BIOGRAPHICAL SKETCH

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NAME: Mouradian, M. Maral

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

POSITION TITLE: Distinguished Professor of Neurology / William Dow Lovett Professor / Institute Director

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)*	Start Date MM/YYYY	Completion Date MM/YYYY	FIELD OF STUDY
American University of Beirut, Lebanon	B.Sc.	10/1975	06/1978	Biology - Chemistry
American University of Beirut, Lebanon	M.D.	09/1978	06/1982	Medicine
University of Cincinnati Medical Center, Ohio	Resident	07/1982	06/1985	Neurology

A. Personal Statement

My research is focused on elucidating the molecular pathogenesis of neurodegeneration in Parkinson's disease as well as understanding the mechanisms underlying the complications and adverse effects of currently available symptomatic therapies. The ultimate goal is to identify novel therapeutic targets and agents to slow down or stop progression of the disease, and mitigate the shortcomings of current therapies. My interest in this line of investigation began at the NIH intramural program and continues at Rutgers University - Robert Wood Johnson Medical School where I hold an endowed chair for Parkinson's disease (PD) research and serve as Founding Director of the Institute for Neurological Therapeutics. My early research elucidated dysregulation of the brain's responsiveness to the gold standard treatment of the disease and led to the pharmaceutical development of several new improved formulations. With the support of several grants from the NIH and foundations, my lab has made a number of discoveries about the molecular pathogenesis of PD and related proteinopathies. Among the therapeutic strategies we have identified to date include the use of a microRNA and small molecules to downregulate levels of the key pathogenic protein α-synuclein, reducing its phosphorylation state by enhancing the activity of Protein Phosphatase 2A, and preventing its aggregation by transglutaminase 2. We have also identified the role of opioid receptors in the complications of the gold standard therapy of the disease. Compounds targeting each of these mechanisms are at various stages of testing using experimental approaches ranging from in vitro and cell-based molecular and cell biologic studies, to genetically modified mice, and primates.

Ongoing and recently completed projects that I would like to highlight include:

1 RF1NS130702 3/1/2023 – 2/28/2026
Mouradian (PI)
PME-1: Pathogenetic Role and Therapeutic Opportunity in Neurodegenerative Mixed Proteinopathies

T32NS115700 7/1/2021 - 6/30/2026
Mouradian (PI)
Training in Translating Neuroscience to Therapies

R21AG075656 8/15/2022 – 7/31/2024
Mouradian and Vatner (MPI)
Alzheimer's Disease Protection by Reduced Adenylyl Cyclase Type 5

R01NS101134 5/1/2017 - 4/30/2023
Mouradian and Nicholls (MPI)
PP2A Dysregulation in the Pathogenesis of α-Synucleinopathies

UG3/UH3 NS116921 6/1/2020 – 5/31/2023
Mouradian and Disney (MPI)
RNA Targeted Drug Discovery and Development for Parkinson Disease

R21NS123770 7/1/2021 – 12/31/2023
Mouradian (PI)
Role of Transglutaminase 2 in Synucleinopathies

Michael J. Fox Foundation-001006 12/24/2020 – 1/31/2024
Mouradian (PI)
RNA Targeting Small Molecules as Therapeutics for Parkinson's Disease

Michael J. Fox Foundation-022157 11/01/2022 – 10/31/2024
Mouradian (PI)
Developing a TG2 Inhibitor as a Disease Modifying Treatment for Parkinson's Disease

Citations:

1. Zhang, P., Park, H.J., Zhang, J., Junn, E., Andrews, R.J., Velagapudi, S.P., Abegg, D., Vishnu, K., Costales, M.G., Childs-Disney, J.L., Adebikian, A., Moss, W.N., **Mouradian, M.M.*,** Disney, M.D.: Translation of the intrinsically disordered protein α-synuclein is inhibited by a small molecule targeting its structured mRNA. Proc. Natl. Acad. Sci. USA, 117(3):1457-1467, 2020. PMID: 31900363. PMCID: PMC6983430 ***Co-corresponding author.**
2. Yan, R, Zhang, J, Park, H-J, Park, ES, Oh, S, Zheng, H, Junn, E, Voronkov, M, Stock, JB, **Mouradian, MM:** Synergistic neuroprotection by coffee components eicosanoyl-5-hydroxytryptamide and caffeine in mouse models of Parkinson's disease and DLB. Proc. Natl. Acad. Sci., 115(51):E12053-E12062, 2018. PMID: 30509990. PMCID: PMC6304960.
3. Lee, K.-W., Chen, W., Junn, E., Im, J.-Y., Gross, H., Sonsalla, P.K., Feng, X., Ray, N., Fernandez, J.R., Chao, Y., Masliah, E., Voronkov, M., Braithwaite, S.P., Stock, J.B., **Mouradian, M.M.:** Enhanced phosphatase activity attenuates α-synucleinopathy in a mouse model. J. Neurosc., 31(19):6963-6971, 2011. PMID: 21562258. PMCID: PMC5038983.
4. Zhang, J., Zhao, M., Yan, R., Liu, J., Maddila, S., Jun, E., **Mouradian, M.M.**: microRNA-7 protects against neurodegeneration induced by □-synuclein preformed fibrils in the mouse brain. Neurotherapeutics. 18(4):2529-2540, 2021. PMID: 34697773. PMCID: PMC8804150.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments:

2021-present	Distinguished Professor of Neurology, Rutgers-Robert Wood Johnson Medical School
2020-present	Chief, Division of Movement Disorders, Department of Neurology, Rutgers-RWJMS
2019-present	Director, American Parkinson Disease Association Center for Advanced Research at Rutgers
2018-present	Vice Chancellor for Faculty Development, Rutgers Biomedical and Health Sciences (RBHS)
2018-present	Founding Director, RWJMS Institute for Neurological Therapeutics, RBHS
2017-present	Chief, Division of Translational Neuroscience, Department of Neurology, Rutgers-RWJMS
2016-2017	Fellow, *Hedwig van Ameringen* Executive Leadership in Academic Medicine (ELAM) program
2014-present	Editor-in-Chief, Neurotherapeutics
2013-2019	Founder and President, MentiNova, Inc. Sublicensed to Trevi Therapeutics Inc. in 2019
2012-present	Professor, Dept. of Biochemistry and Molecular Biology, Rutgers-RWJMS
2008-present	Member, Graduate Faculty, Rutgers - RWJMS Joint Graduate Program in Neuroscience
2004-present	Professor, Department of Neuroscience and Cell Biology, Rutgers-RWJMS
2004-2018	Director, Center for Neurodegenerative and Neuroimmunologic Diseases, Rutgers-RWJMS
2004-2012	Professor, Dept. of Molecular Genetics, Microbiology and Immunology, Rutgers-RWJMS
2003-present	William Dow Lovett Professor of Neurology, Rutgers-Robert Wood Johnson Medical School

2003-present	Director of Research, Dept. of Neurology, Rutgers-Robert Wood Johnson Medical School
1992-2003	Medical Officer and Chief Neurologist, Experimental Therapeutics Branch, NINDS, Bethesda
1990-2003	Chief, Genetic Pharmacology Unit, Experimental Therapeutics Branch, NINDS, Bethesda, MD
1988-1990	Guest Researcher, Marshall Nirenberg's Lab. of Biochemical Genetics, NHLBI, Bethesda, MD
1987-2003	Attending physician, NIH, Clinical Center, Bethesda, MD
1985-1988	Clinical Associate, Experimental Therapeutics Branch, NINDS, NIH, Bethesda, MD
1984-1985	Chief Resident, Department of Neurology, University of Cincinnati, OH

Other Experiences and Professional Memberships:

Associate Editor, Pharmacology and Therapeutics (2001–2014); Editorial Board Member: Neurology (2004 – 2006), Neurodegenerative Disease Management (2009–present). Member, Scientific Advisory Board, American Parkinson Disease Association (1996 - present); Chair, NIH Clinical Center Medical Record Committee (2000–2003); Member: American Academy of Neurology (1986 – present; Fellow since 1998), Society for Neuroscience (1987–present), Movement Disorder Society (1987 - present), American Society for Gene Therapy (1997–2000), American Society for Experimental Neurotherapeutics (2009 - present), New York Academy of Sciences (2011 - 2017), NINDS Animal Care and Use Committee (2000 - 2003). Grant reviewer: VA PADRECC, Committee Member (2001), Israel Science Foundation (2002, 2010, 2014), DOD, US Army Medical Research and Materiel Command (2006), Catalan Agency for Health Technology Assessment and Research (2006), CNNT Study Section (2007-2008), United States-Israel Binational Science Foundation (2008), The National Health and Medical Research Council of Australia (2008), The Wellcome Trust, UK (2009), ZRG1 BDCN N(02) Special Emphasis Panel, NIH (2009), National Science Foundation (2009), Medical Research Council UK (2010), Special Emphasis Panel/Scientific Review Group 2010/08 ZRG1 BCMB-A (51) R meeting (2010), NIH Small Business Special Emphasis Panel ETTN-C11) SBIR (2010, 2011), NIH NOMD (Neural Oxidative Metabolism and Cell Death) Study section (2011, 2012); NIA SBIRs Special Emphasis Panel/SRG 2012/05 ZAG1 ZIJ-1 (2012); Research Grant Council of Hong Kong (2012, 2014); Alzheimer's Association (2012); Parkinson's UK (2012); National Medical Research Council (NMRC) of the Ministry of Health of Singapore (2013); Member, Clinical Neuroplasticity and Neurotransmitters (CNNT) Study Section (2012-2013); Swedish Research Council (2014); Czech Science Foundation (2015); Israeli Ministry of Science, Technology & Space (2015). Board of Directors, American Society for Experimental Neurotherapeutics (2014-present); Rutgers University Senate (2014-2017; Executive Committee 2016-2017); Lead Faculty Mentor, Rutgers - Robert Wood Johnson Medical School (2015-2018). Member, Scientific Review Committee, Parkinson Study Group (2018-2019); Member: NIH NOMD (Neural Oxidative Metabolism and Cell Death) Study Section (2018-2020); Co-Chair, Scientific Review Committee, Parkinson Study Group (2020-present); Science Committee of the Republic of Armenia (2020-present); Grant assessor, Michael J. Fox Foundation; NINDS P50 Udall Centers of Excellence Reviews 2021/05 ZNS1 SRB-H (17), 2022/05 ZNS1 SRB-H (22) 1; NINDS T32 Institutional National Research Service Award (NRSA) ZNS1-SRB-R (09).

Selected Honors:

2023	Excellence in Research Award, New Jersey Health Foundation
2022	Daniel Gorenstein Memorial Award, Rutgers University
2020	Member, Association of American Physicians
2020-present	Director, American Neurological Association Board of Directors
2019	Honorary Alumni Award, Rutgers - Robert Wood Johnson Medical School
2017	Board of Trustees Award for Excellence in Research, Rutgers University
2015	Outstanding Medical Research Scientist Award, Edward J. III Excellence in Medicine Fdn.
2013	Excellence in Research Award, Foundation of UMDNJ
2012	Norman H. Edelman Clinical Science Mentoring Award, Rutgers – RWJMS
2010	Dean's Research Award, Rutgers-Robert Wood Johnson Medical School (RWJMS)
2003	Roger C. Duvoisin, MD, Research Scholar Award, American Parkinson Disease Association
2000, 2001, 2002	Special Act or Service Award, NINDS, NIH
1997-present	Elected Fellow, American Neurological Association
1992	National Institutes of Health Award of Merit
1981	Alpha Omega Alpha Honor Medical Society

C. Contributions to Science

1. My early work in PD focused on the clinical pharmacology of L-dopa and the pathogenesis of motor response complications associated with its chronic use. Among my contributions in this area is experimental evidence that conventional intermittent L-dopa therapy promotes the development of motor complications and dyskinesias in advanced PD whereas continuous dopaminergic stimulation prevents or even reverses them. I showed that continuous L-dopa infusions reverse the maladaptive pharmacodynamic changes in the brain that correlate with an unstable motor response. Subsequently, a large number of preclinical and clinical studies by other investigators came to the same conclusion. These findings constituted the fundamental rationale for the development of practical means of delivering dopaminergic drugs continuously. In early 2015, the FDA approved two new L-dopa formulations to accomplish this goal, a duodenal pump and an extended release capsule. Subcutaneous pumps are also nearing approval.
    a. **Mouradian, M.M.,** Juncos, J.L., Fabbrini, G., Chase, T.N.: Motor response fluctuations in Parkinson's disease: Pathogenetic and therapeutic studies. Ann. Neurol., 22:475-479, 1987. PMID: 3435068
    b. **Mouradian, M.M.,** Fabbrini, G., Juncos, J.L., Schlegel, J., Bartko, J.J., Chase, T.N.: Motor fluctuations in Parkinson's disease: central pathophysiologic mechanisms, Part II. Ann. Neurol., 24(3):372-378, 1988. PMID: 32228271
    c. **Mouradian, M.M.,** Heuser, I.J.E., Baronti, F., Chase, T.N.: Modification of central dopaminergic mechanisms by continuous levodopa infusion therapy for advanced Parkinson's disease. Ann. Neurol., 27:18-23, 1990. PMID: 2301923
    d. Davis, T.L., Brughitta, G., Baronti, F., **Mouradian, M.M.**: Acute effects of pulsatile levodopa administration on central dopamine pharmacodynamics. Neurology, 41(5):630-633, 1991. PMID: 2027476

2. In the 1990s shortly after dopamine receptors were cloned and our understanding of the regulation of gene transcription was taking off, I carried out a series of fundamental studies to elucidate the mechanisms by which D1 and D2 dopamine receptor genes are transcribed. This line of investigation related to the altered response to drugs that target dopamine receptors, both agonists for PD and antagonists for psychiatric disorders. We also demonstrated the role of steroid hormones in regulating dopamine receptor gene transcription. Additionally, my laboratory cloned a new transcription factor that regulates these receptors, and another that is induced by the trophic factor GDNF.
    a. Minowa, M.T., Minowa, T., Monsma, F.J.Jr., Sibley, D.R., **Mouradian, M.M.**: Characterization of the 5' flanking region of the human D_{1A} dopamine receptor gene. Proc. Natl. Acad. Sci. USA, 89:3045-3049, 1992. PMCID: PMC48800
    b. Okazawa, H., Imafuku, I., Minowa, M.T., Kanazawa, I., Hamada H., **Mouradian, M.M.**: Regulation of striatal D_{1A} dopamine receptor gene transcription by Brn-4. Proc. Natl. Acad. Sci. 93(21):11933-11938, 1996. PMCID: PMC38161
    c. Yajima, S., Lammers, C.-H., Lee, S.-H., Hara, Y., Mizuno, K., **Mouradian, M.M.**: Cloning and characterization of murine glial cell-derived neurotrophic factor inducible transcription factor (MGIF). J. Neurosci., 17(22):8657-8666, 1997. PMID: 9348334
    d. Hwang, C.-K., D'Souza, U.M., Eisch, A.J., Yajima, S., Lammers, C.-H., Yang, Y., Lee, S.-H., Kim, Y.-M., Nestler, E.J., **Mouradian, M.M.**: Dopamine receptor regulating factor, DRRF: a zinc finger transcription factor. Proc. Natl. Acad. Sci. USA. 98(13):7558-7563, 2001. PMCID: PMC34707

3. Shortly after the first Parkinson gene, *SNCA*, was identified in 1997, I shifted my research focus from transcription regulation of dopamine receptor genes to studying the molecular pathogenesis of PD. We were the first to report that α-synuclein is degraded through the proteasome and that the pathogenic point mutant A53T is cleared slower than the wild-type protein. We also demonstrated that over-expression of not only the mutant but also wild-type protein increases intracellular reactive oxygen species levels rendering cells more susceptible to dopamine. Evidence for cell cycle aberrations due to α-synuclein indicative of attempts by cells to re-enter the cell cycle, analogous to findings in Alzheimer's disease, was also noted in a cellular model and in the brains of PD patients. Additionally, we found that cells containing cytoplasmic inclusions that have morphologic and molecular features of Lewy bodies are cytoprotective raising the possibility that residual surviving neurons with Lewy bodies seen in postmortem brains may be relatively protected than those who do not have these inclusions. We were also the first to identify microRNA-7 to target the 3'-UTR of α-synuclein mRNA, repress its expression and confer neuroprotection.

a. Bennett, M.C., Bishop, J.F., Leng, Y., Chock, P.B. Chase, T.N., **Mouradian, M.M.**: Degradation of α-synuclein by proteasome. J. Biol. Chem., 274(48):33855-33858, 1999. PMID: 10567343
b. Lee, S.S., Kim, Y.M., Junn, E., Lee, G., Park, K.-H., Tanaka, M., Ronchetti, R.D., Quezado, M., **Mouradian, M.M.:** Cell cycle aberrations by α-synuclein over-expression and cyclin B immunoreactivity in Lewy bodies. Neurobiol. Aging, 24(5):687-696, 2003. PMID: 12885576
c. Tanaka, M., Kim, Y.M., Lee, G., Junn, E., Iwatsubo, T., **Mouradian, M.M.**: Aggresomes formed by α-synuclein and synphilin-1 are cytoprotective. J. Biol. Chem., 279(6):4625-4631, 2004. PMID: 14627698
d. Junn, E., Lee. K.W., Jeong, B.S., Chan, T.W., Im. J.-Y., **Mouradian, M.M.:** Repression of α-synuclein expression and toxicity by microRNA-7. Proc. Natl. Acad. Sci. USA, 106(31):13046-13051, 2009. PMCID: PMC2722353

4. In addition to α-synuclein, my laboratory has been investigating the neuroprotective mechanisms of another PD gene, DJ-1, which is inherited as a loss-of-function recessive gene. We demonstrated that DJ-1 activates the Nrf2 pathway and induces thioredeoxin 1 expression. DJ-1 also interacts with the death protein Daxx in the nucleus and prevents its translocation to the cytoplasm and activation of the apoptotic kinase ASK1. Our studies of ASK1 also led to the discovery that it not only mediates the toxicity of MPTP, but also modulates the phenotype of α-synuclein transgenic mice, since ASK1 deletion mitigates the phenotype of these mice. These observations make ASK1 an intriguing target as a potential neuroprotective strategy.
   a. Junn, E., Taniguchi. H., Jeong, B.S., Zhao, X., Ichijo, H., **Mouradian, M.M.:** Interaction of DJ-1 with Daxx inhibits ASK1 activity and cell death. Proc. Natl. Acad. Sci. USA, 102(27): 9691-9696, 2005. PMCID: PMC1172235
   b. Im, J.-Y., Lee, K.-W., Woo, J.M., Junn, E., **Mouradian, M.M.:** DJ-1 induces thioredoxin 1 expression through the Nrf2 pathway. Hum. Mol. Genet. 21(13):3013-3024, 2012. PMCID: PMC3373246
   c. Lee, K.-W., Zhao, X., Im, J.-Y., Grosso, H., Jang, W.H., Chan, T., Sonsalla, P.K., German, D.C. Ichijo, H., Junn, E., **Mouradian, M.M.:** Apoptosis Signal Regulating Kinase 1 mediates MPTP toxicity and regulates glial activation. PLoS ONE 7(1): e29935, 2012. PMCID: PMC3254627
   d. Oh, S.E., Park, H.-J., He, L., Skibiel, C., Junn, E., **Mouradian, M.M.:** The Parkinson's disease gene product DJ-1 modulates microRNA-221 to promote neuronal survival against oxidative stress. Redox Biology, 19:62-73, 2018. PMID: 30107296, PMCID: PMC6092527.

5. Considering my long-standing interest in the experimental therapeutics of PD, my laboratory has engaged in a number of projects aimed at identifying novel therapeutic targets and developing improved therapies both for symptomatic relief and disease modification. In addition to studies described above aimed at repressing α-synuclein expression by microRNA, we have found that transglutaminase 2 (TG2) induces α-synuclein aggregation and exacerbates its toxicity, suggesting TG2 can be a potential therapeutic target, a project that is funded by the Michael J. Fox Foundation. Our work leading to the identification of eicosanoyl-5-hydroxytryptamide in coffee as a neuroprotective agent stems from our finding that the phosphatase that dephosphorylates α-synuclein is dysregulated in PD and Dementia with Lewy Bodies. We have also found that Apoptosis Signal-Regulating Kinase 1 (ASK-1) modulates the toxicity of α-synuclein and, hence, blocking ASK1 is expected to be protective. For symptomatic therapies, we demonstrated the ability of the dual kappa opioid agonist/ mu antagonist nalbuphine in reduced L-dopa induced dyskinesia in the primate model of PD. All these in vivo therapeutic studies include evidence for target validation.
   a. Junn, E., Ronchetti, R.D., Quezado, M.M., Kim, S.-Y., **Mouradian, M.M.:** Tissue transglutaminase-induced aggregation of α-synuclein: Implications for Lewy body formation in Parkinson's disease and dementia with Lewy bodies. Proc. Natl. Acad. Sci. USA, 100(4):2047-2052, 2003. PMCID: PMC149956
   b. Grosso, H., Woo, J.-M., Lee, K.-W., Im, J.-Y., Masliah, E., Junn, E., **Mouradian, M.M.:** Transglutaminase 2 exacerbates α-synuclein toxicity in mice and yeast. FASEB J. 28(10): 4280-4291, 2014. PMCID: PMC4202112
   c. Potts, L.F., Park, E.S., Woo, J.M., Dyavar Shetty, B.L., Singh, A., Braithwaite, S.P., Voronkov, M., Papa, S.M., **Mouradian, M.M.:** Dual κ-agonist / μ-antagonist opioid receptor modulation reduces L-dopa induced dyskinesia and corrects dysregulated striatal changes in the non-human primate model of Parkinson's disease. Ann. Neurol., 77(6):930-941, 2015. PMID: 25820831
   d. Zhang, J., Park, E.S., Park, H.J., Yan, R., Grudniewska, M., Oh, S.E., Yang X., Baum J., **Mouradian, M.M.:** Apoptosis Signal Regulating Kinase 1 deletion mitigates α-synuclein pre-formed fibril propagation in mice. Neurobiol. Aging, 85:49-57, 2020. PMID: 31734439.

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