub*.
81. Gewandter JS, Burke L, Cavaletti G, Dworkin RH, Gibbons C, Gover TD, Herrmann DN, McArthur Mb JC, McDermott MP, Rappaport BA, Reeve BB, Russell JW, **Smith AG**, Smith SM, Turk DC, Vinik AI, Freeman R (2016). Content validity of symptom-based measures for diabetic, chemotherapy, and HIV peripheral neuropathy. *Muscle Nerve*, *Epub*.
82. Wynn D, McCorquodale D 3rd, Peters A, Juster-Switlyk K, **Smith AG**, Ansari S (2016). Rapidly Progressive Quadriplegia and Encephalopathy. *JAMA Neurol*, *2016*, Sept 6.
83. Abenroth DC, **Smith AG**, Greenlee JE, Austin SD, Clardy SL (2016). Lambert-Eaton myasthenic syndrome (LEMS): Epidemiology and therapeutic response in the national Veterans Affairs (VA) population. *Muscle Nerve*, *2016*, Dec 20.
84. Juster-Switlyk K, **Smith AG**, Kovacsovics T, Stephens D, Glenn M, Palmer CA, Quigley EP, Kolb N (2017). MTHFR C667T Polymorphism is Associated with Methotrexate Induced Myelopathy Risk (Epub ahead of print). *Neurology*.

REVIEW ARTICLES

1. **Smith AG**, Bromberg MB (1999). The treatment of inflammatory demyelinating neuropathy. [Review]. *J Clin Neuromuscular Dis*, *1*, 21-31.
2. Bromberg MB, **Smith AG** (2002). Towards an efficient method to evaluate peripheral neuropathies. [Review]. *J Clin Neuromuscular Dis*, *3*, 172-182.
3. Singleton JR, **Smith AG** (2003). Painful sensory neuropathy in patients with impaired glucose tolerance: diagnosis and pathophysiology. [Review]. *Clin Geriatr*, *11*(3), 28-34.
4. **Smith AG**, Bromberg MB (2003). A rational diagnostic approach to peripheral neuropathy. [Review]. *J Clin Neuromuscular Dis*, *4*(4), 190-198.
5. Singleton JR, **Smith AG**, Russell JW, Feldman EL (2003). Microvascular complications of impaired glucose tolerance. [Review]. *Diabetes*, *52*(12), 2867-73.
6. **Smith AG** (2004). Pearls and pitfalls in the therapeutic use of botulinum toxin. [Review]. *Semin Neurol*, *24*(2), 165-74.
7. Singleton JR, **Smith AG**, Russell J, Feldman EL (2005). Polyneuropathy with impaired glucose tolerance: Implications for diagnosis and therapy. [Review]. *Curr Treat Options Neurol*, *7*(1), 33-42.
8. Singleton JR, **Smith AG** (2006). Neurological complications of prediabetes. [Review]. *Nat Clin Pract Neurol*, *2*(5), 276-282.
9. **Smith AG**, Singleton JR (2012). Diabetic neuropathy. [Review]. *Continuum (Minneap Minn)*, *18*(1), 60-84.
10. **Smith AG** (2012). Impaired glucose tolerance and metabolic syndrome in idiopathic neuropathy. [Review]. *Journal of the Peripheral Nervous System Online*, *17 Suppl 2*, 15-21.

Edited Books

1. Bromberg MB, **Smith AG** (Eds.) (2005). *Handbook of Peripheral Neuropathy.* New York: Taylor and Francis.

BOOK CHAPTERS

1. Bromberg MB, **Smith AG**, Forshew DA (2001). Motor neuron disease. In Pourmand R (Ed.), *Neuromuscular disorders, and Expert Clinician's View* (pp. 67-104). Newton, MA: Butterworth Heinemann.
2. **Smith AG**, Lawson VL (2003). The relationship between motor unit number estimates and muscle strength. In Bromberg MB (Ed.), *Motor Unit Number Estimation (Supplements to Clinical Neurophysiology)* (*55*, pp. 258-261).
3. **Smith AG** (2005). Diagnostic Yield for Peripheral Neuropathy. In Bromberg MB, Smith AG (Eds.), *Handbook of Peripheral Neuropathy* (*39*, pp. 677-685). New York: Taylor and Francis.
4. **Smith AG** (2005). Median Mononeuropathies. In Bromberg MB, Smith AG (Eds.). New York: Taylor and Francis.
5. **Smith AG** (2005). Skin Biopsy. In Bromberg MB, Smith AG (Eds.), *Handbook of Peripheral Neuropathy* (pp. 83-90). New York: Taylor and Francis.
6. **Smith AG**, Singleton JR (2005). Diabetic Neuropathy. In Bromberg MB, Smith AG (Eds.), *Handbook of Peripheral Neuropathy* (pp. 179-204). New York: Taylor and Francis.
7. Li J, **Smith AG** (2005). Other Hereditary Neuropathies. In Bromberg MB, Smith AG (Eds.), *Handbook of Peripheral Neuropathy* (pp. 411-435). New York: Taylor and Francis.
8. Dyck PJ, Overland C, Low PA, Litchy W, Davies J, Dyck JB, O'Brien PC, Angersen H, Albers J, Bolton C, England J, Klein CJ, Llewelyn, Mauermann M, Russell JW, Singer W, **Smith AG**, Tesfaye S, Vella A (2010). Evaluation of Diabetic Polyneuropathy: Design of the Neurologic Examination vs Clinical Neurophysiology Tests Trial (CL vs NPhys Trial). In Dyck PJ, Thomas PK (Eds.), *Companion to Peripheral Neuropathy* (1, pp. 313-316). Amsterdam: Saunders.
9. Singleton JR, **Smith AG** (2012). Preventing Neuropathic Pain in Experimental Models and Predictable Clinical Settings. In Simpson DM, McArthur JC, Dworkin RH (Eds.), *Neuropathic Pain: mechanisms, diagnosis and treatment*. New York: Oxford Press.
10. Huan M, **Smith AG** (March 8, 2012). Weakness (Guillain Barré Syndrome). In Roos, K (Eds.), *Emergency Neurology, Diagnosis and Treatment* (2012). Springer.
11. Kolb N, **Smith AG** (2014). The Neurobiology of Disease: Anatomy and Localization in the Peripheral Nervous System. In *Oxford Press* (2014).

CONFERENCE PROCEEDINGS

1. **Smith AG**, Bromberg MB (1999). The pattern of motor unit loss in Charcot Marie Tooth disease and spinal muscular atrophy. *Proceedings of the XI international congress of EMG and clinical neurophysiology*.

Other (Commentary/Letters/Editorials/Case Reports/Video/Film)

Book Reviews

1. **Smith AG** (2009). Electromyography and Neuromuscular Disorders. [Review of the book *A Trial Proficiency of Nerve Conduction: Greater Standardization Needed.*]. *Muscle & Nerve*.

Letters

1. Windebank AJ, **Smith AG** (1994). Cisplatin Neuropathy [Letter to the editor]. *Neurology*, *45*, 596.

Other

1. Smith, A. Gordon (2011). Whittling away at the unknown: the fight against idiopathic neuropathy. *The Foundation for Peripheral Neuropathy (FPN) News* (Fall 2011).

Video/Film/CD/Web/Podcast

1. Smith, A. Gordon (2010). Does head trauma cause ALS? Are professional athletes at greater risk? [Web]. Available: AAN.com (http://www.aan.com/news/?event=read&article_id=9005).
2. Smith, A. Gordon (2010). Is the neurological examination a dying art? [Web]. Available: AAN.com (http://www.aan.com/news/?event=read&article_id=9094).
3. Smith, A. Gordon (2010). Do you own your own genes? [Web]. Available: AAN.com (http://www.aan.com/news/?event=read&article_id=9099).
4. Smith, A. Gordon (2011). What's a good teacher worth? [Web]. Available: AAN.com (http://www.aan.com/news/?event=read&article_id=9324).
5. Smith A. Gordon (2013). Practical Pedagogy the Art and Neuroscience of Teaching [Web]. NeuroLearn. Available: www.AAN.com.
6. **Smith AG** (2014). Cutaneous and motor point biopsies [Web]. Waltham, MA: UpToDate. Available: www.uptodate.com.

PENDING PUBLICATIONS

Journal Articles

1. de Havenon A, Stoddard G, Wang H, **Smith A**, Chung L, Majersik J (In Press). Increased blood pressure variability is associated with worse outcome in acute ischemic stroke patients with penumbra. *Stroke Res Treat*.
2. de Havenon A, Tirschwell DL, Sultan-Qurraie A, Majersik J, **Smith A**, Mossa-Basha M (In Press). High-risk features on carotid MRI do not correlate with emboli monitoring on TCD. *J Neurol Neurosurg Psychiatry*.
3. Stino M, SmithAG (Submitted). Peripheral Neuropathy in Diabetes and Prediabetes. Journal of Diabetes Investigation.

PUBLISHED ABSTRACTS

1. **Smith AG**, Windebank AJ (1994). *The effect of ACTH analogs on cisplatin neurotoxicity using embryonic rat dorsal root ganglia explant as an in vitro model* [Abstract]. *Neurology*, *42*(3), 144.

2. Windebank AJ, **Smith AG** (1994). *Melanocortin peptides no not protect neurons by direct potentiation of nerve growth factor* [Abstract]. *Neurology*, *42*(3), 144.
3. **Smith AG**, Blaivias M, Russell JW, Urbanits S, Grisold W, Feldman EL (1997). *The clinical and pathologic features of focal myositis* [Abstract]. *Ann Neurol*, *42*, 414.
4. **Smith AG**, Russell J (1997). *Autonomic Dysfunction in Fabry disease* [Abstract].
5. Singleton JR, **Smith AG**, Bromberg MB (1998). *Glucose tolerance testing (GTT) in the evaluation of idiopathic neuropathy* [Abstract]. *Muscle Nerve*, *7*, S115.
6. **Smith AG**, Singleton JR, Bromberg MB, Forshew DA (1998). *Bedside case presentation as an educational tool in the ambulatory care setting* [Abstract]. *Neurology*, *50*, A50.
7. **Smith AG**, Baurle J, Bromberg MB (1998). *Pitfalls in quantitative motor unit analysis* [Abstract]. *Muscle Nerve*, *21*, 1602.
8. Singleton JR, **Smith AG**, Bromberg MG (1998). *Glucose tolerance testing in the evaluation of idiopathic neuropathy* [Abstract]. *Ann Neurol*, *43*, 477.
9. **Smith AG**, Singleton JR, Meekins G (1999). *Peripheral neuropathy and restless legs syndrome* [Abstract]. *Annals of Neurology*, *46*, 484.
10. Taher ME, Jones C, Singleton JR, Meekins G, **Smith AG** (1999). *Changes in excitability of motor cortical circuitry in primary restless legs syndrome* [Abstract]. *Neurology*, *52*, A112-113.
11. **Smith AG**, Bromberg MB, O'Brien (1999). *Proximal and distal MUNE in Charcot Marie Tooth disease* [Abstract]. *Neurology*, *52*, A217.
12. **Smith AG**, Singleton JR, Meekins G (1999). *Restless legs syndrome and peripheral neuropathy* [Abstract]. *Journal of the Peripheral Nervous System*, *4*, 151.
13. **Smith AG**, Bromberg MB, Dolan C (2000). *The effect of electrode size on intraobserver and interobserver reliability of nerve conduction parameters* [Abstract]. *Muscle Nerve*, *23*, 1629-1630.
14. Lipton R, Singleton JR, Taher M, Jones C, **Smith AG** (2000). *Cortical and peripheral silent period in restless legs syndrome associated with peripheral neuropathy* [Abstract]. *Neurology*, *54*, A26.
15. Singleton JR, **Smith AG** (2000). *Clinical features and follow-up in painful sensory neuropathy associated with impaired glucose tolerance* [Abstract]. *Annals of Neurology*, *48*, 471.
16. **Smith AG**, Tripp S, Singleton JR (2000). *Skin biopsy findings in patients with neuropathy associated with diabetes and impaired glucose tolerance* [Abstract]. *Neurology*, *54*, A368.
17. **Smith AG**, Singleton JR, Bromberg MB (2001). *A prospective evaluation of a standardized approach to peripheral neuropathy* [Abstract]. *Neurology*, A396.
18. Smith SM, **Smith AG**, Riley KD, Davis RK (2001). *A quantitative analysis of spinal accessory nerve function following neck dissection* [Abstract]. *Muscle Nerve*, *24*, 1424-1425.
19. Lawson VL, **Smith AG**, Bromberg MB (2002). *Motor unit number estimation in Charcot Marie Tooth disorder* [Abstract]. *Neurology*, 58A.
20. **Smith AG**, Kroll R, Ramachandran P, Singleton JR (2002). *Cutaneous measures of diabetic neuropathy* [Abstract]. *Ann Neurol*, *52*, S47.

21. **Smith AG**, Kroll R, Ramachandran P, Hauer P, McArthur JM (2002). *The reliability of skin biopsy with measurement of intraepidermal nerve fiber density* [Abstract]. *Neurology*, *58*, A500.
22. Singleton, JR, Howard JR, Goldstein J, Russell J, Feldman E, Peltier A, **Smith AG** (2003). *Diet and exercise compliance decreases neuropathic pain in patients with polyneuropathy associated with prediabetes* [Abstract]. *Ann Neurol*, *54*, S73.
23. **Smith AG**, Howard JM, Kroll R, Singleton JR (2003). *Microvascular dysfunction in diabetic and idiopathic neuropathy* [Abstract]. *Neurology*, *60*, A386.
24. **Smith AG**, Howard JR, Goldstein J, Russell J, Feldman E, Peltier A, Singleton JR (2003). *Clinical features of impaired glucose tolerance neuropathy* [Abstract]. *Muscle Nerve*, *Suppl 12*, S183.
25. **Smith AG**, Howard JR, Goldstein J, Russell J, Feldman E, Peltier A, Singleton JR (2003). *The Utah Early Neuropathy Scale, a clinical scale sensitive to early small fiber neuropathy* [Abstract]. *Ann Neurol*, *54*, S44.
26. Peltier AC, Feldman EL, Goldstein JM, **Smith AG**, Singleton JR, Russell JW (2003). *Autonomic testing improves the diagnostic certainty in IGT related neuropathy* [Abstract]. *Muscle Nerve*, *Suppl 12*, S194.
27. **Smith AG**, Howard JR, Russell J, Peltier A, Feldman EL, Goldstein J, Singleton JR (2004). *Impaired Glucose Tolerance Causes Neuropathy Study; Baseline Characteristics and 1 Year Follow-up* [Abstract]. *Ann Neurol*, *56*, S283.
28. Peltier AC, Singleton JR, Goldstein J, Howard JR, **Smith AG**, Feldman EL, Russell J (2004). *Reproducibility of Quantitative Sensory Testing in the Clinical Trial Setting* [Abstract]. *Ann Neurol*, *56*, S276.
29. Singleton JR, Howard JR, Russell J, Peltier A, Feldman EL, Goldstein J, **Smith AG** (2004). *Compliance with Diet and Exercise Modification Decreases Neuropathic Pain in Patients with Impaired Glucose Tolerance and Polyneuropathy (6 Month Follow-up)* [Abstract]. *Neurology*, *62*, A262.
30. Peltier AC, Howard JR, **Smith AG**, Goldstein JR, Feldman EL, Singleton JR, Russell J (2004). *Quantitative Sudomotor Axon Reflex Testing is a Sensitive Measure of Small Fiber Function in Impaired Glucose Tolerance Related Neuropathy* [Abstract]. *Neurology*, *62*, A222.
31. Smith S, **Smith AG**, Bixby B, Hamwi J, Feldman EL, Russell JR, Peltier A, Goldstein J, Singleton JR (2005). *Diet and exercise is associated with sustained improvement in neuropathic pain in patients with prediabetes* [Abstract]. *Ann Neurol*, *58*(Suppl 9), 216.
32. Russell JW, Peltier AC, Sheikh K, Howard J, Goldstein J, **Smith AG**, Feldman EL, Singleton JR (2005). *Autonomic dysfunction in subjects with impaired glucose tolerance* [Abstract]. *Journal of the Peripheral Nervous System*, *10*(Supp), 78-9.
33. **Smith AG**, Russell JR, Feldman EL, Peltier A, Goldstein J, Singleton JR (2005). *The electrophysiologic features of impaired glucose tolerance neuropathy* [Abstract]. *Muscle Nerve*, *32*, 390.
34. **Smith AG**, Bixby B, Smith S, Howard J, Russell J, Peltier A, Goldstein J, Feldman EL, Singleton JR (2005). *Peripheral neuropathy and the metabolic syndrome* [Abstract]. *Ann Neurol*, *58*(Suppl 9), 116.
35. **Smith AG**, Bixby B, Smith S, Howard J, Russell JW, Peltier AC, Goldstein J, Feldman EL, Katz B, Singleton JR (2005). *The effect of diet and exercise on*

neuropathy progression in subjects with impaired glucose tolerance [Abstract]. *Journal of the Peripheral Nervous System*, *10*(Supplement), 88.
36. **Smith AG**, Bixby B, Singleton JR, Smith S, Hamwi J, Feldman EL, Russell JW, Peltier A, Goldstein J (2005). *The Utah Early Neuropathy Scale Is a Sensitive Measure of Early Neuropathy Associated with Impaired Glucose Tolerance* [Abstract]. *Neurology*, (06), 124.
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38. Bixby B, Singleton JR, **Smith AG** (2006). *Cutaneous microvascular reactivity in diabetic and prediabetic neuropathy* [Abstract]. *Neurology*, *65*(02), 034.
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41. Rose K, **Smith AG**, Singleton JR (2006). *The relationship between pain glucose and in impaired glucose tolerance neuropathy* [Abstract]. *Neurology*, *65*(05), 103.
42. Bradley DF, **Smith AG**, Wade J, Singleton JR (2007). *Comparative Evaluation of Timed Vibration Detection as a Measure of Diabetic Peripheral Neuropathy* [Abstract]. *Neurology*, *68*.
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44. **Smith AG**, Tobias J, Pollari D, Sutton MA, Muhammad N, Babbar S, Chanda S, Singleton JR, Bley K (2007). *Counting Rules Count: Effects of Counting Criteria on Quantitation of Capsaicin-Induced Epidermal Denervation* [Abstract]. *American Academy of Neurology Annual Meeting*, *68*, A411.
45. Singleton JR, Bixby B, Feldman EL, Goldstein, Russell J, Peltier A, Wade J, Katz BJ, **Smith AG** (2007). *Diet and Exercise Counseling Alone Does Not Prevent Long Term Neuropathy Progression in IGTN* [Abstract]. *American Academy of Neurology Annual Meeting*, *68*, A410.
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47. Wagner JC, Singleton JR, Bixby B, Dolan C, Wade J, Bradley D, **Smith AG** (2007). *Prevalence and risk for upper extremity compressive mononeuropathies in diabetes* [Abstract]. *Journal of the Peripheral Nervous System*, *12*, 592-593.
48. Weintraub, MI, Herrmann DN, **Smith AG**, Bckonja, Cole SP, on behalf of the Magnetic Stimulation Group (2008). *A Randomized, Double-Blind, Placebo-Controlled Trial of Simultaneous Static and Time-Varying Electromagnetic Fields (PEMF) on Neuropathic Pain (NP) in Painful Diabetic Neuropathy (DPN)* [Abstract]. *Neurology*, *70*, S39.002.
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Neurology, *70*, S39.001.

50. Singleton JR, Marcus RL, Smith SB, Arsenault C, Burch A, **Smith AG** (2008). *Structured exercise improves small fiber function in diabetic subjects without overt neuropathy* [Abstract]. *Neurology*, *70*, S39.005.
51. Weintraub MI, Herrmann DN, **Smith AG**, Backonja MM, Cole SP (2008). *Correlation of Epidermal Nerve Fiber Density (ENFD) Changes and Anti-Nociceptive Effect Following Simultaneous Exposure to Static and Time-Varying Electromagnetic Fields (PEMF) in Painful Diabetic Neuropathy (DPN)* [Abstract]. *Neurology*, *70*, P03.159.
52. **Smith AG**, Bixby B, Burch A, Arsenault CJ, Singleton JR (2008). *Diagnosis of early diabetic neuropathy* [Abstract]. *Neurology*, *70*, S39.001.
53. **Smith AG**, Dolan J, Singleton JR (2008). *Diagnostic utility of nerve conduction studies for early diabetic neuropathy* [Abstract]. *Muscle & Nerve*, *38*(4), S80.
54. Kareus S, Singleton JR, Bragg E, **Smith AG** (2008). *Subepidermal Nerve Plexus Density (SENPD) Measurement Increases Diagnostic Sensitivity of Skin Biopsy in Subjects with Diabetic Neuropathy* [Abstract]. *Annals of Neurology*, *64*(S12), M-17.
55. **Smith AG**, Bragg E, Arsenault C, Burch A, Singleton JR (2009). *Early diabetic neuropathy is characterized by progressive small fiber loss* [Abstract]. *Journal of the Peripheral Nervous System*.
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57. **Smith AG**, Singleton JR (2009). *Metabolic syndrome is a risk factor for idiopathic and diabetic neuropathy* [Abstract]. *Annals of Neurology*.
58. **Smith AG**, Colin Arsenault, Charles Latner, Michael T. Porzio, Haimei Wang, J. Rob Singleton (2010). *The Effect of Lifestyle Intervention on Nerve Regeneration in Metabolic Syndrome* [Abstract]. *Scientific Sessions: Peripheral Nerve: Clinical Advances in Peripheral Neuropathy*.
59. J. Robinson Singleton, Collin J. Arsenault, **Smith AG** (2010). *Timed Vibration Predicts Progression to Symptomatic Neuropathy in Diabetic Subjects* [Abstract]. *Poster Session VI: Peripheral Nerve: Diabetic Neuropathy*.
60. **Smith AG**, Arsenault C, Latner C, Porzio MT, Wang H, Singleton JR (2010). *The effect of lifestyle intervention on nerve regeneration in metabolic syndrome* [Abstract]. *Neurology*.
61. Singleton JR, Marcus RL, Smith SB, Arsenault C, Burch A, **Smith AG** (2010). *Timed vibration predicts progression to symptomatic neuropathy in diabetic subjects* [Abstract]. *Neurology*.
62. **Smith AG**, Arsenault C, Latner C, Porzio M, Wang H, Singleton JR (2010). *Lifestyle intervention improves nerve regenerative capacity in metabolic syndrome* [Abstract]. *Proceedings of the Neurodiab Meeting*.
63. Hamid HS, Hayes JM, Robell NJ, Porzio M, Singleton JR, **Smith AG**, Lentz SI, Feldman EL (2010). *Alterations in mitochondrial dynamics within intraepidermal nerve fibers associated with the progression of diabetic neuropathy* [Abstract]. *Annals of Neurology*.
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Alexander NB, Russell JW (2011). *Assessing Autonomic Dysfunction in Early Diabetic Neuropathy: The Survey of Autonomic Symptoms (SAS)* [Abstract]. *CR01 2011 Boston: 18th Conference on Retroviruses and Opportunistic Infections*.

65. Singleton JR, Arsenault C, Porzio M, Wange H, **Smith AG** (2011). *Early decline in intraepidermal nerve fiber density predicts progression to symptomatic neuropathy in patients with diabetes* [Abstract]. *Neurology*.
66. Arsenault C, Sinlgeton JR, Porzio M, Wang H, **Smith AG** (2011). *Nerve regenerative capacity in diabetes and metabolic syndrome* [Abstract]. *Neurology*.
67. Singleton JR, Latner C, Arsenault CJ, Porzio MT, **Smith AG** (2011). *Accelerated intraepidermal nerve fiber density (IENFD) decline precedes progression to neuropathic symptoms in patients with diabetes* [Abstract]. *Diabetes*, *60*(S1).
68. Singleton JR, Marcus R, Arsenault CJ, Porzio MT, Cameron JM, **Smith AG** (2011). *Weight loss and lowered triglycerides improves cutaneous re-innervation in non-neuropathic subjects with diabetes or prediabetes* [Abstract]. *Diabetes*, *60*(S1).
69. **Smith AG**, Singleton JR (2011). *Early loss of epidermal nerve fibers in asymptomatic subjects predicts future development of symptomatic diabetic neuropathy* [Abstract]. *Journal of the Peripheral Nervous System*.
70. Gibbons CH, Lafo J, **Smith AG**, Singleton JR, Freeman R (2011). *The quantification of sudomotor nerve fibers: a multicenter study in diabetes* [Abstract]. *Journal of the Peripheral Nervous System*.
71. Zilliox LA, Peltier AC, Wren PA, Anderson A, **Smith AG**, Singleton JR, Feldman EL, Alexander NB, Russell JW (2011). *Assessing autonomic dysfunction in early diabetic neuropathy: the survey of autonomic symptoms* [Abstract]. *Journal of the Peripheral Nervous System*.
72. Cheng HT, Dauch JR, **Smith AG**, Singleton JR, Yanik BM, Feldman EL (2011). *Characterization of intraepidermal nerve fiber morphology in pain associated with diabetic neuropathy and impaired glucose tolerance* [Abstract]. *Journal of the Peripheral Nervous System*.
73. Hamid HS, Hayes JM, Robell NJ, Porzio M, Singleton JR, **Smith AG**, Lentz SI, Feldman EL (2011). *Quantifying changes in mitochondria within human intraepidermal nerve fibers associated with diabetes and diabetic peripheral neuropathy* [Abstract]. *Journal of the Peripheral Nervous System*.
74. **Smith AG**, Singleton JR, Chung L, Burbank E, Afra P, Hoesch R, Ledyard H, Dolan C, Smith S (2012). *Clinical and Electrodiagnostic Features of an Outbreak of Foodborne Botulism Due to Home-Brew Alcohol among Prisoners* [Abstract]. *The American Academy of Neurology*.
75. **Smith AG**, Leonard M, Gerardi R, Porzio M, Kim G, Digre K, Mifline M, Keung B, Singleton JR (2013). *Corneal Confocal Microscopy (CCM) is a sensitive measure of early diabetic neuropathy* [Abstract]. *Journal of the Peripheral Nervous System*.
76. **Smith AG**, Gerardi R, Lessard M, Reyna SP, Singleton JR (2013). *Sudoscan as a diagnostic tool for peripheral neuropathy* [Abstract]. *Journal of Peripheral Nervous System*.
77. **Smith AG**, and Singleton JR (2013). *Corneal Confocal Microscopy as surrogate measure of diabetic neuropathy* [Abstract]. *Annals of Neurology*.
78. Singleton JR, Marcus R, **Smith AG** (2013). *Weight loss and lowered glucose*

improve cutaneous reinnervation in non-neuropathic subjects with diabetes or prediabetes [Abstract]. *Journal of Peripheral Nervous System*.

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80. **Smith AG**, Kim G, Keung B, Allen B, Porzio M, Latner C, Singleton JR (2012). *The reliability of corneal nerve fiber assessment using corneal confocal microscopy* [Abstract]. *Neurology*.
81. **Smith AG**, Kim G, Porzio M, Alen B, Digre, K, Mifflin M, Singleton JR (2013). *Confocal microscopy is a reliable measure of corneal innervation* [Abstract]. *Annals of Neurology*.
82. Chenge H, Dauch JR, Porzio M, Yanik BM, Hsieh W, **Smith AG**, Singleton JR, Feldman E (2012). *Useful biomarkers for the diagnosis of painful diabetic neuropathy* [Abstract]. *Neurology*.
83. Singleton JR, Marcus R, Arsenault CJ, Porzio M, Jackson JE, **Smith AG** (2012). *Metabolic syndrome reduces cutaneous nerve regenerative capacity* [Abstract]. *Annals of Neurology*.
84. Nevoret ML, Vinik A, **Smith AG**, Freedman B, Singleton JR (2014). *Sudoscan: An alternative tool in the understanding of the microvascular complications of diabetes* [Abstract]. *American Academy of Clinical Endocrinology*.
85. Singleton JR, Volckmann E, Graham T, **Smith AG** (2014). *[I6-1.008] Neuropathy Associated with Nondiabetic Obesity* [Abstract]. *Neurology*.
86. **Smith AG**, Lessard M, Singleton JR (2014). *[P7.003] Sudoscan as a Diagnostic Tool for Diabetic and Idiopathic Peripheral Neuropathy* [Abstract]. *Neurology*.
87. Hannon PM, Austin J, McCauley M, Smith D, **Smith AG**, Salari A, Majersik JJ (2014). *Telestroke: Expanding Access and Coordination of Care From Acute Stroke to Follow-up* [Abstract]. *Poster Session at AHA/ASA Quality of Care and Outcomes Research (QCOR) Meeting 2014, Baltimore, MD*.
88. Kolb N, **Smith AG**, Singleton JR, Brown SM, Wong B, Dunson WA, Wujcik D, Beck SL, Mooney KF (2015). *A novel evidenced based phone system reduces symptoms of chemotherapy induced neuropathy* [Abstract]. *Neurology*.
89. Kolb N, **Smith AG**, Singleton JR, Brown SM, Wong B, Beck SL, Mooney KF (2015). *Neuropathy symptoms are associated with increased fall risk in patients receiving potentially neurotoxic chemotherapy [P7.082]* [Abstract]. *Neurology*, *84*(14).
90. **Smith AG**, Lessard M, Singleton JR (2015). *The diagnostic utility of nerve conduction studies and skin biopsy for diabetic neuropathy: a Bayesian analysis (S42.007)* [Abstract]. *Neurology*, *84*(14).
91. Ajroud-Driss S, Vinik AI, **Smith AG**, Cha B-S, Choi SH, Wymer JP, Shaibani A, Kessler JA, and the VM202 DPN-II Study Group (2015). *Double-blind, placebo-controlled study of hepatocyte growth factor gene therapy in painful diabetic neuropathy* [Abstract]. *The Journal of Peripheral Nervous System*.
92. Kolb N, Brown SM, Singleton JR, **Smith AG** (2015). *The impact of neuropathy severity of neurotoxic chemotherapy dose modification* [Abstract]. *The Journal of Peripheral Nervous System*.

93. Baets J, Duan X, Wu Y, **Smith AG**, Seeley W, Mademan I, McGrath NM, Beadell NC, Khoury J, Botuyan M-V, Mer G, Worrell GA, Hojo K, DeLeon J, Laura M, Liu Y-T, Senderek JP, Weis J, Van den Bergh P, Merrill SL, Reilly MM, Houlden H, Grossman M, Scherer SS, De Jonghe P, Dyck PJ, Klein CJ (2015). *Defects of mutant DNMT1 are linked to a spectrum of neurological disorders* [Abstract]. *The Journal Peripheral Nervous System*.
94. Kolb N, Brown SM, Wang V, Wong B, Beck SL, Mooney K, Singleton JR, **Smith AG** (2015). *The association between chemotherapy induced peripheral neuropathy related numbness and tingling and falls in cancer patients* [Abstract]. *The Journal of Peripheral Nervous System*.
95. **Smith AG**, Volkmann E, Graham T, Solis V, Singleton JR (2015). *Neuropathy risk among bariatric surgery candidates* [Abstract]. *The Journal of Peripheral Nervous System*.
96. Ajroud-Driss S, Simpson D, **Smith AG**, Freeman RL, Hoke A (2015). *Peripheral neuropathy research registry* [Abstract]. *The Journal of Peripheral Nervous System*.
97. Brown SM, Wang V, **Smith AG**, Singleton R, Kolb N (2015). *A prospective study examining the association of paclitaxel acute pain syndrome and chemotherapy induced peripheral neuropathy [P0053]* [Abstract]. *Translational Cancer Epidemiology: From Cells To Clinic And Population*.
98. Daniel C, Abenroth A, **Smith AG**, Greenlee JE, Clardy SL (2015). *Lambert-Eaton Myasthenic Syndrome: Epidemiology and Therapeutic Response in the National Veteran Affairs (VA) Population* [Abstract]. *Annals of Neurology*, *78*(S19), 10.
99. Sanders DB, Juel VC, Harratt Y, **Smith AG**, Peltter A, Marburger T, Lou J-S, Pascuzzi RM, Richman DP, Xte T, Jacobus LR, Ales KL, Jacobus DP, DAPPER Study Team (2015). *Results From the Dapper Study: Inpatient Double-Blinded Placebo-Controlled Withdrawal Study of 3,4-Diaminopyridine Base (3,4-DAP) in Subjects with Lambert-Eaton Myasthenic Syndrome (LEMS)* [Abstract]. *AANEM*.
100. Abenroth D, **Smith AG**, Greenlee J, Clardy S (2015). *Epidemiology of Lambert-Eaton Myasthenic Syndrome in the Veterans Affairs Population* [Abstract]. *AANEM*.
101. Sanders DB, Juel VC, Harati Y, **Smith AG**, Peltier A, Marburger T, Lou JS, Pascuzzi RM, Richman DP, Xie T, Jacobus LR, Alex KL, Jacobus DP, DAPPER Study Team (2015). *Results of a Double-Blind Placebo-Controlled Study of 3,4-Diaminopyridine (DAP) in Lambert-Eaton Myasthenic Syndrome (LEMS)* [Abstract]. *Annals of Neurology*, *78*(S19), 16.
102. Kolb NA, Singleton JR, Brown SM, Curtin K, **Smith AG** (2015). *Prevalence of Chemotherapy Induced Peripheral Neuropathy (CIPN)* [Abstract]. *Annals of Neurology*, *78*(S19), 10.
103. Ajroud-Dris S, Vinik A, **Smith AG**, Cha BS, Choi SH, Whymer J, Shaibani A, Kessler JA, VM202 DPN-II Study Group (2015). *Double-Blind, Placebo-Controlled Study of Hepatocyte Growth Factor Gene Therapy in Painful Diabetic Neuropathy* [Abstract]. *Ann Neurol*, *78*(S19), 15.
104. Thakkar N, Peloquin C, Ales K, Jacobus D, Jacobus L, Cohen-Wolkowiez M, Guptill J.T., Gonzalez D, for the DAPPER Study Group, University of North Carolina at Chapel Hill, Chapel Hill, NC, University of Florida, Gainsville, FL,

Jacobus Pharmaceutical Company, Inc., Plainsboro NJ, Duke Clinical Research Institute, Durham NC, Duke University, Department of Neurology, Durham NC, DAPPER Study Group site investigators: Juel VC, Harati Y, **Smith AG**, Peltier A, Lou J-S, Marbuger T, Pacuzzi RM, Richman DP (2016). *Population Pharmacokinetics/Pharmacodynamics of 3,4-Diaminophridine Free Base In Patients with Lambert-Eaton Myasthenic Syndrome* [Abstract].

105. O'Donnell s, Majersik J, Chung L, **Smith AG**, Dunleavy B, deHavenon A (2016). *CT-Based Collateral Scoring Can Predict Ischemic Penumbra Volume in Acute Ischemic Storke [P2.330]* [Abstract]. *American Academy of Neurology, 2016 Annual Meeting, Vancouver, BC*.
106. **Smith AG**, Graham T, Volckmann E, Hauer P, Aperghis A, Solis V, Singleton J (2016). *Bariatric Surgery Improves Peripheral Nerve Function and Intraepidermal Nerve Fiber Density in Obese Patients without Symptomatic Neuropathy [P1.44]* [Abstract]. *American Academy of Neurology, 2016 Annual Meeting, Vancouver BC,*.
107. deHavenon A, O'Donnell S, Wang H, Chung L, **Smith AG**, Majersik J (2016). *A Comparison of Three Different CTA Collateral Scoring Systems' Ability to Predict MR Lesion Volume and Outcome after Ischemic Stroke [P6.010]* [Abstract]. *American Academy of Neurology, 2016 Annual Meeting, Vancouver, BC*.
108. **Smith AG**, Kowalsky G, Hauer P, Aperghis A, Singleton J (2016). *The Diagnostic Performance and Clinical Relevance of Corneal Confocal Microscopy (CCM) in Patients with Diabetic Peripheral Neuropathy [S44.001]* [Abstract]. *American Academy of Neurology, 2016 Annual Meeting, Vancouver, BC*.
109. Kolb N, Brown S, Singleton J, **Smith AG** (2016). *Carefully Phenotyped Changes in Neuropathy Measures with Exposure to Neurotoxic Chemotherapy [P4.231]* [Abstract]. *American Academy of Neurology, 2016 Annual Meeting, Vancouver, BC*.
110. Brown S, **Smith AG**, Singleton JR, Kolb N (2016). *The Clinical Phenotyped and Neuropathic Outcomes of Paclitaxel-Acute Pain Syndrome [P4.233]* [Abstract]. *American Academy of Neurology, 2016 Annual Meeting, Vancouver, BC*.

ORAL PRESENTATIONS

Keynote/Plenary Lectures

International

2012	Why do therapies that work in rodent models fail to do so in humans? Innovative Therapies for Peripheral Neuropathies, the 2012 Foundation for Peripheral Neuropathy International Research Symposium
2012	Measurement of Painful Neuropathy--Correlations of Nerve Conduction Velocity, Skin Biopsy and Nerve Biopsy, and Corneal Nerve Measurements. American Diabetes Association Scientific Meetings, Philadelphia PA
2014	Advances in the diagnosis and clinical interventions for metabolic neuropathy, International Congress on Neuromuscular Diseases, Nice France

National

2009	Speaker & Organizer, Peripheral Neuropathy Society, Peripheral Neuropathy Conference: Neuropathy and You
2010 - Present	Impaired Glucose Tolerance and Neuropathy, The Neuropathy Association, Peripheral Neuropathy Summit, Washington D.D.

Local/Regional

2009	Therapeutic Development for Diabetic Neuropathy, Western Intermountain Neurological Organization, Salt Lake City Utah

Meeting Presentations (Not Published Abstracts and Not Unpublished Posters)

International

2001	A Diagnostic Approach to Peripheral Neuropathy, American Academy of Neurology Peripheral Neuropathy Course, Philadelphia PA
2001	Motor Unit Number Estimation and Strength Correlates, First International Symposium on MUNE, Snowbird, UT
2005	The effect of diet and exercise on neuropathy progression in subjects with impaired glucose tolerance, Peripheral Nerve Society, Tuscany Italy
2009	Early diabetic neuropathy is characterized by progressive small fiber loss, Meeting of the Peripheral Nerve Society, Wurzberg, Germany
2012	Diabetic Neuropathies. Peripheral Neuropathy Course. American Academy of Neurology Annual Meeting. New Orleans LA.
2013	Inclusion Exclusion Criteria. Food and Drug Administration Peripheral Neuropathy Consensus Meeting
2013	Neuromuscular Update. Neurology Update. American Academy of Neurology Annual Meeting, San Diego California
2014	Therapy in Neurology: Neuromuscular, American Academy of Neurology Annual Meeting, Philadelphia, PA
2014	Neurology Update II: Neuromuscular, American Academy of Neurology Annual Meeting, Philadelphia, PA
2015	Peripheral Neuropathies - Diabetic Neuropathy. American Academy of Neurology Annual Meeting. Washington, DC.
2015	Diagnosis of Small Fiber Neuropathy: Pearls and Pitfalls of Skin Biopsy as a Diagnostic Test. American Association of Neuromuscular and Electrodiagnostic Medicine Annual Meeting. Honolulu, HI.
2015	Population Screening for Diabetic Neuropathy: Has Its Time Arrived?, American Association of Neuromuscular and Electrodiagnosis Medicine Annual Meeting, Honolulu, HI
2016	Plenary Session: Neurology Year in Review, Neuromuscular, American Academy of Neurology Annual Breakthroughs in Neurology Conference, Orlando, FL.
2016	AAN/ABPN Maintenance of Certification Informational Session, American Academy of Neurology, Breakthroughs in Neurology

Conference, Orlando, FL.

2016 The Diagnostic Performance and Clinical Relevance of Corneal Confocal Microscopy (CCM) in Patients with Diabetic Peripheral Neuropathy. American Academy of Neurology, Annual Meeting, Vancouver, Canada

National

2000 The Effect of Electrode Size on Nerve Conduction Study Reproducibility, American Academy of Electrodiagnostic Medicine, Philadelphia PA

2001 A Prospective Evaluation of a Standardized Approach to Peripheral Neuropathy, American Academy of Neurology, Philadelphia PA

2001 A quantitative analysis of spinal accessory nerve function following neck dissection. American Academy of Electrodiagnostic Medicine, Albuquerque, NM

2002 The Reliability of Skin Biopsy with Measurement of Intraepidermal Nerve Fiber Density, American Academy of Neurology, Denver CO

2003 A Diagnostic Approach to Peripheral Neuropathy, American Academy of Neurology Peripheral Neuropathy Course, Honolulu HI

2004 A Diagnostic Approach to Peripheral Neuropathy, American Academy of Neurology, Peripheral Neuropathy Course, San Francisco CA

2005 The Utah Early Neuropathy Scale Is a Sensitive Measure of Early Neuropathy Associated with Impaired Glucose Tolerance, American Academy of Neurology, Miami Beach Florida

2005 The Efficacy of a Practical Diet and Exercise Counseling Regimen on Metabolic Parameters and Neuropathy Progression in Patients with Impaired Glucose Tolerance and Neuropathy, American Academy of Neurology, Miami Beach Florida

2006 Increased prevalence of metabolic syndrome in peripheral neuropathy, American Academy of Neurology, San Diego CA

2006 Diet and exercise result in epidermal reinnervation in impaired glucose tolerance neuropathy, American Academy of Neurology, San Diego California

2007 Counting Rules Count: Effects of Counting Criteria on Quantitation of Capsaicin-Induced Epidermal Denervation. American Academy of Neurology Annual Meeting, Portland, Oregon

2008 Diagnosis of early diabetic neuropathy, American Academy of Neurology Annual Meeting, Chicago, Illinois

2008 Skin biopsy is a highly sensitive measure of early diabetic neuropathy progression, American Academy of Neurology Annual Meeting, Chicago, Illinois

2010 The Effect of Lifestyle Intervention on Nerve Regeneration in Metaboloc Syndrome, American Academy of Neurology, Toronto, Canada

2012 Neuromuscular Emergencies. Brainstorm. Park City Utah

2012 Neuromuscular Update. American Academy of Neurology Fall Meeting. Las Vegas, Nevada

Local/Regional

1998 Current Thought in Diabetic Neuropathy. Western Intermountain Neurologic Organization (WINO) biannual meeting

2001 The Therapeutic Use of Botulinum Toxin, Western Intermountain Neurologic Organization biannual meeting

2005 Post Polio Syndrome, Western Intermountain Neurologic Organization, Salt Lake City Utah

2012 NOMAD - NeuroNEXT

2015 Continuum: Test Your Knowledge: A Multiple Choice Question Review, American Academy of Neurology Fall Conference, Las Vegas, NV

2015 Neurology Update III: Neuro-Infectious Disease, Neuro-Ophthalmology and Neuromuscular Disease, American Academy of Neurology Fall Conference, Las Vegas, NV

Invited/Visiting Professor Presentations

International

2012 Impaired Glucose Tolerance and Neuropathy: smoking gun, guilt by association or therapeutic window. University of Toronto, Citywide Endocrinology Rounds

2015 Painful generalized diabetic polyneuropathy. AAPT Neuropathic Pain, Copenhagen, Denmark

2016 New Strategies to Treat or Prevent Diabetic Neuropathy, 59th Annual Meeting of
Diabetes Society

National

1997 Toxic neuropathy. Grand rounds, Creighton University, Omaha Nebraska

1997 Models of neurotoxicity. Grand rounds, State University of New York (SUNY) Stonybrook

2002 A Diagnostic Approach to Peripheral Neuropathy, American Academy of Neurology Peripheral Neuropathy Course, Denver CO

2004 Peripheral Neuropathy Emergencies. Pearls and Pitfalls of Emergency Neurology Course, San Francisco CA

2006 A Neuromuscular CPC, Indiana University Department of Neurology

2006 Symptomatic Management of Diabetic Neuropathy - Meet the Professor, Endo Annual Update, San Francisco California

2007 Symptomatic Management of Diabetic Neuropathy - Meet the Professor, Endo Annual Update, San Antonio Texas

2008 "Update of Impaired Glucose Tolerance Neuropathy", Peripheral

Neuropathy Update, Wayne State University

2008 "Does Hyperglycemia Cause Diabetic Neuropathy" Festscrhift Honoring Dr. James W. Albers, University of Michigan Medical Center, Ann Arbor Michigan

2009 Therapeutic Development for Diabetic Neuropathy, Grand Rounds Beth Israel Deaconess Medical Center, Boston Massachusetts

2012 "Size matters: Small versus Large Nerve Fiber-New Models for Diabetic Neuropathy Trials" UCSD Neuroscience Grand Rounds

2012 Size Matters: Small Versus Large Fibers - New Models of Diabetic Neuropathy Clinical Trials, University of California San Diego Neurology Grand Rounds

2013 The conundrum of diabetic neuropathy - new models for therapeutic development. Grand Rounds, New York University

2013 The conundrum of diabetic neuropathy - new models for therapeutic development. University of Michigan

2015 Metabolic Neuropathy: A Tale of Two Trials Grand Rounds, Kansas University Medical Center, Kansas City, KS

2016 Metabolic Neuropathy: A Tale of Two Trials. Grand Rounds University of Vermont Medical Center, Burlington, VT

Local/Regional

1997 Spinal Cord Compression, Emergency Neurology Lecture Series, University of Utah Neurology

1997 Campylobacter and GBS, University of Utah Infectious Disease Conference

1998 Peripheral Neuropathy, Clinical Neuroscience Series, University of Utah Neurology

1998 Axonal Transport, Basic Neuroscience Series, University of Utah Neurology

1998 Basics of EMG, University of Utah Neuropsychiatric Institute

1999 Peripheral Sensory Organs, Basic Neuroscience Series, University of Utah Neurology

1999 The Effects of Alcohol on the Nervous System, Internal Medicine Conference

1999 CIDP, Idaho State University Family Practice Grand Rounds

2000 Myasthenia Gravis, Clinical Neuroscience Series, University of Utah

2000 Guillain Barré Syndrome, Physical Medicine in-service, University of Utah

2001 Therapeutic Uses of Botulinum Toxin, University of Utah Neurology Special Interest Group

2001 Botulinum Toxin, Utah Dystonia Support Group

2002 New treatment for cervical dystonia, Neurology Association of Southern California

2002 Peripheral Neuropathy, University of Utah Student Interest Group in

Neurology

2003 Time and meeting management. Chief Resident as Manager Course, Salt Lake City, UT

2014 Novel Trial Design For Peripheral Neuropathy Studies. Clinical Trials Day Symposium, University of Utah Clinical Neurosciences Center, Salt Lake City, UT.

Grand Rounds Presentations

1998 Sensory Neuropathy, University of Utah Neurology Grand Rounds

1998 A Case of Mushroom Poisoning, University of Utah Neurology Grand Rounds

1999 Update on Diabetic Neuropathy, University of Utah Family Practice Grand Rounds

2000 Hexosaminidase A deficiency, University of Utah Neurology Grand Rounds

2000 CIDP, University of Utah Neurology Grand Rounds

2001 The Therapeutic Uses of Botulinum Toxin, University of Utah Family Practice Grand Rounds

2002 A Case of Polyneuropathy in Utah, Clinical Pathology Grand Rounds, University of Utah

2005 The problem of idiopathic neuropathy, diabetes prediabetes and metabolic syndrome, University of Utah Neurology Grand Rounds

2006 Therapy in Peripheral Neuropathy, University of Utah Neurology Grand Rounds

2011 Challenges in diabetic neuropathy research, new models for trial design. Endocrinology Grand Rounds. University of Utah

2012 NeuroNEXT, Advancing Therapeutic Development in Neurology

2015 Treating (and Preventing) Metabolic Neuropathy. University of Utah, Neurology Grand Rounds.

Outreach Presentations

2009 Speaker & Organizer, Peripheral Neuropathy Society, Peripheral Neuropathy Conference: Neuropathy and You

ABF Letter of Intent

Letter of Intent Form

Prefix
Dr.
First Name
A. Gordon
Last Name
Smith
Suffix
MD
Title
Professor and Vice Chair of Neurology
Institution
University of Utah
Office Address
Department of Neurology 30 North 1900 East SOM3R242
City
Salt Lake City
State
Utah
Postal Code
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gordon.smith@hsc.utah.edu
Office Phone
801-581-8960
Office Fax

Project Details

Project Title
Axonal mitochondrial failure precedes chemotherapy induced neurotoxicity in breast cancer patients
General focus
ALS & Neuromuscular Technology & Innovation
Specific Disease Focus
Chemotherapy Induced Peripheral Neuropathy
Project Description
Chemotherapy-induced peripheral neuropathy (CIPN) is the most common dose-limiting side effect of first line chemotherapeutic agents including the microtubule inhibitor paclitaxel, a common agent in the treatment of

breast cancer. Paclitaxel infusion frequently causes acute widespread pain that is thought to be neuropathic in origin (paclitaxel acute pain syndrome, P-APS). Our preliminary data suggest patients with P-APS have a higher risk of subsequent CIPN. The mechanisms by which paclitaxel causes P-APS and CIPN are unknown, and there are no effective preventative or treatment strategies.

Data from animal models of CIPN suggest paclitaxel and other neurotoxic chemotherapy agents impair microtubular dynamics and mitochondrial calcium signaling leading to increased mitochondrial permeability, swelling, and toxicity. Mitochondrial injury is a well recognized contributor to axonal degeneration in other forms of neuropathy, including diabetes (which is itself a CIPN risk factor). We hypothesize that paclitaxel leads to acute mitochondrial stress in small unmyelinated nociceptive axons resulting in P-APS. Continued exposure leads to length dependent mitochondrial toxicity and, ultimately axonal degeneration manifested as clinical CIPN. Preliminary data indicate that 70% of paclitaxel patients develop P-APS and 42% CIPN. Among those with clinically defined CIPN, nerve conduction studies (NCS) are normal in 46%, and 86% of these have normal intraepidermal nerve fiber density (IENFD). These findings are consistent with functional axonal failure preceding axonal degeneration.

We propose to address our hypothesis by fulfilling the following two specific aims:

Specific Aim #1: Determine if mitochondrial injury leads to functional axonal failure prior to degeneration. 20 breast cancer patients with planned paclitaxel therapy will undergo a baseline evaluation including validated neuropathy scales, NCS and distal leg skin biopsy for IENFD determination. Immunohistochemistry with quantitative image analysis will be used to evaluate axonal mitochondrial numbers and distribution. Electron microscopy (EM) will be used to directly visualize and analyze the size and structure of mitochondria in axons and keratinocytes for comparison. These procedures will be repeated 2 weeks after the final paclitaxel dose. We anticipate that patients with functional axonal failure (CIPN with normal NCS and IENFD) will have greater axonal mitochondrial injury compared to keratinocytes, and that the severity will be intermediate between those without CIPN and those with evidence of axonal degeneration based on NCS and IENFD.

Specific Aim #2: Determine if PAP-S is associated with abnormalities of mitochondrial structure. The first 5 patients who develop PAP-S will undergo a distal leg skin biopsy, which will be processed and analyzed as outlined in SA#1. We anticipate that mitochondria from both axons and keratinocytes will have abnormal structure and distribution, suggesting generalized mitochondrial injury. If mitochondrial or other structural axonal abnormalities are observed, skin biopsies will be obtained from 5 patients without P-APS at the same time point for comparison.

How will your project contribute to the treatment, prevention or cure of a neurological disease(s)?

Multiple forms of peripheral and central nervous system neurodegeneration share mitochondrial injury as a common element. Among these, CIPN represents an ideal model in which to study axonal degeneration because it is foreseeable, predictable, can be followed from onset through recovery, and the target tissue is accessible for investigation. Peripheral nervous system axons (particularly unmyelinated nociceptive fibers) have excellent regenerative capacity, making peripheral neurodegeneration an appealing target for therapeutic approaches that can subsequently be applied to other neurodegenerative disorders. The results of the proposed studies promise to fundamentally impact our understanding of CIPN. Demonstration of mitochondrial changes in P-APS would provide the first evidence of disease mechanism for this enigmatic and clinically significant condition. Association with mitochondrial derangement would inform new mechanistic research and therapeutic approaches for CIPN prevention, potentially leading to significantly improved quality of life for cancer survivors. Development of preventative strategies for CIPN will permit more aggressive chemotherapy dosing leading to improved survival. Recognition of mitochondrial failure as an important mechanism in P-APS and CIPN would suggest a similar role in other common neurological disorders such as diabetic and idiopathic peripheral neuropathies and diffuse unexplained pain syndromes such as fibromyalgia.

Project Budget

Total expense budget

An estimated total is acceptable.

$150,000

Value of existing funding or in-kind support

What portion of the above total expense has funding already received or promised?

$75,000

Portion to be raised through crowdfunding

How much are you seeking from the crowdfunding platform?

$75,000

Attachments and Verifications

Please download, fill out, and upload the Financial Disclosures & Conflict of Interest form.

Financial Disclosures & Conflicts of Interest Form

Package1.pdf

CV of Principal Investigator

SmithCV02-01-2017.pdf

I understand that the American Brain Foundation will not post approved projects for crowdfunding until documentation of IRB approval or exemption is provided.

Yes

University Health Care
Department of Neurology

Stefan-M. Pulst, M.D., Dr. med
Professor and Chair
Stefan.Pulst@hsc.utah.edu

27 March 2017

A. Gordon Smith, M.D.
Professor of Neurology
Vice Chair for Research
Chief of Neuromuscular Medicine
University of Utah Health

Dear Dr. Smith:

I am delighted to write in support of your application to the American Brain Foundation requesting selection of your proposal to study mitochondrial structure in chemotherapy induced peripheral neuropathy (CIPN) for a crowdfunding philanthropic campaign. CIPN is a major cause for morbidity among cancer survivors. Your proposal is innovative, and builds on your ongoing project examining CIPN natural history and risk factors. Given your team's extensive experience in neuropathy clinical research I have no doubt regarding the project's successful completion. The Utah Cutaneous Nerve Laboratory is internationally recognized as a leader in the study of cutaneous innervation in peripheral neuropathy, and you will benefit from the substantial resources of the University of Utah Cell Imaging Core.

I can assure the review panel that you will continue to benefit from the resources necessary to carry out this proposal including laboratory space and administrative support.

I wish you the best of luck in your efforts to raise funds to support this exciting project.

Sincerely,

Stefan-M. Pulst, M.D., Dr. med.
Professor and Chair
Department of Neurology
University of Utah

The University of Utah
Department of Neurology
175 North Medical Drive East
Salt Lake City, Utah 84132-2305
Telephone (801) 585-2886
Fax (801) 581-6707
www.utahneurology.org

Budget: Early distal axonal mitochochondrial injury with paclitaxel

Personnel	Role	FTE	Salary	Benefits	Total
	Cutaneous Nerve Laboratory Technician	0.5	$80,000	0.37	$54,800
	Study Coordinator	0.75	$60,000	0.37	$61,650
	Total				$116,450
Participant evaluations	Baseline	25			
	Paclitaxel paresthesias	5			
	Controls	5			
	Followup visits	20			

Study procedures		number	cost	Total
Light microscopy	Confocal Imaging	55	$45	$2,475
	Imaris Image Analysis	55	$21	$1,155
Electron microscopy	Epon processing	55	$30	$1,650
	Electron microscopy grids	55	$48	$2,640
	Electron Microscopy analysis	55	$240	$13,200
Nerve conduction studies	Sural and Peroneal with conduction and F	55	$165	$9,075
Materials	reagents for immunohistochemistry and electron microscopy		$3,500	$3,500
Total				$150,145

Budget justification

Personnel.
Summer Malia Karafiath MD will be the Study coordinator (75% FTE). She has extensive experience leading and coordinating CIPN clinical research and is responsible for an ongoing CIPN natural history study from which patients will be recruited for this project. She will be responsible for participant recruitment from among breast cancer clinic at the Huntsman Cancer Institute. She will obtain consent, schedule and coordinate all in-person study procedures including performance of skin biopsies.

Peter Hauer will be the Skin Technician (50% FTE). Mr. Hauer led the development of the currently used technique to study cutaneous nerves during his 25 year tenure leading the Cutaneous Nerve Lab at the Johns Hopkins School of Medicine. He was recruited to lead the University of Utah Laboratory in 2014. Mr. Hauer currently oversees a multi-university quality control consortium of similar laboratories. He has trained over 50 other laboratories world-wide and has extensive experience with all of the techniques proposed in this proposal, including successful use of each proposed antibody. He has overseen use of skin biopsy in many large multicenter clinical trials (including international trials). Under Mr. Hauer's leadership, the Cutaneous Nerve laboratory current provides similar research support to NIH funded investigators at other Universities. He will be responsible for oversight of all biopsy processing, interpretation/quantitation, and laboratory data management. He will fix, and process skin biopsies for light microscopic immunohistochemical analysis, and will provide all quantification of intraepidermal nerve fiber density and axonal mitochondrial number. He will coordinate confocal and EM imaging with the Cellular Imaging Core.

Study procedures. 25 women with breast cancer scheduled for paclitaxel chemotherapy will be recruited, and each will undergo baseline evaluation consisting of physical exam, *nerve conduction studies (NCS)* following a standardized protocol, and skin biopsy for assessment of IENFD using brightfield PGP9.5 immunohistochemistry (IHC). Fluorescent IHC using confocal microscopy will be used to image axonal and keratinocyte mitochondria. EM will be performed to directly visualize axonal mitochondria. A 20% attrition rate is anticipated. Therefore, 20 participants will undergo the same evaluation following chemotherapy (on average 3 months). 5 Patients with P-APS will undergo this evaluation at the time of P-APS development. Assuming there are axonal mitochondrial changes compared to baseline, 5 more participants without P-APS will be evaluated. In total there will be 55 biopsy and NCS evaluations. The imaging costs above include reagent and Cell Imaging Core costs.

Cost sharing
This project will be embedded in an ongoing IRB approved study of CIPN natural history and risk factors. The Division of Neuromuscular Medicine will provide matching funds to those raised by the ABF crowdfunding platform. We are therefore requesting a total of $75,000 to support this project.

INSTITUTIONAL REVIEW BOARD
THE UNIVERSITY OF UTAH

75 South 2000 East Salt Lake City, UT 84112 | 801.581.3655 | IRB@utah.edu

IRB: IRB_00070295

PI: Noah Kolb

Title: Predicting and Characterizing Chemotherapy Induced Peripheral Neuropathy

CR: CR_11/16/2016 2:41 PM

Date: 12/12/2016

Effective 12/12/2016, the above-referenced Continuing Review is approved to continue research procedures outlined in the University of Utah IRB-approved application and documents.

APPROVAL DOCUMENTATION

Review Type: Convened Board Review
Risk Level: Greater Than Minimal
Approval Date: 12/7/2016
Expiration Date: 12/6/2017 11:59 PM

APPROVED DOCUMENTS

Informed Consent Document
Consent Clean 2017 (no changes)

Company Protocol
protocol 2017 (no changes)

Other Documents
TissueBankManagementPlanCIPN.doc

ONGOING SUBMISSIONS FOR APPROVED PROJECTS

- **Continuing Review:** The research protocol must be re-reviewed and re-approved prior to the expiration date via the continuing review application: http://irb.utah.edu/submit-application/reviews/index.php
- **Amendment Applications:** All changes to the research application, protocol, or approved documents must be submitted and approved prior to initiation: http://irb.utah.edu/submit-application/amendments.php
- **Report Forms:** The research must adhere to the University of Utah IRB reporting requirements for unanticipated problems and deviations: http://irb.utah.edu/submit-application/forms/index.php
- **Final Project Reports for Study Closure:** The research application must be closed with the IRB once the research activities are complete: http://irb.utah.edu/submit-application/final-project-reports.php

Click CR_00023919 to view the application and access the approved documents.

Please take a moment to complete our customer service survey. We appreciate your opinions and feedback.

For New and Renewal Applications (PHS 398) – DO NOT SUBMIT UNLESS REQUESTED
For Non-competing Progress Reports (PHS 2590) – Submit only Active Support for Key Personnel

PHS 398/2590 OTHER SUPPORT

Provide active support for all key personnel. **Other Support includes all financial resources, whether Federal, non-Federal, commercial or institutional, available in direct support of an individual's research endeavors, including but not limited to research grants, cooperative agreements, contracts, and/or institutional awards.** Training awards, prizes, or gifts do not need to be included.

SMITH, A.G.
ACTIVE

1U10NS077305-01 (Smith) 09/01/2011-06/30/2018 1.2 calendar
NIH/NINDS $1,400,000
The Utah Regional Center for Excellence in Neuroscience Clinical Trials (UR-NEXT)

UR-NEXT will provide an ideal mechanism ideal mechanism for coordinating recruitment and access throughout a 5 state region in the Intermountain West. The coordinated efforts of a leadership team with a track record of collaboration and experience in both pediatric and adult clinical studies and trials and an experienced clinical trials manager will ensure the performance of high quality neuroscience trials across a broad range of diseases.
Role: PI

Impeto-Medical, Inc. (Smith) 01/01/2014-01/31/2018 0.6 calendar
Chemotherapy Induced Peripheral Neuropathy $365,760

The major goals of this project are to determine if Sudoscan can be used in a screening paradigm to predict CIPN risk or identify patients with subclinical CIPN early in their course of chemotherapy and include development of Sudoscan as a potential endpoint for future clinical trials and use of CIPN as a disease model to establish the clinical meaning of decline in Sudoscan.
Role: PI

R01DK064814-09 (Smith/Singleton) 04/01/2015-03/31/2020 1.8 calendar
NIH/ NIDDK $2,446,785
Activity for the Diabetic Polyneuropathy: The ADAPT Study

The major goals of this project are to evaluate the efficacy of a lifestyle intervention that integrates moderate supervised exercise and actigraphy based counseling to reduced sedentary behavior on diabetic peripheral neuropathy with a focus on patient relevant outcomes and quality of life and validation of biomarkers including intraepidermal nerve fiber density (IEFND).
Role: Co-PI

DP3 DK104394 (Smith/Singleton) 09/30/2014-08/31/2017 3.6 calendar
NIH/NIDDK $999,141
Developing Corneal Confocal Microscopy as a Screening Tool and Biomarker for Diabetic Neuropathy

The major goal of this project is to develop corneal confocal microscopy (CCM) as a screening tool that can be used to identify patients with, or at high risk for, early neuropathy.
Role: Co-PI

SMITH, A.G.
PENDING

U01NS095388 (Smith) 12/01/2016-11/30/2020 1.2 calendar
NIH/NINDS $7,563,257
Topiramate as a Disease Altering Therapy for Cryptogenic Sensory Peripheral Neuropathy (The TopCSPN Study)

Double blind randomized controlled trial of topiramate for CSPN associated with obesity and metabolic syndrome using the NeuroNEXT clinical trials network.
Role: PI

OVERLAP:
None

ABF Full Application

Applicant Information

Prefix

Dr.

First Name

A. Gordon

Last Name

Smith

Suffix

Title

Professor and Vice Chair of Neurology

Institution Name

University of Utah

E-mail

gordon.smith@hsc.utah.edu

Office Phone

801-581-8960

Office Fax

Project Details

Project Title

Axonal mitochondrial failure precedes chemotherapy induced neurotoxicity in breast cancer patients

Project Start Date

July 01, 2017

Project End Date

June 30, 2018

Disease focus

ALS & Neuromuscular
Technology & Innovation

Specific Disease Focus

Chemotherapy Induced Peripheral Neuropathy

Project Summary/Abstract

Chemotherapy induced peripheral neuropathy (CIPN) is the most common dose-limiting side effect of paclitaxel, a first line breast adenocarcinoma treatment. CIPN causes disability due to pain, numbness, and gait instability. Up to 45% of patients develop acute widespread neuropathic pain (paclitaxel acute pain syndrome, P-APS). P-APS patients are at risk for greater CIPN severity. The etiologies of P-APS and CIPN are poorly understood; there are no effective treatments. Half of patients with early CIPN have normal nerve conduction studies

(NCS) and intraepidermal nerve fiber density (IENFD) consistent with pre-degenerative functional failure. CIPN animal models show impaired axonal microtubular dynamics, mitochondrial permeability with swelling and vacuolization. We hypothesize P-APS is due to axonal mitochondrial stress that progresses to distal axonal failure and axon loss. 20 Breast adenocarcinoma patients who will receive paclitaxel will undergo CIPN specific disease severity scales, NCS and skin biopsy for IENFD prior to treatment. Immunohistochemistry with quantitative image analysis will evaluate mitochondrial size, number and distribution in epidermal axons and keratinocytes. This evaluation will be repeated 2 weeks following the final paclitaxel dose. The first 5 patients who develop P-APS have a skin biopsy. If mitochondrial changes are noted 5 age-matched patients without P-APS will evaluated at the same time point for comparison. We anticipate P-APS will be associated with structural mitochondrial changes including increased distal mitochondrial volume with vacuolization, swelling, and clusters of small mitochondria, and that these changes will increase in severity with progression to functional axonal failure and ultimately degeneration among CIPN patients.

Project Narrative

Nerve damage is the most common dose limiting side effect of paclitaxel, one of the most important chemotherapy drugs used to treat breast cancer. Nerve damage (chemotherapy induced peripheral neuropathy -- CIPN) causes numbness and pain in the feet and legs and can lead to trouble walking and falls. Some patients treated with paclitaxel develop pain all over their body after infusions. This is called paclitaxel acute pain syndrome (P-APS). P-APS is associated with more severe CIPN. We do not know what causes P-APS or CIPN and there are no treatments. Animals treated with paclitaxel develop abnormalities in the mitochondria in the nerves. Mitochondria are responsible for producing energy for the cell. We hypothesize that P-APS is due to damaged mitochondria in the nerves and that with more paclitaxel the damage worsens resulting in abnormal nerve function and ultimately nerve damage. We will test this theory by evaluating nerve function in 20 people with breast cancer who will be treated with paclitaxel. We will perform a small skin biopsy above the ankle about the size of the letter "O". Using a powerful microscope we will look at the nerve mitochondria. We will repeat this evaluation after the end of chemotherapy. We will also do this test in 5 people who develop P-APS and 5 more who do not have P-APS. We expect to see increasing severity of mitochondrial damage from P-APS to CIPN. This observation could lead to new treatments to prevent or treat CIPN.

Facilities and Equipment

The Cutaneous Nerve Laboratory serves as a core resource for NIH and foundation-funded research projects as well as industry sponsored studies in humans and animal models. The laboratory has experience using multiple immunohistochemistry markers of peptidergic and non-peptidergic innervation, nerve regeneration, growth factor receptor expression and inflammation. Through the University of Utah's Cell

Imaging Core Facility, the lab has access to four inverted confocal microscopes, including a Nikon A1 and A1R, and two Olympus FV1000 spectral confocal microscopes. The core utilizes software analysis tools for quantitative analysis of image data, including Metamorph, Imaris and Volocity software for 2D and 3D analysis. In the Cutaneous Nerve Laboratory, a Nikon Eclipse 80i microscope with a digital camera and image analysis system is used for nerve quantitation and morphometric analysis (Spot Diagnostics Imaging software 5.2). An Olympus BH2 microscope is also located in the lab. Other laboratory equipment include two Microm freezing-sliding microtomes, two Olympus SZ61 dissecting microscopes, a mixing plate, and a pH meter as well as other essential equipment. Four freezers with backup systems and alarms are located in the lab. Peter Hauer, the laboratory manager, is responsible for coordinating scheduled quality control procedures in collaboration with labs at Johns Hopkins University, University of Rochester and Icahn Mount Sinai medical center. As a clinical diagnostic/research laboratory, the lab is CAP and CLIA certified, and FDA-compliant.
The University of Utah Neurophysiology Core Laboratory provides electophysiologic testing for NIH, foundation, investigator and industry funded studies. Equipment Oxford Synergy and Viking-Natus electrodiagnostic equipment.

Specific Aims

Chemotherapy-induced peripheral neuropathy (CIPN) is the dose-limiting side effect of paclitaxel, a commonly used agent for breast adenocarcinoma. Paclitaxel causes acute widespread neuropathic pain in 45% of patients (paclitaxel acute pain syndrome, P-APS); over 40% develop CIPN. Animal models suggest paclitaxel is mitotoxic(1). We hypothesize paclitaxel causes acute mitochondrial stress in small unmyelinated axons resulting in P-APS; continued exposure causes length-dependent mitochondrial toxicity and axonal degeneration.
SA#1: Determine if mitochondrial injury is associated with predegenerative functional axonal failure. CIPN scales, nerve conduction studies (NCS) and calf skin biopsy for intraepidermal nerve fiber density (IENFD) determination will be performed on 20 patients prior to paclitaxel. Immunohistochemistry with quantitative image analysis will evaluate axonal mitochondrial number and distribution(2). Electron microscopy will measure mitochondrial size and structure. These procedures will be repeated 2 weeks after the final dose. We anticipate patients with functional axonal failure (CIPN with normal NCS and IENFD) will have greater axonal mitochondrial injury (e.g. swelling, vacuolization, reduced size and increased numbers) compared to keratinocytes, and that the severity will be greater in those with evidence of axonal degeneration.
SA#2: Determine if PAP-S is associated with mitochondrial structural changes. The first 5 patients who develop PAP-S will undergo a repeat biopsy and clinical scales at that time. We anticipate that axonal, but not keratinocyte, mitochondria will have abnormal structure, size and distribution, but that IENFD and NCS will remain normal. If

mitochondrial axonal abnormalities are observed, 5 age-matched patients without P-APS will be evaluated at the same time.

Research Strategy

Significance, Innovation, Approach, Timeline

Significance

CIPN is the most common dose limiting side effect of many of the most commonly used chemotherapies. CIPN causes numbness, weakness, pain and gait instability, leading to reduced quality of life and increased fall risk(3,4). Over 1/3rd of CIPN patients have a significant reduction in chemotherapy dose or cessation of therapy, likely leading to suboptimal outcomes and potentially reduced survival(5). There are no effective prevention or treatment strategies. The microtubular inhibitor Paclitaxel, a first-line therapy for breast adenocarcinoma, causes CIPN in over 40% of patients. Infusion causes widespread neuropathic pain (PAP-S) in 45%. Our preliminary data suggest PAP-S is associated with greater CIPN severity. The pathophysiology of P-APS is unknown.

Animal models suggest paclitaxel impairs microtubular dynamics and mitochondrial calcium signaling, increasing permeability and causing swelling, and vacuolization(1). Mitochondrial injury is a well-recognized contributor to axonal degeneration in other neuropathies, including diabetes (a CIPN risk factor)(6). We hypothesize paclitaxel leads to acute mitochondrial stress in small unmyelinated nociceptive axons resulting in P-APS. Continued exposure causes length-dependent mitochondrial toxicity and axonal degeneration. Preliminary data suggest 45% develop P-APS and 42% CIPN. Among those with CIPN signs and symptoms, NCS are normal in 46%, of whom 86% have normal IENFD, consistent with functional, potentially reversible, axonal failure.

The results promise to fundamentally enhance understanding of CIPN, link the mechanism of PAP-S to CIPN, and suggest novel therapeutic approaches. Demonstration of mitochondrial changes in P-APS would provide the first evidence of a disease mechanism for this enigmatic condition. Association with mitochondrial derangement would inform new mechanistic research and therapeutic approaches for CIPN prevention, potentially leading to significantly improved quality of life for cancer survivors. Development of preventative strategies for CIPN will permit more aggressive chemotherapy dosing leading to improved survival.

Innovation

Skin biopsies are routinely used to assess IENFD for neuropathy diagnosis and as an outcome measure in clinical trials(7). Use of human skin biopsies for discovery research has been limited. We have previously utilized the proposed techniques to study painful versus non-painful diabetic neuropathy(2). Application of similar techniques in this population is innovative and promises to further establish skin biopsy as a promising method explore disease mechanism in human subjects across neuropathy subtypes.

Approach

We are currently completing a natural history study of CIPN that is enrolling patients receiving potentially neurotoxic chemotherapy. We propose to enroll 20 additional breast cancer patients with planned paclitaxel therapy in this protocol. Those with a history of existing neuropathy or prior exposure to neurotoxic chemotherapy will be excluded.
SA#1: Prior to receiving paclitaxel the following procedures will be performed: EORTC-CIPN20 (a PRO)(8), Rasch Transformed Total Neuropathy Scale(9), CIPN-RODS (CIPN disability scale)(10), NCS and distal leg skin biopsy. IENFD will be determined using standard techniques and immunohistochemistry with quantitative image analysis will be used to evaluate axonal mitochondrial numbers and distribution as we have previously described(2). EM will be used to measure mitochondrial number, size and structure in epidermal axons and keratinocytes. The evaluation will be repeated 2-weeks after paclitaxel completion. Total dose will be recorded and modifications cataloged.
Expected results and potential problems: We anticipate axonal mitochondrial volume will increase from baseline, and there will be similar morphological changes to those observed in diabetic neuropathy(2). EM is expected to show vacuolization and swelling with clusters of small mitochondria, consistent with animal models(1). We expect mitochondria from keratinocytes to be relatively normal. These findings will be milder in those with functional axonal failure compared to those with evidence of axonal degeneration based on NCS and IENFD. We do not anticipate difficulty with recruitment based on our ongoing CIPN natural history study. Our collaborative team has experience with the proposed immunohistochemical studies. While we have not used EM in this fashion our laboratory manager has extensive EM experience and we do not foresee difficulties (we have reviewed the proposed studies and protocol with our microscopy core in preparation for this submission).
SA#2: The first 5 patients recruited for SA#1 who develop PAP-S will be asked to undergo the procedures outlined in SA#1 at that time. If mitochondrial or other structural axonal abnormalities are observed, 5 age-matched patients without P-APS will be recruited for comparison at a similar time point.
Expected results and potential problems: We anticipate that axonal, but not keratinocyte, mitochondria will have abnormal structure and distribution, suggesting generalized mitotoxicity. We expect those with the greatest degree of mitochondrial changes will be at greatest CIPN risk (recognizing this study is underpowered for this analysis). One potential problem is that patients may be reluctant to undergo additional evaluation. Given our recruitment success in other CIPN studies and the small number of patients we do not expect recruitment to be a challenge.
Timeline

Recruitment will be completed over 5 months and data acquisition by 9 months. Pathological studies and data analysis will require an additional 3 months.

List up to 5 milestones you will reach within the first 6 months of your study.

We anticipate the full project to take approximately 12 months to complete. During the first 6 months we will complete the following 5 milestones.

1. Month 1: We will enroll the first participants by the end of the first month.
2. Month 2: During the first two months we will refine the immunohistochemistry and electron microscopy protocols using banked tissue from a normal control, a patient with CIPN and normal IENFD, and a CIPN patient with reduced IENFD. This will allow us to identify and resolve any unanticipated technical issues.
3. Month 3: By the end of the third month we anticipate having enrolled 5 P-APS patients.
4. Month 4: By the end of the fourth month we project recruitment will be 50% completed
5. Month 5: By the end of month 5 we will have determined if there are mitochondrial changes in P-APS patients and if so will have enrolled 5 non P-APS patients. If there is uncertainty regarding the extent of mitochondrial abnormalities we will enroll non P-APS patients for comparison.

Age of Population Group(s) that will potentially benefit from this research

(check boxes that apply)

All Ages

Scientific Literature References

Reference 1

1. Cashman CR, Höke A. Mechanisms of distal axonal degeneration in peripheral neuropathies. Neurosci Lett. 2015 Jun;596:33--50. PMCID: PMC4428955

Reference 2

2. Hamid HS, Mervak CM, Münch AE, Robell NJ, Hayes JM, Porzio MT, et al. Hyperglycemia- and neuropathy-induced changes in mitochondria within sensory nerves. Ann Clin Transl Neurol. 2014 Oct;1(10):799--812. PMCID: PMC4241807

Reference 3

3. Cavaletti G. Chemotherapy - induced peripheral neurotoxicity (CIPN): what we need and what we know. Journal of the Peripheral Nervous System. Wiley Periodicals, Inc; 2014 Jun 1;19(2):66--76.

Reference 4

4. Kolb NA, Smith AG, Singleton JR, Beck SL, Stoddard GJ, Brown S, et al. The Association of Chemotherapy-Induced Peripheral Neuropathy

Symptoms and the Risk of Falling. JAMA Neurol. American Medical Association; 2016 Jul 1;73(7):860--6.

Reference 5

5. Speck RM, Sammel MD, Farrar JT, Hennessy S, Mao JJ, Stineman MG, et al. Impact of chemotherapy-induced peripheral neuropathy on treatment delivery in nonmetastatic breast cancer. J Oncol Pract. 2013 Sep;9(5):e234--40.

Reference 6

6. Vincent AM, Edwards JL, McLean LL, Hong Y, Cerri F, Lopez I, et al. Mitochondrial biogenesis and fission in axons in cell culture and animal models of diabetic neuropathy. Acta Neuropathol. 2010 ed. 2010 Oct;120(4):477--89.

Reference 7

7. Lauria G, Hsieh ST, Johansson O, Kennedy WR, Leger JM, Mellgren SI, et al. European Federation of Neurological Societies/Peripheral Nerve Society Guideline on the use of skin biopsy in the diagnosis of small fiber neuropathy. Report of a joint task for

Reference 8

8. Alberti P, Rossi E, Cornblath DR, Merkies ISJ, Postma TJ, Frigeni B, et al. Physician-assessed and patient-reported outcome measures in chemotherapy-induced sensory peripheral neurotoxicity: two sides of the same coin. Ann. Oncol. 2014 Jan;25(1):257--64

Reference 9

9. Binda D, Cavaletti G, Cornblath DR, Merkies ISJ. Rasch-Transformed Total Neuropathy Score clinical version (RT-TNSc((c))) in patients with chemotherapy-induced peripheral neuropathy. Journal of the Peripheral nervous system : JPNS. 2015 Sep;20(3):328--

Reference 10

10. Binda D, Vanhoutte EK, Cavaletti G, Cornblath DR, Postma TJ, Frigeni B, et al. Rasch-built Overall Disability Scale for patients with chemotherapy-induced peripheral neuropathy (CIPN-R-ODS). Eur. J. Cancer. 2013 Sep;49(13):2910--8.

Budget, Attachments and Acknowledgements

Budget

We recognize that changes may have occurred since the time you submitted your Letter of Intent. Please share the most recent accurate numbers below:

Total Project Budget

150145

Total existing funding or in-kind support

75145

Amount to be raised through crowdfunding campaign

75000

Evidence of institutional support (letter)

Smith, Gordon LOS_ABF_CIPN_3.27.17.pdf

Full budget

Paclitaxel Budget justification_3-27-17.docx

Documentation of IRB/IUCAC approval or exemption, if applicable.

IRB Approval Documentation.pdf

Completed conflict of interest & disclosure form

AGS_Other Support_MM_2-9-17.docx

I understand that the ABF will not list approved projects for general public crowdfunding campaigns until documentation of IRB/IUCAC approval or exemption is provided.

Yes

I understand that approval of the project to be shared on the crowdfunding campaign site is dependent on providing and working with the ABF staff to create the requisite materials that present the project in an engaging, easy-to-understand website presentation. I am amenable to working with the ABF staff to create such materials.

Yes

I understand that approval once a project has been completed, I will be required to submit a summary of my findings to be posted online (one page), and will submit this in a reasonably timely fashion. I also agree to submit a financial report, and to co-sign a thank you letter with the ABF that will be sent to donors.

Yes

I understand and agree that the ABF may share the information that I provide (including but not limited to the project description and relevant biographical/background details) in conversations with other potential funders outside the website to bolster fundraising efforts.

Yes

American Brain Foundation Release Agreement

American Brain Foundation
Release Agreement – Research

1. **Grant**. For good and valuable consideration, the receipt and sufficiency of which is hereby acknowledged, I grant to the American Brain Foundation ("ABF") and to the ABF's affiliates (including the American Academy of Neurology), and their respective contractors, agents, assigns, licensees, and successors (collectively, the "ABF Group"), a worldwide, royalty-free, perpetual, irrevocable right to take and use my image, likeness, voice, verbal statements, written testimonials and name and all images, videos, sound recordings, and written and verbal materials that I provide to the ABF (collectively, the "Materials "), in all forms and media, including composite or modified representations, for the purpose of promoting and supporting the missions of the ABF. For the avoidance of doubt, the Materials include all research project proposal information, project reports and other research-related information submitted to the ABF. I understand and agree that the ABF may publish the Materials on any and all media, including printed matter, promotional materials, e-mail, websites and social media platforms.

2. **Acknowledgement of Use**. I understand that the ABF Group may use the Materials on any and all media, including printed matter,

   promotional materials, e-mail, websites and social media platforms. I understand that the ABF's use of the Materials may intentionally or unintentionally give rise to the impression that either I or a family member suffers from brain/neurologic disease, and I nevertheless consent to this use. The ABF is not obligated to utilize any of the rights granted in this agreement. I waive the right to inspect or approve any uses of the Materials in connection with this grant.
3. **Warranty**. I warrant that I have the full power to enter into this agreement and to grant the aforementioned rights.
4. **Release**. I release the ABF Group from all liability for any claims that may arise regarding the use of Materials, including any claims of defamation, invasion of privacy, or infringement of moral rights, rights of publicity, or copyright. The ABF is permitted, although not obligated, to include my name as a credit in connection with any use of the Materials.**I have read and understood this agreement, I understand that it contains a release of liability, and I am over the age of 18**. This agreement expresses the complete understanding of the parties and shall be binding on me and my heirs, legal representatives and assigns. I understand that I am entering into a legally binding agreement and that clicking "I Accept" below shall have the same legal effect as my signature on this Release Agreement.

I Accept

AMERICAN BRAIN FOUNDATION®

April 10, 2017

A. Gordon Smith
Department of Neurology
30 North 1900 East SOM3R242
Department of Neurology
30 North 1900 East SOM3R242
Salt Lake City, Utah 84132

Dear Dr. Smith,

Congratulations! On behalf of the American Brain Foundation, I am pleased to inform you that your project has been selected to post on the Foundation's crowdfunding site.

An email was sent requesting several documents. It is critical that you provide all of the requested documents in order for your project to be posted on the crowdfunding site.

As a reminder, you will have 90 days from when your project goes live on the site to raise the funds needed to complete your proposed project. Once the funds are raised, a gift agreement will be sent to you and your institution to review and sign. As soon as the American Brain Foundation receives the signed gift agreement, the first payment for your project will be sent to your institution. The final payment for your project will be sent after your progress report has been reviewed and approved by the Foundation.

Please respond to this letter with the name of and contact information for the contact at your institution that the Foundation should work with to process payments. Please send your response to grants@americanbrainfoundation.org.

Again, congratulations on being selected for this opportunity.

Sincerely,

Suzi Sherman
Program Officer, Research & Digital Grants

CC: [Institution Department Chair]