

Dr. Justin McArthur
*Professor of Neurology, Pathology, Medicine
and Epidemiology
Director, Department of Neurology
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Edward Miller, M.D.
Dean of the Medical Faculty
The Johns Hopkins University
School of Medicine
Medical Administration, Suite 100

Re: Nicholas Maragakis, MD

Dear Dr. Miller:

Dr. Maragakis is currently in his sixth year as an Associate Professor in the Department of Neurology. This letter summarizes his accomplishments as an internationally-recognized research scientist in amyotrophic lateral sclerosis, glial biology, and cell-based therapeutics. As a clinical researcher, he has either spearheaded or participated in numerous clinical trials and clinical research efforts. He has mentored in his laboratory and taught in the classroom and clinic at every level in the School of Medicine. As a clinician, he has cared for patients with neuromuscular disorders, and in particular ALS, both regionally and with international referrals. In each of these efforts, he has built programs and has leadership roles. This letter is in support of his promotion to the rank of Professor in the Department of Neurology.

Introduction

After completing medical school and an internal medicine internship at the University of Utah in 1995, he came to Johns Hopkins University School of medicine as a Neurology Resident which and completed his residency in 1998. He completed a one year Neuromuscular Fellowship here and, after receiving an NIH K08 award, joined the faculty as an Assistant Professor of Neurology in 1999. He was promoted to the rank of Associate Professor in 2006 and is currently in that position full time.

Research Scholarship

Basic Science Scholarship

Dr. Maragakis' basic science interests are focused on understanding motor neuron disease mechanisms and translating this understanding towards translational research. Much of this work revolves around using stem cells (specifically glial restricted progenitors) as tools for investigating disease pathobiology as well as for their therapeutic potential in treating neurodegenerative disorders, specifically Amyotrophic lateral Sclerosis. For the last decade his laboratory has been investigating the biology of these glial progenitor cells both from rodent and human fetal tissues.

His laboratory has used these cells for two primary purposes. The first was to investigate the hypothesis that these cells could be transplanted into the spinal cords rodent models of ALS and result in the slowing of disease progression. If this hypothesis was correct, then the use of these cells for transplantation into patients with ALS could be a reasonable therapeutic target. In 2008 this culminated in his laboratory demonstrating that the transplantation of wildtype glial progenitor cells was sufficient to slow disease progression in the SOD1 rat model of ALS. This work was published in Nature Neuroscience. The result of this experimental approach has

led to similar efforts at using non-neuronal cells (astrocytes, neural stem cells, and mesenchymal stem cells) for transplantation studies. Using his research efforts as a model, the California Institute for Regenerative medicine funded an \$11.5 grant from Dr. Larry Goldstein at UCSD in an effort to find which type of human stem cells could produce similar efficacy. Dr. Maragakis serves as a research consultant for this group. His effort at bringing stem cell therapeutics to ALS patients has also resulted in his role as principle investigator on two Maryland Stem Cell Research Fund Grants. The first to study the role of human glial restricted precursors in slowing ALS disease progression and the second to create a repository of skin fibroblasts from ALS patients for developing induced pluripotent stem cells. He is also now the principle investigator on a U01 grant to investigate human glial progenitor transplantation in ALS. The goal of this grant is to file an IND with the Food and Drug administration for the use of human glial restricted progenitors in ALS patients.

The second major focus of his laboratory is to use glial progenitor cells derived from ALS rodent models (and now human iPS cells) to understand what influences ALS glia have on motor neuron degeneration. Studies in his lab demonstrated that the transplantation of glial progenitors—which differentiated into astrocytes—from SOD1 mice (a model of ALS) were sufficient to induce motor neuron death in a wildtype rodent model. These data, for the first time in vivo, suggested that mutations in ALS astrocytes were sufficient to induce wildtype motor neuron loss. This work was recently published in 2011 in the Proceedings of the National Academy of Sciences. These laboratory investigations have resulted in private, state, and federal funding to continue this theme. In collaboration with Dr. Hongjun Song he is currently the principle investigator on a grant from the Department of Defense's ALS Research Program to first obtain fibroblast samples from ALS patients, create induced pluripotent stem cells and differentiate them into both astrocytes and motor neurons, and finally to introduce these cells into animal models both to study the biology of human ALS astrocytes as well as to investigate their therapeutic potential.

Clinical Research Scholarship

Dr. Maragakis has also been heavily involved in clinical research as the principle investigator, site principle investigator, or co-investigator for over 10 clinical trials in ALS, many coordinated by the Northeast ALS Consortium for which he is an executive board member. He is currently the principle investigator of a multicenter clinical trial to study the role of resistance and endurance exercise in ALS. This is the first multicenter randomized control study of its kind for ALS and is coordinated through Johns Hopkins.

Teaching Scholarship

In addition to his research and clinical activities, Dr. Maragakis is active as a teacher, instructing at every level of medical education. As outlined in his CV, he teaches 2nd year medical students in their Neuropathology course serving as both a lecturer and lab instructor. He interacts with all of the 3rd and 4th year medical students during their Neurology clerkship through his lectures on neuromuscular disease which he gives on a regularly scheduled basis. As an attending physician on the neurology wards or on the neurology consult service, he teaches and interacts with Neurology and Internal Medicine residents as well as medical students. In his outpatient clinic, he regularly teaches neuromuscular fellows, neurology and internal medicine residents as well as medical students. In 2009, he received the Johns Hopkins Department of Medicine Teaching Award in recognition of outstanding contributions to Osler Housestaff teaching.

In his laboratory he has served as a mentor to high school students, undergraduate students, and postdoctoral fellows. Of the postdoctoral fellows, Dr. Andrea Pardo completed her postdoctoral fellowship in his laboratory and has recently finished a pediatric neurology residency at Cincinnati Children's Hospital. Dr. Angelo Lepore received several training grants while under his mentorship including a NRSA grant from the NIH and a Craig H. Neilsen Foundation: Post-Doctoral Fellowship Grant to study the "Role of astrocyte glutamate transporters in secondary cell loss after spinal cord injury. He is currently at assistant professor at Thomas Jefferson University. Dr. Sophia Papadeas recently completed her postdoctoral training. He currently mentors two postdoctoral fellows: Dr. Haidet-Phillips who has recently received an ALS Association fellowship grant award to study induced pluripotent stem cells and Dr. Akshata Almad who is studying connexin biology in his lab

Clinical Scholarship

Dr. Maragakis' clinical commitments complement his research initiatives. In his outpatient clinic, he cares for patients with a variety of neuromuscular disorders. The majority of his patients, however, suffer from ALS. Over the last decade, over 1200 new patients with ALS have been seen at Johns Hopkins, of those, Dr. Maragakis has cared for nearly 400. Because of his clinical expertise in this disease, he has received referrals from physicians throughout the United States and North America, Europe, Asia, South America, and Africa.

In addition to these ALS related clinical activities he is also an electromyographer and sees patients once weekly for a half-day clinic. These patients are sent from around the world as outpatients and as inpatients for the electrodiagnosis of a variety of neuromuscular disorders. He serves as a ward attending for the general neurology service one month per year and provides consulting neuromuscular services for one month per year as well.

Organizational and Administrative Activities/Program Building

Dr. Maragakis has organized the creation, with a generous \$25 million philanthropic gift, of the Michael S. and Karen G. Ansari ALS Center for Cell Therapy and Regeneration Research at Johns Hopkins. Over two years of design has gone into the proposal and organization of this center. Dr. Maragakis solely developed the vision of the Ansari ALS Center will particularly focus on the use of stem cells for investigating disease mechanisms, drug screening, and cell transplantation for ALS. He has organized a team of principle investigators within Johns Hopkins who have a clinical focus on ALS but also who have unique backgrounds in motor neuron biology, glial biology, and neuroregeneration research. As part of the development of the newly created center, he is now organizing collaborations with other programs within the institution including the Institute for Cell Engineering and the Brain Sciences Institute. . The mission of the Ansari ALS Center is to establish a platform for investigations into mechanisms of Amyotrophic Lateral Sclerosis pathogenesis and strategies for treatment. The Ansari ALS Center will provide flexibility for Johns Hopkins researchers in collaboration with other investigators with promising ideas to use a variety of novel methods for aggressively translating basic science discoveries to clinical application.

He is also the Co-Medical Director the Johns Hopkins ALS Clinic. The Johns Hopkins ALS Clinic treats over 160 new ALS patients and has over 480 patient visits per year. The clinic is not only involved in the clinical management of ALS patients but has also been a major force in multicenter ALS clinical trials, and collaborative efforts for collecting ALS biomarkers. Since becoming a Co-Medical Director, he has initiated a trial of Resistance and Endurance Exercise in ALS, created a repository of nearly 100 fibroblast samples from ALS patients for use in making induced pluripotent stem cells, and initiated the creation of an ALS database for all ALS patients seen within the last 10 years.

Citizenship/Commitment to Johns Hopkins

Dr. Maragakis has served on numerous departmental and institutional committees during his tenure as an Associate Professor. He has served as Chair of the Neurology Residency Selection Committee for the last three years and continues to serve as a member. As the School of Medicine moved to redesign the Medical School curriculum, he served on the committee to help design and implement the Neuroscience and Special Senses Curriculum and served as the Module Leader of the General Sensory Motor Section of that curriculum. Other institutional committees have included the Johns Hopkins Medical School Council as well as the Department of Neurology's Appointment and Promotions Committee. In addition to these educational commitments to the institution, he also has had the opportunity to serve the Hopkins basic science community as a member of the Brain Science Institute's Junior Faculty Advisory Committee and the Packard Center for ALS Research's Operating Committee.

National Leadership and International Recognition

As evidenced in his curriculum vitae he has shared both his clinical and basic science research to national and international audiences and served as a scientific reviewer for organizations in similar arenas. These national and international forums have particularly centered on his investigation of astrocyte stem cells from animal

models and human subjects. This work has been focused, with other colleagues worldwide, in attempting to use these cells for the investigation of mechanisms of disease, the creation of drug screening platforms, and for cell-based therapeutic strategies.

As a leader in the field of ALS clinical and basic science research he has received nationally recognized awards including the Diamond Award for ALS Research. He was recently elected by his peers doing ALS clinical research to join the Executive Board of the Northeast ALS Consortium. This is the largest national consortium of ALS clinics providing not only the most current clinical care, but has also shepherded the most relevant clinical trials from investigators and pharmaceutical companies to the ALS patient.

Anticipated Future Progression

As the new Director of the Ansari ALS Center for Cell Therapy and Regeneration Research at Johns Hopkins, he plans to lead a coordinated effort from both within Hopkins as well as with national and international collaborators to develop novel strategies for ALS therapeutics with emphases on both neuroprotection and neuroregeneration. This new effort will require oversight and coordination of over 25 new Hopkins employees encompassing basic scientists, research technicians, and administrative staff amongst 4 different laboratories within Johns Hopkins. Continued development of cell-based therapeutics for ALS clinical trial using human glial restricted precursors is part of a continued translational research commitment.

Summary Statement

Dr. Maragakis has established himself as a national leader with an international reputation in both clinical and basic science aspects of motor neuron disease biology and therapeutics. He has made major scientific contributions to the renowned Johns Hopkins research and clinical programs on the diagnosis and treatment of amyotrophic lateral sclerosis, and he is able to continue these programs forward through continued basic science and clinical research funding.

Sincerely,

Justin McArthur, MBBS, MPH
Professor and Director
Department of Neurology