BIOGRAPHICAL SKETCH

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NAME: Trushina, Eugenia

POSITION TITLE: Professor of Neurology

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

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Saratov State University and Moscow Institute of Physiological Active Compounds, Russia	M.S.	1980-1985	Organic Chemistry
Saratov State University, Saratov, Russia	Ph.D.	1987-1993	Synthesis of Biologically Active Heterocyclic Compounds
Mayo Clinic and Foundation, Rochester, MN, USA	Postdoctoral	1996-1998	Neuroscience Neurochemistry
Mayo Clinic and Foundation, Rochester, MN, USA	Postdoctoral	1998-2000	Cell Biology Mitochondrial dynamics and function

A. PERSONAL STATEMENT

My research program is focused on neurodegenerative diseases including Alzheimer's (AD), Huntington's (HD) and Parkinson's Diseases (PD) particularly as they intersect with studies on aging and metabolic disorders. Within my program, we utilize primary neuronal cultures, primary and established human cell lines and iPSCs, multiple animal models (mice, rats, Drosophila, *c elegans*), and human and murine biofluids and tissues. Specific strengths of my research endeavors include the development of innovative techniques relevant to *mitochondrial biology and metabolism* including *in vivo* axonal trafficking assays, 3-dimensional reconstruction of mitochondrial structures in intact brain tissue using electron microscopy, confocal and super resolution fluorescence microscopy, development of methods to measure respiration and mitochondrial energetics in the broad array of systems including isolated mitochondria and intact neurons, application of multiple systems biology approaches such as metabolomics, epigenetics, proteomics, and transcriptomics to establish signatures of disease, and novel animal models useful for the understanding of disease mechanisms, diagnosis, prognosis and monitoring therapeutic efficacy. These studies have driven a drug discovery program (hit-to-lead and preclinical development to clinical candidates) directed toward the prevention and treatment of neurodegenerative diseases, AD in particular. During the past five years, we successfully identified the molecular target and mechanism of a novel class of small molecule therapeutic agents for AD, completed an extensive preclinical *in vivo* efficacy studies in multiple mouse models of AD, and received a patent allowing our proprietary compounds. Extensive interactions with medicinal chemistry and other CROs and Pharma consultants position me well to direct the proposed project. My demonstrated track record of successful and productive research and training in areas that are highly relevant to human health and drug development, and my expertise in studying the molecular mechanisms of neurodegeneration and experimental therapeutics in multiple animal models should contribute uniquely to the proposed research.

B. POSITIONS AND HONORS

2019 – present Professor of Neurology, Mayo Clinic Rochester, MN

2013 - 2018 Associate Professor of Neurology and Pharmacology, Department of Neurology and Department of Molecular Pharmacology and Experimental Therapeutics, Mayo Clinic Rochester, MN
2011 - 2013 Assistant Professor, Department of Neurology, Mayo Clinic Rochester, MN
2005 - 2011 Assistant Professor, Department of Molecular Pharmacology and Experimental Therapeutics, Mayo Clinic College of Medicine, Mayo Clinic Rochester, MN
2004 - 2005 Instructor, Department of Molecular Pharmacology and Experimental Therapeutics, Mayo Foundation, Rochester, MN
2000 - 2004 Research Associate, Department of Molecular Pharmacology and Experimental Therapeutics, Mayo Foundation, Rochester, MN
1996 - 2000 Research Fellow, Department of Molecular Pharmacology and Experimental Therapeutics, Mayo Foundation, Rochester, MN
1993 - 1995 Instructor, Assistant Dean, Saratov State Academy of Veterinary Medicine and Biotechnology, Saratov, Russia
1985 - 1987 Research Scientist, Department of Organic Chemistry, Saratov State University, Saratov, Russia

AWARDS

1984 Outstanding Undergraduate Achievement Award in Organic Chemistry – Saratov State University, Russia
1985 Graduated with Honors - Saratov State University, Russia
2000 - 2003 Training grant CA09441 - National Institutes of Health, Bethesda, Maryland
2007 Young Investigator Award - Gordon Research Conference on CAG Triplet Repeat Disorders, Aussois, France
2013 Travel Fellowship from Alzheimer's Association International Conference, Boston, USA
2015 Mayo Clinic Press Release http://advancingthescience.mayo.edu/discussion/quest-for-alzheimers-disease-treatments-mitochondria-renders-clues/
2016 Travel Award for the 7th Annual Alliance for Healthy Aging Conference, Jacksonville, Florida

PATENTS

1. Sedavkina V.A., Safonova A.A., **Ponomaryova (Trushina) E.V**., Bespalova G.V. Pharmacological properties of novel pyrrolidone compounds. Patent N247217, 04.01.1987, USSR.
2. **Trushina E.,** Greenhouse R., Greenman K., and Thomas W. Compounds for modulating mitochondrial function. Patent No.: US 10,336,700 B2, issued on July 2, 2019.Priority date is march 3, 2015.
3. **Trushina E.,** Greenhouse R., Greenman K., and Thomas W. Compounds for modulating mitochondrial function. Divisional, application number 16/433,254 filed on 06/2019.

ADVISORY AND CONSULTANT WORK

2018 – present Reviewer for the DOD Congressionally Directed Medical Research Program study sections
2014– present NIH Federal Advisory Committee – a reviewer on the NIH Study Sections including Neural Oxidative Metabolism and Death (NOMD), RG1 ETTN-H (11): Small business panel on Drug Discovery for Aging, Neuropsychiatric and Neurologic Disorders; Special Emphasis Study Sections, etc.
2013- present Scientific Advisory Board for Alzheimer's Drug Discovery Foundation (ADDF)
2016 - 2019 Society for Neuroscience (SFN) Council, Chair of the Theme C "Neurodegenerative Disorders and Injury" Subcommittee of the Program Committee
2013- present Frontiers Editorial Board: Review Editor for Chemistry and Molecular Biosciences
2017 – present Journal of Alzheimer's Disease (JAD): Associated Editor
2008 - present Journal Reviewer: Alzheimer's & Dementia, Journal of Alzheimer's Disease, Translational

Psychiatry, The Journal of Metabolomics, Neurobiology of Disease, PLoS ONE, Biological Psychiatry, BBA, etc.

2010– present Grant Reviewer for Alzheimer's Association, National Science Centre of Poland, Czech Science Foundation and other National and International Foundations

2015 - present Mayo Clinic Metabolomics Core, member of the Advisory Panel

PROFESSIONAL MEMBERSHIPS

- Society for Neuroscience (SFN)
- The Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment (ISTAART)
- Mayo Alumni Association
- Metabolomics Society

C. CONTRIBUTION TO SCIENCE

A *The role of mitochondrial dynamics and function in health and disease*: My most exciting and innovative work is dedicated to the understanding of the role mitochondrial dynamics including axonal trafficking, fission and fusion affect cellular energetics and mechanisms of aging and neurodegeneration. We were the first to show that inhibition of axonal trafficking is an early and underlying dysfunction in AD and HD. We later demonstrated that restoration of axonal trafficking in AD mice resulted in a delay in the development of cognitive dysfunction Recently, using a 3D EM reconstruction technique developed in our laboratory, we identified novel mitochondrial fission arrest phenotype that we termed "mitochondria on a string" (MOAS). Detailed investigation revealed that MOAS are formed to provide temporary protection against conditions where energy is deprived.

a. Zhang L., Trushin S., Christensen T. A., Tripathi U., Hong C., Geroux R. E., Howell K. G., Poduslo J. F., **Trushina E. (2018)** Differential effect of amyloid beta peptides on mitochondrial axonal trafficking depends on their state of aggregation and binding to the plasma membrane. ***Neurobiology of Disease***, https://doi.org/10.1016/j.nbd.2018.02.003
b. Zhang L., Trushin S., Christensen TA., Bachmeier BV., Gateno B., Romanes JP., Schroeder A., Yao J., Itoh K., Sesaki H., Poon W., Gylys KH., Parisi JE., Brinton RD., Salisbury JL., and **Trushina E.** (**2016**) Altered brain energetics induces mitochondrial fission arrest in Alzheimer's Disease. ***Scientific Reports (Nature)***, 6, 18725; doi: 10.1038/srep18725. PMID: 26729583
c. **Trushina E**., Nemutlu E., Zhang S., Christensen T., Camp J., Mesa J., Siddiqui A., Tamura Y., Sesaki H., Wengenack TM., Dzeja PP., and Poduslo JF. (**2012**) Defects in Mitochondrial Dynamics and Metabolomic Signatures of Evolving Energetic Stress in Mouse Models of Familial Alzheimer's Disease. ***PLOS One***, 7(2): p. e32737; doi: 10.1371/journal.pone.0032737; PMID: 22393443.
d. **Trushina E.,** Dyer R., Badger JD., Ure D., Eide L., Tran DD., Vrieze BT., Legendre-Guillemin V., McPherson PS., Mandavilli BS., Van Houten B., Zeitlin S., McNiven M., Aebersold R., Hayden M., Parisi JE., Seeberg E., Dragatsis I., Doyle K., Bender A., Chacko C., McMurray CT. (**2004**). Mutant huntingtin impairs axonal trafficking in mammalian neurons *in vivo* and *in vitro*. ***Mol. Cell. Biol***, 24, 8195-8209; PMID: 15340079.

B. *Development of small molecule mitochondria-targeted therapeutics*: We demonstrated that modulation of mitochondrial function with small molecule partial inhibitors of mitochondrial complex I prevents the development of cognitive and behavior phenotypes in multiple transgenic animal models of familial AD (FAD). Treatment was successful in pre- and symptomatic mice. Studies into the molecular mechanism revealed that these molecules compete with the flavin mononucleotide for binding to the redox center of mitochondrial complex I. This treatment induced mild energetic stress that enhanced mitochondrial biogenesis, autophagy, cellular energetics and neuronal resistance to oxidative stress, and reduced inflammation and levels of Aβ and pTau. Using rational design and multiple *in vitro* and *in vivo* assays developed based on the understanding of the molecular mechanism, we synthesized proprietary small molecule complex I inhibitors (Dr. Trushina and *Mayo Clinic owns the IP*). Our data suggest that this approach represents a novel strategy that could be safe and efficacious in AD patients but could also be applicable to other diseases including HD, metabolic disorders, hypoxia and reperfusion, radiation, CIPN, sepsis, polycystic kidney disease and promote healthy aging. The manuscript reporting efficacy of MCI inhibitors in symptomatic AD mice is under submission to *Nature Medicine.*

e. Zhang L, Zhang S, Maezawa I, Trushin S, Minhas P, Pinto M, Jin LW, Prasain K, Nguyen TDT, Yamazaki Y, Kanekiyo T, Bu G, Gateno B, Chang KO, Nath KA, Dzeja P, Pang YP, Hua DH, and **Trushina E.** (**2015**) Modulation of mitochondrial complex I activity averts cognitive decline in multiple transgenic mouse models of familial Alzheimer's Disease. ***EBioMedicine***. 2(4):294-305. PMID 26086035.

f. **Trushina E***, Rana S, McMurray CT, Hua DH. (**2009**) Tricyclic pyrone compounds prevent aggregation and reverse cellular phenotypes caused by expression of mutant huntingtin protein in striatal neurons. ***BMC Neuroscience***, 10:73; doi: 10.1186/1471-2202-10-73. PMID 19586540. *, corresponding author.

g. Flannery P and **Trushina E** (**2019**) Mitochondrial Dysfunction in Alzheimer's Disease and Progress in Mitochondria-Targeted Therapeutics. DOI 10.1007/s40473-019-00179-0***. Current Behavioral Neuroscience Reports (Springer Nature).***

C. ***Molecular mechanisms of AD and biomarker discovery:*** We applied multiple approaches including metabolomics, transcriptomics and epigenetics to address the hypothesis that metabolic changes associated with early mitochondrial dysfunction could be used for disease diagnosis, prognosis, and monitoring therapeutic efficacy. Metabolomics conducted in cells, tissue and biofluids (CSF and plasma) from AD patients and animal models of AD and PD allowed identifying unique changes in energy utilization that were specific only to AD. We currently investigate sex-specific differences related to metabolic-epigenetic alterations in AD. Two manuscripts are currently under resubmission in *Alzheimer's and Dementia*.

h. **Trushina E***, Dutta T, Perssen XT, Mielke MM, Petersen R (**2013**) Identification of Altered Metabolic Pathways in Plasma and CSF in Mild Cognitive Impairment and Alzheimer's Disease Using Metabolomics. ***PLOS One*** 8(5): e63644. doi:10.1371/journal.pone.0063644; PMID: 23700429. *, corresponding author.

i. Tonnies E and **Trushina E** (**2017**) Oxidative Stress, Synaptic Dysfunction, and Alzheimer's Disease. ***Journal of Alzheimer's Disease***, doi: 10.3233/JAD-161088

j. Wilkins J, Sakrikar D, Petterson AM, Lanza IR, **Trushina E** (**2019**) A comprehensive protocol for multiplatform metabolomics alasyis in patient-derived skin fibroblasts. ***Metabolomics***, 15:83, DOI: 10.1007/s11306-019-1544-z

k. Klosinski LP, Yao J, Yin F, Fonteh AN, Harrington MG, Christensen TA, **Trushina E,** Brinton RD. (2015) White Matter Lipids as a Ketogenic Fuel Supply in Aging Female Brain: Implications for Alzheimer's Disease. ***EBioMedicine***, 2(12):1888-904. doi: 10.1016/j.ebiom.2015.11.002.

D. ***Molecular mechanisms of HD, PD, CIPN and novel therapeutics:*** We investigated molecular mechanisms associated with the expression of mutant huntingtin protein (mhtt) using multiple mouse models of HD (YAC72, HD150KI, R6/2). We identified caveolin 1 as a novel binding partner of mhtt, and demonstrated that mhtt/caveolin 1 interaction induces detrimental effect on endocytosis and cholesterol homeostasis in neurons. Reduction of mhtt/caveolin interaction via pharmacological intervention or genetic ablation alleviated the phenotype suggesting novel therapeutic target.

l. **Trushina E**, Canaria CA, Lee DY, McMurray CT (**2014**) Loss of Caveolin-1 Expression in Knock-in Mouse Model of Huntington's disease Suppresses Pathophysiology *in vivo*. ***Hum. Mol. Genet***. 23(1):129-44. doi: 10.1093/hmg/ddt406, PMID: 24021477.

m. **Trushina E**, Singh RD, Dyer R, Cao S, Shah VH, Parton R, Pagano R, McMurray CT (**2006**) Mutant huntingtin inhibits clathrin-independent endocytosis and causes accumulation of cholesterol in vitro and in vivo. ***Hum. Mol. Genet***. 15, 3578-91 (Figure was selected for the Cover Art). PMID: 17142251

n. Yue M, Hinkle K, Davies P, **Trushina E,** Fiesel F, Christenson T, Schroeder A, Zhang L, Bowles E, Behrouz B, Lincoln S, Beevers J, Milnerwood A, Kurti A, McLean PJ, Fryer J, Springer W, Dickson D, Farrer M, Melrose H (**2015**) Progressive dopaminergic alterations and mitochondrial abnormalities in LRRK2 G2019S knock in mice. ***Neurobiology of Disease,*** 78:172-95, DOI: 10.1016/j.nbd.2015.02.031.PMID:25836420. PMCID:PMC4526103.

o. Podratz J, Lee H, Knorr P, Koehler S, Lambrecht K, Arias S, Schmidt K, Yudintsev G, Yang A, **Trushina* E,** Windebank A (**2016**) Cisplatin induces mitochondrial deficits in Drosophila larvae segmental nerve in the absence of motor neuron apoptosis. ***Neurobiol of Disease***. 97(Pt A):60-69. doi: 10.1016/j.nbd.2016.10.003.* Senior author.

E. ***Providing expertise on identification of the best strategies to advance science in the field of neurodegenerative diseases:*** participated in a number of panels, round tables and webinars to identify roadblocks in the development of the field and approaches to move forward including the utilization of systems biology techniwues, human and animal models.

p. Snyder HM, Carrillo MC, Henriksen K, Jeromin A, Lovestone S, Mielke M, O'Bryant S, Sarasa M, Sjøgren M, Soares H, Teeling J, **Trushina E**, Ward M, West T, Bain LJ, Shineman D, Weiner M, Fillit HM (**2014**) Developing

Novel Blood-Based Biomarkers for Alzheimer's Disease. ***Alzheimer's & Dementia*****,** 10 (1): 109-14; PMID: 24365657

q. Pistollato F, Ohayon EL, Lam A, Langley GR, Novak TJ, Pamies D, Perry G, **Trushina E**, Williams RSB, Roher AE, Hartung T, Harnad S, Barnard N, Morris MC, Lai MC, Merkley R and Chandrasekera PC (**2016**) Alzheimer disease research in the 21st century: past and current failures, new perspectives and funding priorities. ***Oncotarget,*** DOI: 10.18632/oncotarget.9175. PMID: 27229915

r. ***Webinar:*** ***Beyond the Failed Beta Amyloid Hypothesis***: - Alzheimer's Experts to Discuss Need for New Medicines with Alternative Mechanisms of Action in Pre-CTAD Conference Webinar. Accera's Senior Medical Advisor, Michael Gold, M.D., to Moderate with Presentations by R. Swerdlow, MD, and **E. Trushina,** PhD, Nov. 29, **2016**
https://www.prnewswire.com/news-releases/beyond-the-failed-beta-amyloid-hypothesis----alzheimers-experts-to-discuss-need-for-new-medicines-with-alternative-mechanisms-of-action-in-pre-ctad-conference-webinar-300369786.html

s. **Trushina E.** and Wilkins J. Sex specific metabolic and epigenetic changes in primary fibroblasts from patients with Alzheimer's disease. **Sex as a Biological Variable Workshop**, NIH, Bethersda, MD, 10/26-27, **2017**. https://commonfund.nih.gov/sexdifferences/workshop; https://www.youtube.com/watch?v=LQk3HFpodoA&feature=youtu.be&t=20m5s

My papers are available in My Bibliography:
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/41806255/?sort=date&direction=descending

D. Research Support (Active)

1. NIH NIA RF1 AG055549 **Trushina (PI)** 04/2017 – 03/2022
Mitochondrial Complex I as a Target for neuroprotection in AD (the grant is in 3%; Impact Factor 20). The goal is to advance the understanding of the details of molecular mechanisms of mitochondrial Complex I inhibitors as new therapeutics for Alzheimer's Disease

2. Alzheimer's Drug Discovery Foundation (ADDF) **Trushina (PI)** 01/2018 – 12/2019
Small Molecule Inhibitors of Mitochondrial Complex I for Treatment of Alzheimer's Disease.
Development of small molecules partial complex I inhibitors for treatment of AD

3. NIH NINDS R01 NS107265 **Trushina (PI)** 07/2018 – 06/2022
Small Molecule Mitochondria-targeted Therapeutics for Huntington's Disease.
Establish whether strategies designed to promote mitochondrial biogenesis and turnover could delay/slow the progression of HD.

4. NIH NIA RO1 AG59093 R. Kaddurah-Dauok (PI), **Trushina (Co-I)** 04/2018 – 03/2023
Metabolic Networks and Pathways Predictive of Sex Differences in AD Risk and Responsiveness to Treatment

5. NIH NIA R01 AG62135 Lee (PI); **Trushina (Co-PI)** 02/2019 – 01/2024
MPK as a target for neuroprotection in AD
In collaboration with Dr. M. Lee of the University of Minnesota, establish the role of AMPK in the mechanisms of neurodegeneration in AD

COMPLETED.

1. RO1 ES020715 Trushina (PI) 09/20/2011-08/30/2017
NIH/NIEHS
Mitochondrial Dynamics and Metabolomic Biomarkers in Neurodegenerative Disorders
2. ADDF Trushina (PI) 11/01/2009 – 12/31/2018
Lead Discovery of Novel Small Molecule Compounds Effective in Restoration of Mitochondrial Function
3. MN Partnership Grant Trushina, Lee, PIs 01/2016 –01/2018
Molecular Mechanism of Novel Small Molecule Therapeutics for Alzheimer's Disease