C9ALS Initiatives at the Healey Center for ALS

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Healey Center
Sean M. Healey & AMG Center
for ALS at Mass General

Appendix:

Sean M. Healey & AMG Center for ALS: Vision

At the Sean M. Healey & AMG Center for ALS at Mass General there has never been a better time for action in our quest to cure ALS. Utilizing the new tools and technologies available to scientists, we are accelerating the discovery of therapies into action for people with ALS. Our vision is to break down barriers, accelerate the translation of research to care, and welcome people with ALS, many previously without access, to new, innovative and personalized therapeutic trials. To ensure continued progress, we need the most innovative, creative and determined minds working together – a diverse group of experts - to find solutions to help people with ALS today and tomorrow. We welcome and encourage a free flow of ideas and invite courageous, forward-thinking innovators to join our cause and make the game-changing discoveries to solve the challenges of this disease.

We have already made great progress in implementing our vision for the Healey Center. Under the direction of Dr. Merit Cudkowicz and the advice of the Scientific Advisory Council we are attracting top researchers to the ALS field, accelerating the effective evaluation and delivery of therapies to people with ALS today, and tackling disease diversity by developing targeted treatments through the Healey Scholars Program, Grants, International Innovation Prize, and the First Platform Trial in ALS.

Leadership:

Merit Cudkowicz, MD, MSc is the Chief of Neurology, Director of the Sean M. Healey & AMG Center for ALS at Mass General, and Director of the Neurological Clinical Research Institute at Mass General. She is also the Julianne Dorn Professor of Neurology at Harvard Medical School. Dr. Cudkowicz's research and clinical activities are dedicated to the study and treatment of people with ALS. She is an international leader in the search for a cure to this disease and her commitment to ALS research and patient care has set the standard for collaboration, data sharing and the promotion of the best minds and ideas in the field.

Dr. Cudkowicz is also the clinical coordinating center principal investigator for NeuroNEXT, a National Institutes of Health initiative to lead high-impact studies of new treatments for neurological disorders. She completed medical training at the Health Science and Technology Program of Harvard Medical School and obtained a master's degree in clinical epidemiology from the Harvard School of Public Health.

James D. Berry, MD, MPH is the Co-Director of the ALS Multidisciplinary Care Clinic, Assistant Professor of Neurology at Harvard Medical School and Co-Medical Director of the Neurological Clinical Research Institute (NCRI) at Mass General. He serves on the executive committee of the Northeast ALS Consortium (NEALS) and serves on the Biorepository Committee of NEALS. He is a board certified-neurologist and neuromuscular specialist. Dr. Berry leads several biofluid biomarker studies, leads the ALS Living Library biofluid repository and is the principal investigator of several clinical trials in ALS. Dr. Berry also leads the TeleALS and ALS House Call Program.

Katharine Nicholson, MD is an Assistant in Neurology at Mass General and Instructor at Harvard Medical School. Since completing fellowships in neuromuscular and neurodegenerative disease and therapeutic drug development, her clinical expertise and innovative research has focused on people with familial ALS. Dr. Nicholson launched a program to offer C9orf72 repeat expansion testing to any ALS patient at the ALS Multidisciplinary Care Clinic. She leads the ALS component of the Brain Health Clinic at Mass General, providing comprehensive evaluation to asymptomatic family members of people with ALS. She spearheaded an innovative multicenter platform to partner with asymptomatic ALS gene carriers to uncover markers of inciting disease processes. For this work, she received an American Academy of Neurology Clinical Research Training Scholarship in 2018. She currently also leads multidisciplinary research teams at the Healey Center in coordination of exciting and interfacing C9-focused research initiatives in people with C9ALS and asymptomatic C9 carriers.

Clotilde Lagier-Tourenne MD, PhD holds the Sean M. Healey Family ALS Endowed Chair for Research at Mass General, is an Associate Professor at Harvard Medical School and an Associate in Neuroscience at MIND. In 2017 she was awarded the Grass Foundation-American Neurological Association Award in Neuroscience, which honors outstanding young investigators conducting research in basic or clinical neuroscience. Dr. Lagier-Tourenne's lab is exploring disease mechanisms in amyotrophic lateral sclerosis (ALS) to develop targeted therapeutic approaches. The recent discovery of a connection between ALS and frontotemporal dementia, evidenced by progressive paralysis in ALS and language and behavioral dysfunction in frontotemporal dementia, has allowed a more focused investigation of the points of overlap to identify effective therapeutic targets. By analyzing skin biopsies from individuals with ALS, she and her team have screened more than 5,000 drugs for potential therapeutic value. They are also able to differentiate skin cells into neurons and generate mouse models of familial ALS to develop therapeutic strategies.

Darlene E. Sawicki, MSN, NP-BC is the Co-Director of the ALS Multidisciplinary Care Clinic, and the Nurse Director for Ambulatory Neurology. She has cared for patients with ALS in research and clinically since 2005. As a Nurse Practitioner, she is part of a multidisciplinary team in the clinic as well as having started an urgent clinic for ALS that focuses on acute clinical issues in addition to goals of care. Darlene founded and Chaired the Nursing Research Committee for the Northeast ALS Consortium. Darlene has given lectures on both research and in clinical care for people ALS. She actively mentors; nurses, Clinical Research Coordinators and summer interns that are pursuing careers in healthcare (MD, PhD, NP, RN) in healthcare and in research. A passion of Darlene's is ensuring continuity of care in ALS. Darlene has spent her career in ALS educating clinicians on caring for ALS and advocating for patients and caregivers alike.

Nazem Atassi, MD is the Associate Director of the Neurological Clinical Research Institute at Mass General, and Associate Professor of Neurology at Harvard Medical School. He serves on the executive committee of the Northeast ALS Consortium (NEALS), and is the founder and Co-Chair of the Upper Motor Neuron and the Imaging committees at NEALS. He is the Primary Investigator for several research projects focusing on ALS clinical trials, neuroimaging and outcomes measures. He directs the NCRI Imaging core, which leverages a world-class research imaging infrastructure available at Mass General and applies these technologies to develop new ALS therapies. This Core is laser-focused on building novel imaging platforms that can measure the biological activity of experimental treatments in people living with ALS, leading to efficient clinical trial designs and accelerated pace of drug discovery.

Mark W. Albers, MD, PhD is a neurologist and an Assistant Professor of Neurology at Harvard Medical School, specializing in memory and olfactory disorders. He sees outpatients in the Memory Disorders Unit and attends on the inpatient neurologic wards. His clinical research is focused on devising sensitive probes of olfactory function as a possible biomarker for early neurodegenerative disease and directly converting olfactory neuronal precursor cells from the nose into brain neurons to develop cell-based models of neurologic disease. Several years ago, he also began studying models of motor neuron disease and overlaps in mechanisms with other neurodegenerative disorders. He recently discovered a new pathway that is relevant in ALS, frontotemporal dementia and some people with Alzheimer's Disease. He is a member of the Translational Neuroscience committee of the American Academy of Neurology.

Suma Babu, MBBS, MPH is a clinical neuromuscular fellow who received her medical degree from Bangalore Medical College and her Master of Public Health from the University of Maryland School of Public Health. She completed her residency at the Cleveland Clinic Foundation and fellowships at Brigham and Women's Hospital and Mass General. Her research focuses on neuro-imaging biomarkers of ALS. She recently received a grant from the American Association of Neuromuscular & Electrodiagnostic Medicine to extend her studies to visualize disease biology in the spinal cord from people with ALS.

William David, MD, PhD is the Director of the EMG Laboratory and Neuromuscular Diagnostic Center at Mass General, as well as the Associate Program Director for the Harvard Partners Neuromuscular Medicine Fellowship Program. He is an Associate Professor of Neurology at Harvard Medical School. His research, clinical activities and educational/administrative pursuits have centered on his subspecialty interests of neuromuscular medicine and clinical neurophysiology (EMG), with a particular focus on Amyotrophic Lateral Sclerosis (ALS). He is an active participant in the ALS clinic at Mass General and directs the Neuromuscular Diagnostic Center, which encompasses the EMG laboratory, the neuromuscular clinics, an infusion suite, a skin and muscle biopsy program, an autonomic laboratory and a botulinum toxin program for the treatment for dystonia and spasticity.

Sabrina Paganoni, **MD, PhD** is Board-certified in Physical Medicine and Rehabilitation, Neuromuscular Medicine and Electrodiagnostic Medicine. She is an Assistant Professor at Harvard Medical School, Department of PM&R at Mass General and Spaulding Rehabilitation Hospital. Dr. Paganoni specializes in ALS, works in the ALS Multidisciplinary Care Clinic at Mass General and serves on the faculty at the Mass General Neurological Clinical Research Institute. Her research focuses on ALS therapy development and she is passionate about developing innovative assistive technology tools that can improve quality of life for people with ALS. She is the Principal Investigator for three ALS clinical trials and is using novel neuroimaging techniques as pharmacodynamic biomarkers. Dr. Paganoni obtained her MD degree at the University of Milan, Italy and a PhD in Neuroscience at Northwestern University.

Ghazaleh Sadri-Vakili, PhD is an Assistant Professor of Neurology at Harvard Medical School and Assistant in Neuroscience at Mass General. She received her Ph.D. from Boston University School of Medicine in Pharmacology and Biomedical Neuroscience and completed her postdoctoral studies at Mass General. She directs the NeuroEpigenetics laboratory at MIND, studying the molecular mechanisms that underlie alterations in gene expression in disorders of the nervous system using the most current molecular biology tools. Currently, the lab's efforts are focused on Huntington's disease (HD), Amyotrophic Lateral Sclerosis (ALS), as well as addiction. She is currently studying the role of neuroinflammation in ALS and has a lead compound to move forward to testing in people.

Jennifer Scalia, NP is the Mass General ALS Clinic Nurse Manager and the Associate Director for the Neurological Clinical Research Institute (NCRI). She started working at Mass General after receiving her Bachelor's Degree in Biology as a clinical research coordinator for ALS treatment trials and helping to coordinator the multidisciplinary clinic. During this time, she also returned to school to get a Bachelor's Degree in Nursing, and then returned as a clinic nurse in the ALS Clinic. She has had many different roles and process improvement projects as a registered nurse with MGH's ALS Clinic and NCRI, most currently as the associate site director for research, leading 12-14 research coordinators and 6 nurses in ALS clinical and research efforts. She enjoys advocating for patients in clinic and improving processes to help get them the best care, feedback and research involvement as possible. She is currently studying to become a Nurse Practitioner.

Alex Sherman, MS is the Director at Center for Innovation and Biomedical Informatics at the Neurological Clinical Research Institute at Mass General and a Principal Associate in Neurology at Harvard Medical School. He designs and develops technology, platforms and infrastructure for collaborative clinical research and optimization of clinical research operations in a given disease network. He is also interested in developing a system of incentives and supporting technologies for standardized yet flexible approach to secure collaboration, integration, harmonization and sharing of clinical and research information by all clinical research enterprise participants. Patient empowerment in research is a new paradigm he investigates as part of several disease-specific, patient-powered research networks.

Brian Wainger, MD, PhD is Assistant Professor of Neurology and Anesthesiology at Harvard Medical School and a physician scientist at Mass General engaged in clinical practice, translational science and clinical trial research spanning diseases of the motor and sensory nervous systems. He is a Principal Investigator at Mass General, the Harvard Stem Cell Institute, the Harvard Neurobiology Program and the Broad Institute, and his lab research focuses on modeling motor and sensory neuron diseases using stem cell technology. Based on work from his laboratory, a clinical trial of retigabine is currently underway in people with ALS.

A Message from The Healey Center for ALS:

Our understanding of the underlying causes of ALS and the development of novel therapeutic approaches are increasing at a rapid pace thanks to the generosity of our patients and their families. Mass General researchers have a long history of discovery in genetic forms of ALS, having identified the first gene associated with ALS in the 1990s. We are global leaders in ALS therapy development for both familial and sporadic ALS.

At the Sean M. Healey & AMG Center for ALS at Mass General, we have a multidisciplinary team of more than 100 affiliated researchers focused on understanding the cellular roots of ALS to uncover new therapeutic targets and expedite clinical trials evaluating these novel compounds. Within the last two years we launched an exciting new multidisciplinary, prevention program and are working to identify the earliest biological changes in familial ALS. We must accelerate these efforts, so we can treat the disease earlier in those currently suffering from familial ALS and prevent the disease from affecting future generations of ALS gene carriers. Many families affected by ALS harbor the C90rf72 (C9) repeat expansion, the most common gene known to cause ALS. We look forward to partnering with you to focus particularly on C9-related discoveries of critical disease markers and promising potential therapies, fast-tracking C9 drug development from our laboratory researchers to families affected by ALS.

In the funding opportunities outlined on the next few pages, our strategy is to rapidly move the field towards familial ALS prevention. We are excited by the speed of C9-related scientific discovery and by the opportunity to partner with you to think big and boldly about treatment and preventive strategies for ALS. Philanthropy is a critical component in our success. We value your consideration of a partnership with us.

Dominant Inherited ALS (DIALS) Network, A New Approach to Prevention:

At this critical time, marked by the emergence of amazing gene therapy strategies targeting familial ALS, support of the Dominant Inherited ALS (DIALS) Network would notably transform this prevention program and profoundly accelerate our ability to accurately predict disease onset to halt the ALS before the onset of symptoms.

We launched the DIALS Network as a multicenter study to follow people at risk for familial ALS so that we can effectively design preventive strategies in familial ALS. Co-led by Dr. Katie Nicholson at Mass General and Dr. Timothy Miller at Washington University, the goal of the DIALS Network is to identify the earliest biological and clinical markers of disease among individuals with dominantly-inherited ALS, in order to rapidly move the ALS field towards disease prevention. These components are essential in the design of the first prevention trials in those who are asymptomatic and at risk. Philanthropic support will allow us to expand the DIALS network and accelerate the path to be able to conduct prevention trials.

- **Multicenter DIALS Network Expansion**

Currently foundation support will allow for 100 DIALS participants at 2 sites to be followed for up to 5 years. Philanthropic support would enable expansion of the DIALS Network to include several hundred potential ALS carriers across 5 sites. This would allow for more families affected by inherited forms of ALS to access this unique platform across the United States, for genetic testing and support. An expansion would provide the statistical power needed to determine sensitive markers predicting disease onset.

- **Moving DIALS into the Digital Era**

Digital monitoring of symptom status has the potential to increase the accuracy in the detection of the earliest signs of disease with reduced participant burden, for a direct impact on the measures used in the design of a prevention trial where frequent monitoring is key in evaluation of disease onset. Philanthropic support would promote collaboration with leaders in innovative approaches, such as remote monitoring of biological fluids (e.g. blood, urine, gut microbiome) and home-based technology for evaluation of clinical status. Healey Center ALS researchers work to translate the most sensitive outcomes discovered from patients with ALS and DIALS participants into a cell phone application for use in ALS treatment and observational trials. Your support would enable Drs. Nicholson and Miller to launch this cell phone application for remote monitoring within the DIALS Network, and prepare for use of digital outcomes within a prevention trial.

Accelerating Pre-Clinical Discovery in Familial ALS:

Information gathered through the DIALS Network will also leverage the groundbreaking laboratory research underway in the lab of Clotilde Lagier-Tourenne, MD, PhD, who holds the Healey Family ALS Endowed Chair for Research at Mass General. Dr. Lagier-Tourenne and her team investigate the molecular mechanisms driving neuronal death in ALS and frontotemporal dementia (FTD). The laboratory has developed cellular and animal models to uncover mechanistic insights and to determine the most effective therapeutic strategies in C9-related ALS. Dr. Lagier-Tourenne established collaborations with academic and pharmaceutical partners to develop novel approaches to therapy, including RNA-targeting antisense oligonucleotides and immunotherapies for patients with ALS and FTD linked to the C9orf72 expansion. In particular, her work in collaboration with IONIS Pharmaceuticals and Biogen is at the stem of the therapeutic development of antisense oligonucleotides (ASOs) in C9-related ALS and FTD.

Lab-based researchers in the Healey Center work closely with their clinical research colleagues, analyzing patient samples at the molecular level to understand how a genetic mutation leads to disease to facilitate the development of therapies targeting the pathways specific to each mutation. Team members explore different strategies for silencing genes that cause ALS earlier in the disease progression, or even before it begins. Developing strategies that exploit the pioneering efforts of AAV-mediated gene therapy and CRISPR technologies and are personalized to meet the needs of individual patients, are the crucial next steps toward prevention.

Cutting-edge approaches in the laboratory often require start-up support to investigate whether a scientific finding has the potential for meaningful clinical impact. Support would not only promote pre-clinical work on known promising therapies, but also focus on new and groundbreaking strategies in familial ALS. This would include efforts to identify pre-symptomatic markers of disease and gene silencing therapies.

Changing the Face of Familial ALS Through Innovative Clinical Trials:

Clinical trial support would spearhead an initiative focused on innovation in C9-related trials for both people who are affected by neurodegenerative disease and those who are pre-symptomatic and at risk. Fast-paced lab discoveries in familial ALS have led to a growing list of ideas for translation into therapy, including genetic approaches and small molecules. The Healey Center Scientific Advisory Council (SAC) is an international group of ALS experts poised to provide critical advice and review of proposals to move the most exciting compounds into clinical trials quickly. A subset of the SAC will be engaged to advise on the best targets and treatments for C9-related disease.

A major challenge in ALS drug development is the conventional "parallel group" trial design requiring large patient numbers, long trial duration, and expensive cost. Part of the mission would promote "N-of-1" trials, in which a therapy is tested in just one patient or a small group of targeted patients, to determine potential impact. An experienced team at the Healey Center would lead the design of these small trials conducted in a new C9-focused trial network. The most sensitive early biomarkers and clinical outcomes identified by the DIALS Network study will directly inform the design of these trials in C9 ALS.

The first example of an "N-of-1"-type trial for this C9 therapy initiative is the exciting and repurposed use of FDA-approved JAK inhibitors in people with ALS, dementia, and asymptomatic C9 carriers. Work from the Albers Lab at Mass General demonstrated cytoplasmic double-stranded RNA (cdsRNA), a potent activator of inflammation and related signaling of destructive neuronal processes, accumulates in the neurons within the central nervous system of ALS and Alzheimer's disease (AD) patients. Dr. Mark Albers has shown cdsRNA is present in about 97% of patients with ALS (both sporadic and familial), including all cases associated with C9orf72 expansions, and in approximately 50% of patients with AD. A panel of inflammatory and neuronal death biomarkers were found to be elevated in the cerebrospinal fluid of people with ALS and AD. Several JAK1 inhibitors block this inflammatory signaling and protect neurons from death. A proposed study using this concept would determine if an FDA-approved JAK1 inhibitor is safe in people with ALS, dementia, and asymptomatic C9 carriers, penetrates the cerebrospinal fluid, reduces neuroinflammation and neuronal death biomarkers, and changes clinical signs of neurodegenerative disease. This proof-of-concept study would feature an innovative basket clinical trial design to include all three groups, with 30 overall participants enrolled for 12 months and periodic blood and spinal fluid sampling to test our hypotheses.

The Impact of Philanthropy:

Visionary philanthropy will allow The Healey Center to create a multifaceted approach to simultaneously move the field forward in preparedness for prevention, while identifying new therapeutic targets, and testing new compounds in familial ALS.

Thank you for your consideration.

For more information about this initiative, please contact:

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