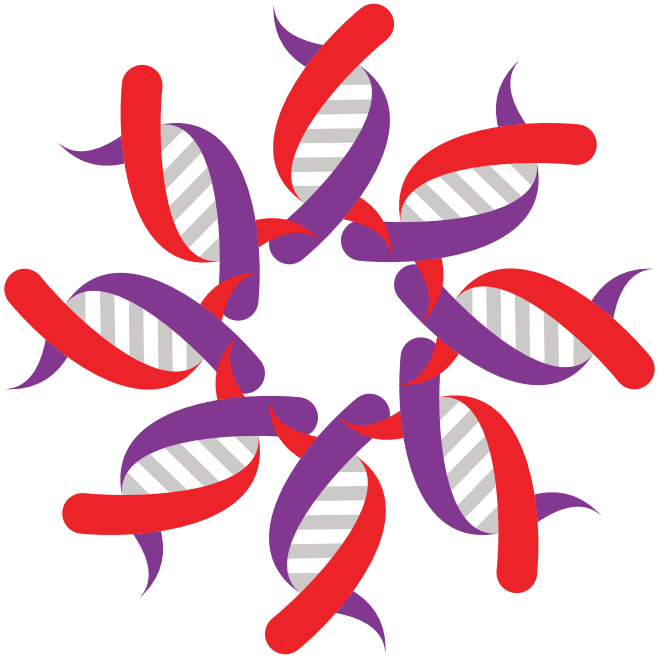
SUNA KIRAÇ CONFERENCES
ON NEURODEGENERATION
ISTANBUL

6th Suna Kıraç Conference on Neurodegeneration - Istanbul

ADVANCES IN GENE AND MOLECULAR THERAPIES FOR NEURODEGENERATIVE DISEASES: RECENT SUBCELLULAR AND CLINICAL INSIGHTS

April 19th-20th, 2024, Online Platform
Times are arranged according to GMT+1 (UK)



Distinguished Guests,

We are proud to welcome all of you to the 6th Suna Kıraç Conference on Neurodegeneration in Istanbul. Like its predecessors, this conference will take a multi-faceted and multi-disciplinary approach to understanding and treating ALS and degenerative diseases of the central nervous system.

Since 2005, the Suna and İnan Kıraç Foundation Neurodegeneration Research Laboratory (NDAL) has been part of the international effort to better understand and treat neurodegenerative diseases. We are honored to work with acclaimed academics around the world, including our close partnerships with University of Massachusetts, Harvard University and Brown University.

In July 2018, NDAL moved to its new home at the Koç University Hospital in Topkapı, İstanbul. NDAL is now part of an elite research hospital and KUTTAM, Koç University's Translational Medicine Research Center, strengthening its ability to collaborate, innovate, discover and contribute to the field. Operating within a hospital setting allows NDAL to access more patients and explore interdisciplinary research projects in new, highly effective ways. Among its efforts, NDAL has in recent years become an active member of several ambitious international consortia, such as Project MinE on sporadic ALS; EJP-RD Initiative PROSPAX on spastic ataxias; and the GP2 Project, Global Parkinson's Genetic Program.

Since its inception, the Suna Kıraç Conference on Neurodegeneration has evolved into an internationally acclaimed meeting point for the global scientific community. The Conference offers a valuable opportunity for prominent scientists to exchange and develop ideas, setting the stage for new collaborations and research projects.

This year's Conference, entitled *'Advances in Gene and Molecular Therapies for Neurodegenerative Diseases: Recent Subcellular and Clinical Insights'* will kick off by exploring the genes associated with neurodegeneration and the underlying cellular mechanisms of neuronal vulnerability, continuing with RNA dysfunction in neurological diseases and non-neuronal pathology. The complex architecture of ALS in Turkey and an interactive discussion on sporadic ALS will close the Conference, which is the first one held since the passing of its eponymist, the bright, and inspired Suna Kıraç. This Conference, like the previous ones, is held in Suna Kıraç's honor and dedicated to her respected memory.

On behalf of the millions of patients who suffer from neurodegenerative diseases, and their families, we would like to extend our deepest gratitude to everyone who has contributed to this year's Conference, in particular to Profs. A. Nazlı Başak, Robert H. Brown, Jr. and Jeffrey D. Macklis. We wish you a productive and inspiring conference, as well as a pleasant stay in Istanbul. More importantly, we hope that this Conference contributes to your efforts in the area of neurodegenerative disease and that you discover new ideas, questions and information that build and strengthen your work.

Suna and İnan Kıraç Foundation

Esteemed Colleagues and dear Friends, distinguished Guests,

On behalf of the Organizing Committee, it is with the greatest pride, pleasure and excitement that we are welcoming you to the 6th Suna Kıraç Conference on Neurodegeneration Istanbul *'Advances in Gene and Molecular Therapies for Neurodegenerative Diseases: Recent Subcellular and Clinical Insights'*, traditionally held and hosted at the beautiful Pera Museum of the Suna and İnan Kıraç Foundation, located in the heart of old Istanbul. This Conference is the sixth of a series of symposia jointly organized by the Suna and İnan Kıraç Foundation and its Neurodegeneration Research Laboratory (NDAL), in collaboration with Professors Robert H. Brown, Jr. and Jeffrey D. Macklis, who have been the co-chairs of the Foundation's Scientific Advisory Committee since NDAL's inauguration in 2005.

As the title *'Advances in Gene and Molecular Therapies for Neurodegenerative Diseases: Recent Subcellular and Clinical Insights'* implies, the Conference will commence with a focus on genes associated with neurodegeneration, gene targeting, gene modulation and neuroprotective therapies in neurodegenerative diseases followed by underlying cellular mechanism of neuronal vulnerability. On the second day, the sessions will explore RNA dysfunction in neurological diseases, the complexity of the corticospinal circuitry, subtype- and context-dependent subcellular machinery in the cortex, and non-neuronal pathology. Turkey as a rich genetic resource for neurodegenerative diseases and an interactive session on sporadic ALS will conclude the Conference. We plan five sessions on two days with lots of think-tank-style moderated discussion. There will be also a poster session dedicated to the work of KUTTAM graduate students.

The Suna Kıraç Conferences Istanbul are typically highly interactive and have large national attendance from across Turkey. With the invited speakers staying the entirety of the Symposium, there is ample opportunity to connect with scientists who are world leaders in their fields.

This year's Conference coincides with the 20th year of the Suna and İnan Kıraç Foundation, as well as the 100th anniversary of the Turkish Republic. At the same time, this Conference will be the first one held since the passing of the brilliant and visionary Suna Kıraç in 2020. In her memory and honor, we are privileged to be holding this Conference at such a special time, as an expression of her legacy and of our evolution, resilience, and perseverance, both scientifically and beyond.

A few words about Istanbul: The city is an extraordinary site for a meeting. Spanning the Bosphorus and two continents, Europe and Asia, it represents an intriguing intermingling of multiple cultures. The former capital of the Roman, Byzantine and Ottoman empires, it has a rich history and remarkable architecture that set against the Bosphorus waterway, is unique. Istanbul in the fall is especially beautiful, and the food is superb year-round.

It is a profound honor to co-chair this landmark event which promises to offer so very much through its visionary, state-of-the-art lectures, delivered by pioneers in the field, as well as the priceless opportunity it provides for us all to meet and to connect. We would like to extend our deepest gratitude to the Suna and İnan Kıraç Foundation, not only for their generous hospitality, but also for supporting NDAL's growth and development over the years. Our very special thanks go also to Pera Museum and its wonderful team led by Mr. M. Özalp Birol, whose enthusiasm, experience, assistance and sincere friendship make the organization of these Conferences a delight.

Last but not least, we thank you, distinguished speakers and dear guests, for joining us at the 6th Suna Kıraç Conference Istanbul, *'Advances in Gene and Molecular Therapies for Neurodegenerative Diseases: Recent Subcellular and Clinical Insights'*. We wish you a pleasant stay in Istanbul and promise a productive and successful Conference.

We feel honored to host you, and welcome to Istanbul!

Robert H. Brown, Jr. Jeffrey D. Macklis A. Nazlı Başak

SCIENTIFIC PROGRAM

Times are arranged according to GMT+1 (UK)

DAY 1
FRIDAY, April 19th, 2024

Welcome
İpek Kıraç, Robert H. Brown, Jr., Jeffrey D. Macklis, A. Nazlı Başak
Video: The Legacy of Suna Kıraç
13:30-14:00

Session 1
Genes and Gene Targeting in Neurodegenerative Diseases

What do we know about ALS genetics?
Ammar Al-Chalabi (UK)
14:00-14:40

Toward Gene Modulation Therapy in Amyotrophic Lateral Sclerosis
Robert H. Brown, Jr. (USA)
14:40-15:20

The journey to develop better neuroprotective therapies for ALS:
Are we winning?
Pamela J. Shaw (UK)
15:20-16:00

Moderated Discussion
16:00-16:20

Bio Break
16:20-16:30

Meet the speakers 1-3 from Day1
(Al-Chalabi, Brown, Shaw)
16:30-17:00

Session 2
Subcellular Insights to Selective Vulnerability in Neurodegenerative Diseases

Lysosomes moonlight as central regulatory hubs of
local protein synthesis in axons
Michael E. Ward (USA)
17:00-17:40

Nuclear pore complex dysfunction and repair:
Common contributor to sporadic ALS and TDP-43 loss of function
Jeffrey D. Rothstein (USA)
17:40-18:20

Building and maintaining precise and durable corticospinal circuitry is complex:
Subtype- and context-dependent subcellular
molecular machinery in cerebral cortex
Jeffrey D. Macklis (USA)
18:20-19:00

Moderated Discussion
19:00-19:20

Bio Break
19:20-19:30

Meet the speakers 4-6 from Day1
(Ward, Rothstein, Macklis)
19:30-20:00

DAY 2
SATURDAY, April 20th, 2024

Session 2 cont.
Subcellular Insights to Selective Vulnerability in Neurodegenerative Diseases

Differential role of SNARE proteins in
various cortical projection neuron populations
Zoltán Molnár (UK)
13:30-14:10

Dynamic subtype- and context-specific subcellular RNA regulation in
growth cones of neocortical projection neurons
Anne Engmann (USA)
14:10-14:50

Moderated Discussion
14:50-15:10

Bio Break
15:10-15:20

Meet the speakers 1-2 from Day2
(Molnár, Engmann)
15:20-16:00

Session 3
Dysfunction of RNA Processing in Circuit-Specific Neurologic Disease

Resolving the localization and dynamics of RNA
and protein synthesis within neurons
Paul Donlin-Asp (UK)
16:00-16:40

mRNA association with endosomes in neurons
Jean-Michel Cioni (IT)
16:40-17:20

Moderated Discussion
17:20-17:40

Session 4
Non-neuronal Pathology in Neurodegenerative Diseases

Gain-of-function and loss-of-function effects of iPSC-derived astrocytes from ALS patients on human motor units
Ludo Van Den Bosch (BE)
17:40-18:20

Bio Break
18:20-18:30

Meet the speakers 3-5 from Day2
(Donlin-Asp, Cioni, Van Den Bosch)
18:30-19:00

Session 5.1
The Anatiolian Peninsula:
A Rich Genetic Resource for Neurodegenerative Diseases

SUNA KIRAÇ MEMORIAL LECTURE
The Complex Architecture of ALS in Turkey
A. Nazlı Başak (TR)
19:00-19:40

Session 5.2
Thinking out of the Box

Sporadic ALS
Moderators: Ammar Al-Chalabi – Robert H. Brown Jr.
19:40-20:40

Closing Remarks
Robert H. Brown, Jr., Jeffrey D. Macklis, A. Nazlı Başak
20:40

SPEAKERS AND ABSTRACTS

1 AMMAR AL-CHALABI, M.D., PH.D.

King's College London
Director of the King's Motor Neuron Disease Research Center,
Maurice Wohl Professor of Neurology and Complex Disease Genetics
at the Institute for Clinical Neuroscience
Department of Clinical Neuroscience

Ammar Al-Chalabi is a Clinician Scientist at King's College London. His research focuses on causes, modifiers, and potential treatments for ALS. He co-leads the UK National MND Research Institute, chairs the International Symposium on ALS/MND, and is a National Institute for Health Research Senior Investigator. His work has been recognized by multiple prizes, including the Forbes Norris Award from the International Alliance of ALS/MND Associations, the Healey Center International Prize for Innovation in ALS, the Sheila Essey Award from the American Academy of Neurology, a Gold National Clinical Excellence Award, and the Charcot Young Investigator Award from the MND Association.

WHAT DO WE KNOW ABOUT ALS GENETICS?

Since the first ALS gene was identified in 1993, our understanding of what constitutes a genetic risk variant and who this might affect have both changed. Despite significant advances in our understanding of genetic risk in ALS, there remain many unanswered questions such as the role of the 3D structure of the genome, the role of epistasis, the role of regulatory and epigenetic elements, and the interaction of gene variants with environmental risk. All these offer potential avenues of treatment. This talk will cover the current knowledge of the landscape of ALS genetics.

2 ROBERT H. BROWN, JR., M.D., D.PHIL.

UMass Medical School
Department of Neurology

Dr. Brown completed a B.A. in Biophysics (Amherst College, 1969), a D.Phil. in Neurophysiology (Oxford, 1973) and an M.D. (Harvard, 1975). After a neurology residency at the Massachusetts General Hospital/Harvard Medical School (1980), he joined the faculty at the Massachusetts General Hospital where he established the Day Neuromuscular Research Laboratory and co-directed the Neuromuscular Clinic. In 1998, he was awarded tenure as Professor of Neurology at Harvard Medical School. In 2008, he became the chair of neurology at UMass Medical School, where he holds the LaChance Family Chai of Neurology and serves as Director of the ALS Clinic and Director of Neurological Therapeutics. Dr. Brown has a longstanding research interest in identifying gene defects that underlie ALS and related neuromuscular disorders. He was a lead member of the team that identified the first ALS gene (SOD1) and, with colleagues, has subsequently identified several other defective genes in ALS including alsin, dynactin, FUS/TLS, ErbB4 and profilin1. He has identified causative gene defects in other disorders including limb girdle dystrophy type 2B (dysferlin), hereditary sensory neuropathy [serine palmitoyl-transferase], and hyperkalemic paralysis [skeletal muscle sodium channel]. His laboratory team has used insights from these investigations in genetics to generate cell and animal models of each of these disorders. These models have improved our understanding of pathological processes that trigger diseases like ALS and have assisted in therapy development. Most recently, he has initiated trials of ALS gene suppression therapy in non-human primates and now in humans. He has published more than 300 peer-reviewed reports and more than 70 reviews and chapters on these topics. He is a member of the National Academy of Medicine (formerly the Institute of Medicine) and is a past president of the American Neurological Association.

TOWARD GENE MODULATION THERAPY IN AMYOTROPHIC LATERAL SCLEROSIS

Mutations in more than 40 genes are robustly associated with familial and, more recently, sporadic ALS, as well as concurrent ALS and frontotemporal dementia. These genes define multiple targets for therapy. New biological reagents permit unprecedented precision therapies to correct primary defects in specific genes at the DNA and RNA level. It is anticipated that, by reducing the burden of toxic mutant RNAs and proteins or correcting aberrant splicing, targeted therapies will be clinically beneficial. This presentation will review progress in the development of gene modulation therapies for ALS, focusing on methods and subsequent clinical trials centered on the SOD1, C9orf72 and FUS genes.

3 PAMELA J. SHAW, M.D., PH.D.

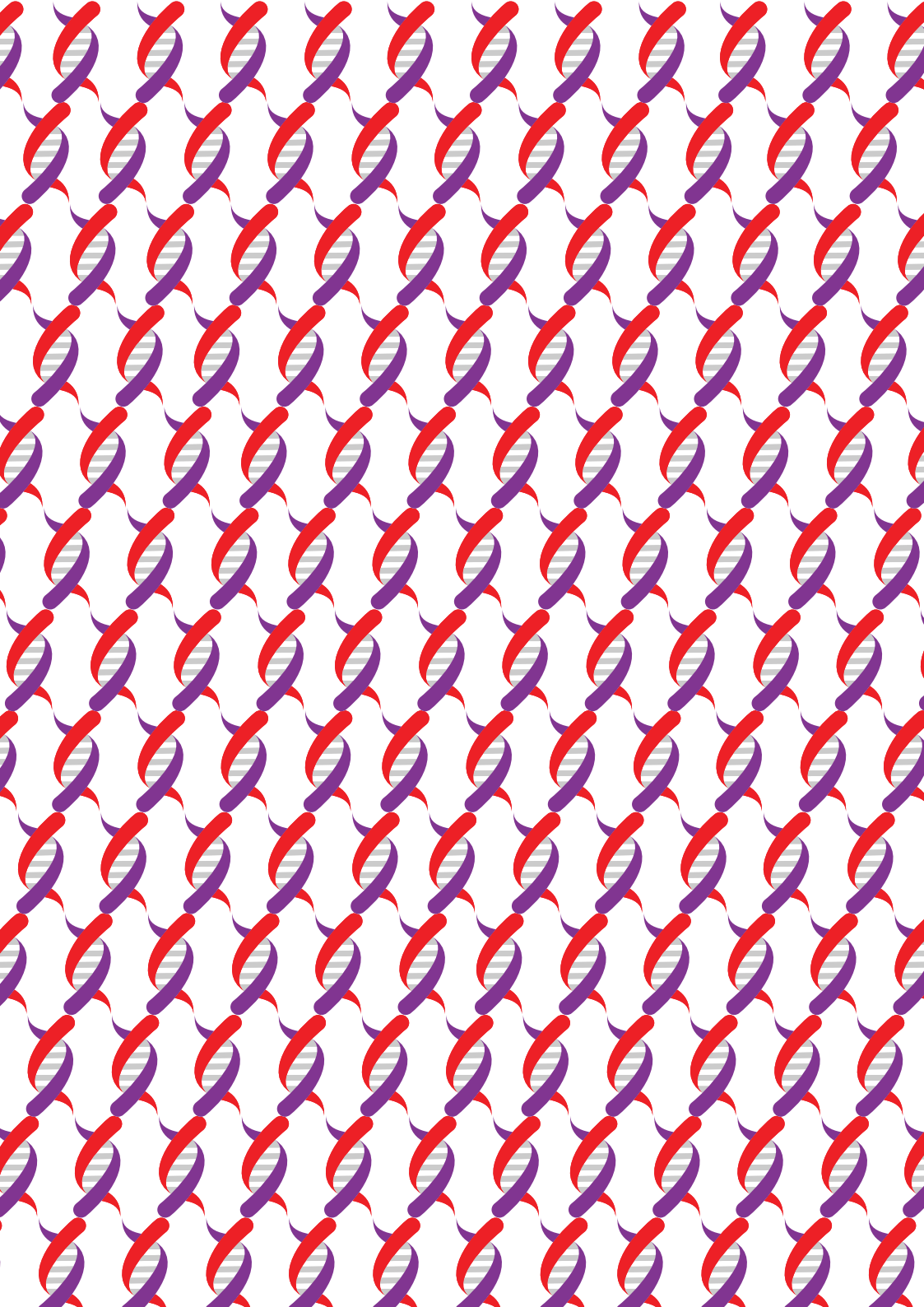
University of Sheffield
Sheffield Institute for Translational Neuroscience (SITraN)
Director of the NIHR Sheffield Translational Neuroscience Biomedical Research Centre and Sheffield Motor Neurone Disorders Care and Research Centre
Department of Neurology

Pamela Shaw is Professor of Neurology at the University of Sheffield and Director of the Sheffield Institute for Translational Neuroscience (SITraN); the NIHR Sheffield Biomedical Research Centre for Translational Neuroscience and the Sheffield Care and Research Centre for Motor Neuron Disorders. She is a Clinician Scientist in Neurology, formerly a Wellcome Trust Senior Fellow and an NIHR Senior Investigator. Her work investigates genetic, molecular and neurochemical mechanisms underlying ALS/MND; identifies new therapeutic targets and translates new neuroprotective and symptomatic treatment approaches into the clinic, including genetic therapy approaches. She has active programmes in systematic biosample collection and biomarker identification in ALS/MND. From 2009-2016 she initiated and led the national UK Clinical Studies Group for ALS/MND, a clinical research and trials network which links 23 ALS/MND Care and Research Centres. Prof. Shaw has taken part in more than 25 ALS/MND clinical trials, including roles as Chief Investigator and Steering Committee member. She has authored more than 570 publications (H-index 118). Her research is funded by NIHR, the UK Medical Research Council, Wellcome Trust, MND Association, MyName'5 Doddie Foundation, Fight MND (Australia) and Department of Defense (US), EU and biotech/pharmaceutical industry partners. Pamela Shaw has received multiple national and international awards for her work including DBE for Services to Neuroscience; American Academy of Neurology Sheila Essey Award; International ALS/MND Alliance Forbes Norris Award; Royal College of Physicians Jean Hunter Award; FMedSci; Fellowship American Association for the Advancement of Science; ABN Medallist-2019; Queen's Anniversary Award to SITraN- 2019; British Neuroscience Association Major Contribution Award 2022.

THE JOURNEY TO DEVELOP BETTER NEUROPROTECTIVE THERAPIES FOR ALS: ARE WE WINNING?

Motor neuron disease (MND) also known as amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disorder with a lifetime risk of approximately 1 in 350. It is the commonest neurodegenerative condition of midlife, can be associated with fronto-temporal dementia (FTD) with an average life expectancy of 2-3 years from symptom onset. Five to 10% of patients have familial disease, but a causative gene will be found in >20% of cases when genetic testing is systematically performed. Multidisciplinary care and improved symptom management, particularly addressing the problem of neuromuscular respiratory failure, have produced some improvements in life expectancy and quality of life. However, the heterogeneity and complex pathophysiological mechanisms contributing to motor neuron injury have posed a challenge for effective neuroprotective therapy development. In recent years genetic advances have identified >30 genes which cause or predispose to ALS. A strategy has emerged where more accurate sub- classification of patients can be made based on identification of risk genes beyond the traditional boundaries of sporadic and familial ALS. This expanded genetic understanding has enabled more effective modelling of ALS in the laboratory, with a variety of in vivo and in vitro models now available. Particularly important has been the development of cellular reprogramming techniques allowing the creation of motor neurons and neighbouring glial cells to allow dissection of disease mechanisms, identification of new therapeutic targets and therapeutic screening using small molecule or genetic therapy approaches. There is a pipeline of genetic therapy approaches for different subtypes of ALS now in clinical trials. Pre-clinical work to achieve reduced expression of the SOD1 (Cu-Zn superoxide dismutase) gene has given confidence to try this approach in patients with SOD1 mutations. Spectacular results have emerged from the Phase1/2/3 anti-sense oligonucleotide trials, and the FDA gave expedited approval for tofersen in April 2023. Genetic therapy approaches to tackle the commonest genetic cause of ALS caused by mutations in the C9orf72 gene will be discussed. Small molecule neuroprotective therapies include several agents of modest effect including the anti-glutamate drug riluzole, the anti-oxidant

edaravone and the combination therapy relyvrio. Promising results have emerged from the recently completed MIROCALS trial of low-dose interleukin-2 as an anti-inflammatory agent. Recent innovations in trial design will enhance outcome measures, patient selection and randomisation, minimize the impact of clinical variability and increase statistical power. Platform trials and patient reported outcomes have the potential to improve the pace of validation of therapeutic agents. This is particularly the case if combined with surrogate biomarkers of disease burden and therapeutic efficacy which are now emerging. In summary, there is great potential for developing improved neuroprotective treatments for ALS in the near future. The huge unmet need of ALS patients is clear, and a range of tools are now poised for effective translation.



4 MICHAEL E. WARD, M.D., PH.D.

Investigator, National Institute of Neurological Disorders and Stroke
NIH Department of Neurology

Dr. Ward received his B.S. from Kenyon College in 1999 and M.D. and Ph.D. degrees from Washington University in St. Louis in 2007. As a graduate student, he worked in Yi Rao's lab and studied the regulation of cell migration during neurodevelopment. Following a neurology residency at the University of California in San Francisco, he sub-specialized in behavioral neurology and completed a postdoctoral fellowship in Li Gan's lab studying basic mechanisms of frontotemporal dementia (FTD). In 2015 he joined the NINDS as an Assistant Clinical Investigator, became an Investigator in 2017, and then a Senior Investigator in 2023. Using human induced pluripotent stem cells (iPSC)s as a cellular model, his research group focuses on identifying intersecting mechanisms of neurodegenerative diseases, with an ultimate goal of developing targeted, disease-modifying therapies for affected patients. In addition to his research efforts, he sees patients with neurodegenerative disorders in the NIH Clinical Center and co-directs the iPSC Neurodegenerative Research Initiative (iNDI), a large-scale effort to generate and phenotype iPSC models of Alzheimer's disease and related dementias.

LYSOSOMES MOONLIGHT AS CENTRAL REGULATORY HUBS OF LOCAL PROTEIN SYNTHESIS IN AXONS

Our group made the surprising discovery that RNA granules are indirectly transported long distances in axons by hitchhiking on moving lysosomes (Liao et al, Cell, 2019), and that this process is disrupted by an ALS-associated mutant protein. Using proteomics, imaging, and biophysics, we showed that this hitchhiking is mediated by a newly discovered ALS protein, ANXA11, which serves as a regulatable molecular tether between RNA granules and lysosomes during transport. ALS-associated mutations in ANXA11 block RNA transport and local translation of RNA in distal neuronal processes. New findings from our group indicate that lysosomes not only transport RNA granules but that local protein translation in axons occurs on the surface of lysosomes. Signaling complexes involved in nutrient sensing and stress pathways localized on the lysosome regulate local translation in space and time, enabling precise control of protein synthesis at distal sites within the neuron.

5 JEFFREY D. ROTHSTEIN, M.D., PH.D.

The John W. Griffin Director Brain Science Institute
Professor of Neurology and Neuroscience
Department of Neurology

Dr. Rothstein's career has been focused on the identification of biological pathways that underlie and contribute to neurodegeneration in ALS and the development of model systems to identify, test and validate therapies. He has over 30 years' experience as a clinician scientist studying neurodegenerative disease/ALS pathophysiology, glial biology, therapy discovery and collaborative science. He is the Director of the Brain Science institute, which coordinates interdisciplinary clinical and basic research among Hopkins 450 University neuroscientists. His lab has repeatedly made the discoveries on fundamental pathways that underlay familial and sporadic ALS including excitotoxicity, astroglial dysfunction, oligodendroglial dysfunction and most recently, the role of nuclear pore complex and nucleocytoplasmic transport as one of the earliest pathophysiological events in familial ALS and likely sporadic ALS cases. His most recent work, relevant to the current proposal is the pathobiology of C9orf72 repeat RNA as a mediator of nuclear pore complex injury. His lab has identified the fundamental pathway responsible for this injury, alterations of the ESCRT3/CHMP7 pathway. He founded, 23 years ago, the Packard Center, an international collaborative consortium of >30 pre-clinical and clinical ALS scientists that focus on building the ALS animal models and drug discovery tools and translates those tools, in collaboration with industry, to new therapeutics. He runs an ALS clinic at Johns Hopkins that evaluates and manages over 450 ALS patients per year. He founded and runs Answer ALS- a national consortium of >100 individuals working as a collaborative team to generate comprehensive omic (whole genome, epigenome, RNA seq, proteome) from >1000 ALS/FTD patients and their IPS motor neurons, employing deep machine learning to subgroup patients based on their CNS biology for future trials, biomarkers and drug optimization He is affiliated with two graduate programs (Neuroscience and Cellular and Molecular Medicine). His educational activities include, for the last 20 years the monthly Packard meeting- bringing together basic and clinician scientists, students, and fellows with researchers worldwide; the annual Packard meeting- a gathering of >250 students and professionals from Hopkins and other academic centers- for exchange of the most current ALS and dementia research. He holds weekly lab meeting where individual

postdoc and graduate student present their science for review and critique. He meets weekly with postdoc and graduate student, individually to review their experimental design and progress. He has bi-weekly 90 min meetings with 2-4 other labs around common themes, eg. NG cells, C9orf72 pathophysiology, where 2 students/ post doc from the various labs present their ongoing research. He has trained more than 60 clinician scientists, basic scientists and graduate students who now occupy positions in USA and foreign government, universities, and pharmaceutical companies.

NUCLEAR PORE COMPLEX DYSFUNCTION AND REPAIR: COMMON CONTRIBUTOR TO SPORADIC ALS AND TDP-43 LOSS OF FUNCTION

Defining a causative pathogenic cascade is essential for effective therapy development. Challenges to the development of therapy for sporadic ALS have been defining a common pathogenic cascade to major subgroups of ALS patients. It's widely acknowledged that defects in the localization of TDP 43 within the nucleus and subsequent loss of function of TDP43 are common to a large percentage of sporadic ALS patients. In that vein, it's particularly important to note that defects in the nuclear pore complex and its subsequent role in the loss of function of TDP43 pathologically and functionally have now been shown to be one such common upstream event. Based on our extensive preliminary and published data we have determined the degradation event that causes ALS nuclear pore complex defects. This pathway is characterized by the inappropriate nuclear enriched of the ESCRT3 protein, CHMP7. CHMP7 functions to monitor changes in the nuclear pore complex and nuclear membranes. Antisense oligonucleotides to CHMP7 can completely repair the nuclear pore complex as well as prevent and repair anatomic and functional defects in TDP43. Given that TDP-43 loss of function is characteristic of almost all sporadic ALS, this is a potentially powerful therapy with a strong biological rationale for sporadic ALS patients. CHMP7 ASO is a particularly strong candidate for sporadic ALS therapy. Other genetic targets responsible for nuclear pore dysfunction are being studied along with a role for nucleoporin protein-coding variants that may contribute to sporadic ALS as candidate first events will be discussed.

6 JEFFREY D. MACKLIS, M.D., PH.D.

Harvard Medical School
Department of Stem Cell and Regenerative Biology

Jeffrey D. Macklis is the Max and Anne Wien Professor of Life Sciences, and Professor of Stem Cell and Regenerative Biology in the Department of Stem Cell and Regenerative Biology, and Center for Brain Science, Harvard University, and Professor of Neurology [Neuroscience] at Harvard Medical School (HMS). He was founding Program Head, Neuroscience, Harvard Stem Cell Institute. He is Director of Graduate Studies in the Department of Stem Cell and Regenerative Biology, and (co-)Director of the Developmental and Regenerative Biology Ph.D. Program at Harvard University. He is an M.I.T. affiliate faculty member in the Harvard- Massachusetts Institute of Technology (M.I.T.) Division of Health Sciences and Technology (HST) and M.D.-Ph.D. Program. His lab is directed toward both: 1) understanding molecular controls and mechanisms over neuron sub- type specification, development, diversity, axon guidance-circuit formation, and degeneration in the cerebral cortex; and 2) applying developmental controls toward both brain and spinal cord regeneration and directed differentiation for in vitro therapeutic and mechanistic screening. The lab focuses on neocortical projection neuron development and sub-type specification; neuronal subcellular molecular machinery for subtype- and stage-specific circuit formation, maintenance, and function; neural progenitor / "stem cell" biology; induction of adult cortical neurogenesis; subtype-specific axonal growth cone biology; and directed neuronal subtype differentiation via molecular manipulation of neural progenitors and pluripotent cells (ES/iPS). He attended M.I.T. as an undergraduate (S.B. Bioelectrical Engineering; S.B. Literature), Harvard Medical School (Harvard-M.I.T. HST Program), and graduate school at M.I.T. within HST, a student of Richard L. Sidman. He was a postdoctoral fellow in developmental neuroscience at HMS, where he also trained clinically in Internal Medicine at Brigham and Women's Hospital (BWH) and Neurology in the Harvard Neurological Training Program (he is no longer clinically active). He is the recipient of a number of awards and honors, including a Rita Allen Foundation Scholar Award, a Director's Innovation Award from the NIH Director's Office, the CNS Foundation Award, a Senator Jacob Javits (MERIT) Award in the Neurosciences from NINDS/NIH, the Cajal-Krieg Cortical Discoverer Prize, and a series of undergraduate and graduate teaching and mentoring prizes over the past 25 years. He is an Allen Distinguished Investigator of the Paul G. Allen Frontiers Group, a Brain Research Foundation Fellow, and recipient of an NIH Pioneer Award from the Office of the NIH Director.

BUILDING AND MAINTAINING PRECISE AND DURABLE CORTICOSPINAL CIRCUITRY IS COMPLEX: SUBTYPE- AND CONTEXT-DEPENDENT SUBCELLULAR MOLECULAR MACHINERY IN CEREBRAL CORTEX

The long-term goals of the work I will discuss are three-fold– in development, disease, and regeneration, but I will discuss only the first two: 1) to elucidate central molecular mechanisms controlling development and diversity of cerebral cortex function-specific circuitry, thus organization and evolution (to some extent) of the cerebral cortex; 2) to identify causes/mechanisms of developmental dysgenesis and selective neuron subtype vulnerability in neurodegenerative disorders, ALS and FTD in particular. The specificity and function of such circuitry underlies how the brain-nervous system senses, integrates, moves the body, thinks, functions with precision, malfunctions with specificity in disease, degenerates with circuit specificity, might be regenerated, and/or might be modeled in culture, but has been previously inaccessible in multiple core aspects. What actually implements and maintains circuit specificity is a key, core issue from developmental specificity of circuits to developmental abnormalities and disease, selective neuron type vulnerability of degeneration (e.g. in MND/ALS-FTD), regeneration (or typical lack thereof) in the CNS for spinal cord injury, and mechanistic and therapeutic modeling of disease using human induced pluripotent stem cell (hiPS)-derived neurons. Growth cones (GCs) are the subcellular structures that "build" circuits with specificity and mature into synapses, but we know little about the diversity and specialization of circuit-specific GCs or synapses. I will present a brief integration of recent work investigating subtype-, stage- /context-, and target-specific GCs and synapses in development, neuronal and circuit diversity, disease, and newly enabled hiPS-based fused organoid "assembloids" to address these critical gaps in knowledge. We have developed and integrate several new approaches (e.g. subtype- and stage-specific subcellular RNA, protein, translational regulation of GCs / synapses directly from brains; mosaic genetic circuit analysis; hiPS "assembloids" with somewhat selective connectivity) to investigate basic "framing rules" of diverse function-enabling CNS circuitry, and potentially explain selective vulnerability in developmental and degenerative nervous system diseases, in particular for ALS and FTD.

7 ZOLTÁN MOLNÁR, M.D., D.PHIL.

University of Oxford
Professor of Developmental Neuroscience
Department of Physiology, Anatomy & Genetics

Zoltán Molnár is Professor of Developmental Neuroscience at the University of Oxford. He is known for key contributions to our understanding of how the birth of cortical neurons is regulated, how they migrate, differentiate, generate axons and assemble into circuits, and how those circuits change over time, partly as a result of activity passing through them. Molnár earned his M.D. at the Albert Szent-Györgyi Medical University, Szeged, Hungary and D.Phil. at the University of Oxford, UK. He also investigated thalamocortical development working at the Institut de Biologie Cellulaire et de Morphologie, Université de Lausanne, Switzerland, and learned optical recording techniques to understand early functional thalamocortical interactions at Kyoto Prefectural School of Medicine, Japan. He was appointed to a University Lecturer position at the Department of Human Anatomy and Genetics at Oxford associated with an Official Fellowship and Tutorship at St John's College from 2000. He was awarded the title Professor of Developmental Neuroscience in 2007. Molnar has been Elected Member of Academia Europaea (Physiology and Neuroscience); European Neonatal Brain Club; Fellow of Royal Society of Biology, Fellow of the Anatomical Society, Awarded New Fellow of the Year Award for 2018.

DIFFERENTIAL ROLE OF SNARE PROTEINS IN VARIOUS CORTICAL PROJECTION NEURON POPULATIONS

Neural communication in the adult nervous system is mediated primarily through chemical synapses, where action potentials elicit Ca^{2+} signals, which trigger vesicular fusion and neurotransmitter release in the presynaptic compartment. The study of the role of specific proteins of the synaptic vesicle release machinery in the establishment, plasticity, and maintenance of neuronal connections during development has only recently become possible, with the advent of mouse models where various members of the N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complex have been genetically manipulated. I shall provide an overview of these models, focusing on the role of regulated vesicular release and/or cellular excitability in synaptic assembly, development and maintenance of cortical circuits, cell survival, circuit level excitation–inhibition balance, myelination, refinement, and plasticity of key axonal projections from the cerebral cortex. Synaptosomal-associated protein 25 kDa (SNAP25) is an essential component of the SNARE complex regulating synaptic vesicle fusion. SNAP25 deficiency has been implicated in a variety of cognitive disorders. We ablated SNAP25 from selected neuronal populations by generating a transgenic mouse (B6-Snap25tm3mcw (Snap25-flox)) with LoxP sites flanking exon5a/5b. In the presence of Cre-recombinase, Snap25-flox is recombined to a truncated transcript. We studied Snap25 cKO in subsets of cortical projection neurons in vivo (L5—Rbp4-Cre; L6—Ntsr1-Cre; L6b—Drd1a-Cre). cKO neurons develop normal axonal projections, but axons are not maintained appropriately, showing signs of swelling, fragmentation and eventually complete absence. Onset and progression of degeneration are dependent on the neuron type, with L5 cells showing the earliest and most severe axonal loss. Ultrastructural examination revealed that cKO neurites contain autophagosome/lysosome-like structures. Markers of inflammation such as Iba1 and lipofuscin are increased only in adult cKO cortex. These models are important for understanding various developmental and psychiatric conditions, and neurodegenerative diseases.

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8 ANNE ENGMANN, PH.D.

University of Harvard
A senior postdoc in the Macklis lab
Department of Neuroscience

Anne is a senior postdoc in the Macklis lab at Harvard University and has a particular interest in the subcellular molecular machinery and its regulation important for the distinct phases of circuit formation during development as well as the shared and distinct mechanisms important for circuit regeneration following injury or degeneration. Anne and her collaborators go at these question from several different angles, by comparing subcellular machinery at the level of the growth cone across different subtypes of cortical projection neurons and by performing deep profiling of molecular mechanisms and their regulation during the time course of circuit formation and regeneration in cell bodies and growth cones of specifically corticospinal growth cones. Prior to joining the Macklis lab for her postdoctoral training, Anne completed her Ph.D. in Neuroscience, supervised by Prof. Martin Schwab at the ETH Zurich, Switzerland. In the Schwab lab Anne worked on understanding and probing the neuroanatomical adaptations underlying spontaneous functional recovery in rodents following incomplete spinal cord injury, with a particular focus on bulbospinal and propriospinal tract systems. Anne did her undergraduate studies in cell biology (M.Sc.) at the ETH Zurich (Switzerland) and molecular biotechnology (B.Sc.) at the University Heidelberg (Germany).

DYNAMIC SUBTYPE- AND CONTEXT-SPECIFIC SUBCELLULAR RNA REGULATION IN GROWTH CONES OF NEOCORTICAL PROJECTION NEURONS

During development, neuronal growth cones (GCs) navigate complex extracellular environments in a subtype- and stage-specific fashion, to reach distant targets and establish functional circuitry. Prior work has identified that local translation of axonally trafficked transcripts is required for directional responses to at least some guidance cues. However, the composition of subtype-specific GC-localized molecular machinery and its dynamic regulation across distinct stages of development are essentially unknown. We apply a combination of subtype-specific labeling, biochemical fractionation, and subcellular fluorescence activated sorting to purify GCs and parent somata of distinct subtypes of cortical projection neurons, directly from the mouse brain. Our investigation of the composition and dynamic regulation of subcellular transcriptomes of callosal projection neurons and corticothalamic projection neurons as well as across developmental stages, finds pronounced overlap, likely reflecting shared subcellular machinery. Intriguingly, we find that GC-localized transcriptomes of these subtypes of projection neurons are enriched for genes associated with neurodevelopmental and neuropsychiatric diseases. In-depth analysis of the context-specific portions of GC-localized transcriptomes reveals potential novel regulators of subcellular RNA localization and translation (Cpeb4) as well as subcellular RNA stability (Rbms1), which likely are involved with distinct phases of circuit development: long-distance growth, gray matter innervation, and synapse formation. Elucidation of the regulatory mechanisms involved in context-specific subcellular RNA localization, stability, and translation is critical toward a detailed understanding of local processes involved in circuit development, maintenance, and function. Even subtle changes in the precision of cortical circuitry can have pronounced effects on cortical function, and lead to neurodevelopmental and neuropsychiatric disorders in the context of callosal or corticothalamic networks as well as neurodegenerative disorders and impaired regenerative capacity in the context of corticospinal connections. Thus, integrated knowledge of GC- and soma-localized molecular controls involved in circuit formation will be necessary to fully understand the etiologies of these diseases and enable targeted therapeutics.

9 PAUL DONLIN-ASP, PH.D.

University of Edinburgh
Postdoctoral researcher at the Max Planck Institute for Brain Research

During my Ph.D. studies at Emory University under the supervision of Dr's Gary J. Bassell, Ph.D. and Wilfried Rossoll, Ph.D. my thesis work focused on Spinal Muscular Atrophy (SMA). SMA results from either a deletion or mutation in the survival of motor neuron 1 gene (SMN1), leading to reduced levels of SMN protein. SMN is essential for all cells and serves an essential housekeeping role in assembling spliceosomal RNA-protein complexes. SMN has previously been found to associate with mRNA-binding proteins, but the nature of this association was unknown. During my Ph.D. work, I could characterize SMN as a regulatory chaperone protein in the association of mRNA and mRNA binding proteins (Donlin-Asp et al. Cell Reports 2017). In addition to this main project, I also worked on a collaborative project with Pfizer to test an experimental compound from Repligen to test in a number of our SMA cellular phenotypes. I found that this drug, which targeted the scavenger mRNA decapping enzyme Dcp2 enhanced total mRNA levels in treated cells- and boosted the association of mRNA binding proteins with mRNA. These data support a model of mRNA binding protein and mRNA association dysregulation as a driving mechanism in SMA pathogenesis (Donlin-Asp et al. Current Opinion in Neurobiology 2016). I also was involved in a project focused on TDP-43 pathology in ALS, contributing to assessing distribution changes in nuclear pore complexes in mutant TDP-43 expressing cells (Chou CC, Nature Neuroscience 2018).

Following my Ph.D. work, I sought to further develop my understanding of the fundamental cellular mechanisms underlying normal neuronal function- specifically concerning synaptic plasticity. For this reason, I joined the laboratory of Dr. Erin M Schuman, Ph.D., at the Max Planck Institute for Brain Research. During this time, I have been working to understand how protein synthesis is regulated during synaptic plasticity- one of the phenomena believed to underlie long-term memory formation. I have found that protein production is widespread throughout the neuron, both in axon terminals and dendritic spines. I also could demonstrate that different forms of synaptic plasticity enhanced protein synthesis in context-specific ways in dendritic spines and axon terminals (Hafner and Donlin-Asp et al. Science 2019). These data demonstrate that protein synthesis is widespread in presynaptic terminals and underscore its

importance in neuronal function and long-term memory formation. Since completing that project, I have been working on understanding the interplay between mRNA dynamics and protein synthesis during plasticity. By tracking mRNA in live cells and visualizing the translation of endogenous proteins in real-time, I have been able to characterize a widespread alteration in dendritic mRNA Dynamics during distinct forms of synaptic plasticity (Donlin-Asp et al. PNAS 2021).

In my own group, which I've started in 2023 at the University of Edinburgh, I'm exploring how the brain can localize and translate thousands of mRNAs in neuronal processes. My group is interested in understanding how the brain controls where these mRNAs are successfully transported to these distal sites, are translationally controlled, and the functional role of locally translating specific proteins. At the crux of regulating RNA, from the moment it is transcribed to when it is degraded, is an ever-expanding list of RNA binding proteins (RBPs) whose association with RNA governs all aspects of RNA biology, including its transport and subsequent translation. Dysregulation of RBPs leads to neurodevelopmental and neurodegenerative disorders, highlighting their critical importance within the brain. Currently, the full complement of neuronal RBPs regulating RNAs is unknown- limiting our understanding of the mechanism neurons employ in controlling RNA localization and local protein synthesis.

RESOLVING THE LOCALIZATION AND DYNAMICS OF RNA AND PROTEIN SYNTHESIS WITHIN NEURONS

The rapid modulation of their proteomes drives the development and adaptability of neurons. At brain synapses, the direct functional connection between two neurons, local regulation of protein synthesis is a critical and essential component for sculpting and modifying the synaptic proteome. With thousands of mRNAs localized and translated in neuronal processes, understanding how the brain controls where mRNAs localize and are translated and the significance of their regulated translational are critical outstanding questions.

I will discuss our recent efforts toward understanding the functional significance of mRNA localization and local protein synthesis in neuronal compartments and highlighting our recent demonstration that local protein production is widespread throughout the neuron, both in mature axon boutons and dendritic spines (Hafner & Donlin-Asp et al. 2019). Significantly, mechanistically distinct forms of plasticity can modulate local protein synthesis, both pre- and postsynaptically, in context-specific ways- highlighting its versatility in sculpting and adapting the local proteome. Furthermore, we have shown that plasticity regulates mRNA transport dynamics, controlling when and where mRNAs associate with synapses. By tracking mRNA in live cells and visualizing the translation of endogenous proteins in real-time, we have characterized a widespread alteration in dendritic mRNA dynamics during distinct forms of synaptic plasticity (Donlin-Asp et al. PNAS 2021). These results enhance our understanding of how the brain regulates and adapts its synaptic proteome during plasticity, aiding our efforts to understand the molecular underpinnings of neurological diseases resulting from dysregulation of local protein synthesis in the brain.

10 JEAN-MICHEL CIONI, PH.D.

San Raffaele Scientific Institute
Department of Neurobiology

Dr. Cioni received his Master from the University of Montpellier (France) in 2008 and then did his PhD in the laboratory of Dr. Ango at the Institute of Functional Genomics (CNRS, INSERM, Montpellier, France), working on neuronal development in the cerebellar cortex. In 2013, he moved for his postdoctoral training to Pr. Christine Holt's laboratory in the Department Physiology, Development and Neuroscience at the University of Cambridge (U.K). There, first as an EMBO postdoctoral fellow and then as a Research Associate, he focused his research on the control of gene expression by mRNA transport and local translation in neuronal compartments. In 2019, Dr. Cioni obtained the Armenise-Harvard Foundation Career Development Award and the ERC starting grant to establish his lab at the San Raffaele Scientific Institute in Milano (Italy).

Our research focuses on understanding how neuronal networks are established and maintained throughout the life of an organism. Neurons are morphologically complex and highly polarized cells that require the tight control of their proteome at the subcellular level. The local synthesis of proteins in restricted neuronal compartments, such as axons, dendrites and synapses, is crucial for neuronal function and survival. Highlighting the importance of this biological process, dysregulation of mRNA transport and/or translation has been linked to several neurodevelopmental and neurodegenerative disorders. Our laboratory studies the molecular mechanisms underlying the transport and translation of specific mRNAs in neuronal subdomains, and the physiological role of this process in neuronal development and function. Additionally, we investigate how alterations in post-transcriptional mRNA regulation participate to the etiology behind neurological disorders.

mRNA ASSOCIATION WITH ENDOSOMES IN NEURONS

RNA localization is a highly conserved process allowing spatial and temporal control of the proteome. This regulation is particularly important in morphologically complex cells such as neurons, where precise expression of specific proteins is necessary to achieve highly compartmentalized functions. In recent years, the discovery that multiple organelles directly participate to mRNA localization and translation is shifting our point of view on how specific transcripts are regulated in neurons. Here I will discuss our findings on mRNA association with endosomes in neurons. By combining multiple advanced sequencing and imaging methods we have identified hundreds of mRNAs associated with endosomal compartments and further obtained new insights into the dynamics of RNA-endosome interactions. Our work further supports the involvement of endosomal trafficking in controlling mRNA distribution in axons and dendrites during neuronal development.

11 LUDO VAN DEN BOSCH, PH.D.

University of Leuven
Director of the Neurobiology Laboratory (Experimental Neurology) of
the VIB Center for Brain and Disease Research
Department of Neurosciences

After obtaining his master's degree in biology, Ludo Van Den Bosch received his PhD in the field of physiology at the KU Leuven (Belgium) in 1990. After postdoctoral positions specializing in molecular biology and neurodegeneration, he co-established the Laboratory of Neurobiology and became assistant professor at the KU Leuven in 2001. He was promoted in 2013 to Full Professor at the Department of Neurosciences. Since 2014, he is also group leader in the VIB Center for Brain & Disease Research (Leuven). In 2017, he took over the directorship of the Laboratory of Neurobiology (Experimental Neurology). The focus of his research is on motor neuron diseases such as amyotrophic lateral sclerosis (ALS), as well as on different neuropathies such as Charcot-Marie-Tooth disease (CMT). The central goal of his research is to understand more in detail the mechanisms of neuronal and axonal degeneration and regeneration and to translate these discoveries into new therapeutic strategies for the different neurodegenerative disorders. Research models range from cell lines, induced pluripotent stem cells (iPSCs), and small animal models including fruit fly and zebrafish to transgenic mouse models for the different neurodegenerative diseases. The main research focus is on the importance of disturbances in intracellular transport processes, including nucleocytoplasmic and axonal transport. In addition, the role of non-neuronal cells such as astrocytes and microglia in these processes is investigated in detail.

GAIN-OF-FUNCTION AND LOSS-OF-FUNCTION EFFECTS OF IPSC DERIVED ASTROCYTES FROM ALS PATIENTS ON HUMAN MOTOR UNITS

Astrocytes play a crucial role in the selective motor neuron pathology in amyotrophic lateral sclerosis (ALS). These cells provide an important neuronal homeostatic support. However, this function is highly compromised in ALS. We established a fully human coculture systems to study the underlying mechanisms of the dysfunctional intercellular interplay. We characterized human induced pluripotent stem cell (hiPSC)-derived astrocytes from FUS-ALS patients and incorporated these cells into a human motor unit microfluidics model to investigate the astrocytic effect on the hiPSC-derived motor neuron network and on the functional neuromuscular junctions (NMJs) using immunocytochemistry and live-cell recordings. FUS-ALS cocultures were systematically compared to their CRISPR-Cas9 gene-edited isogenic control systems. We observed a dysregulation of astrocyte homeostasis, which resulted in a FUS-ALS-mediated increase in reactivity and secretion of inflammatory cytokines. Upon coculture with motor neurons and myotubes, we detected a cytotoxic effect on motor neuron-neurite outgrowth, NMJ formation and functionality, which was improved or fully rescued by isogenic control astrocytes. We demonstrate that ALS astrocytes have both a gain-of-toxicity and loss-of-support function involving the WNT/β-catenin pathway, ultimately contributing to the disruption of motor neuron homeostasis, intercellular networks and NMJs.

12 A. NAZLI BAŞAK, PH.D.

Koç University, School of Medicine
Molecular Biology and Genetics
Suna and Inan Kıraç Foundation, KUTTAM-NDAL

A. Nazlı Başak, earned her BS degree in Chemistry from the University of Göttingen, Germany, and completed her MSc and PhD programs in Molecular Biology and Genetics at the Max Planck Institute (MPI) for Experimental Medicine in Göttingen under the scientific guidance of Prof. Friedrich Cramer on nucleic acid biochemistry, tertiary structure of the tRNA molecule and protein biosynthesis mechanisms. After three years of postdoctoral research work and five years of research assistance at MPI in Göttingen, she returned to Turkey.

Dr. Başak's career at Boğaziçi University in Istanbul started with the establishment of DNA techniques used in the early detection and prevention of hereditary blood disorders. She was instrumental in the establishment of a fully equipped molecular biology and genetics laboratory for the first time in Turkey. Her research laboratory at Boğaziçi University, in collaboration with the Turkish Ministry of Health, played a major role in the implication of a comprehensive nation-wide prevention program for the early prenatal diagnosis of thalassemias and abnormal hemoglobins, based on DNA analysis, in Turkey.

In 1990s Nazlı Başak's research interest shifted from monogenic blood diseases towards complex brain disorders. Dr. Başak's current research agenda focuses on neurodegenerative disease genetics. With her interest in mechanisms giving rise to neurodegeneration, she was appointed in 2005 as the director of NDAL (Neurodegeneration Research Laboratory), established by the prestigious Suna and İnan Kıraç Foundation at Boğaziçi University.

NDAL regularly hosts the prestigious Suna Kıraç Conferences on Neurodegeneration Istanbul in collaboration with UMass and Harvard Medical Schools and the Suna Kıraç Workshops on Genetic Models of Neurodegenerative Disease with Brown University's Carney Institute for Brain Science. The laboratory has a nationwide recognition as a center of excellence in the molecular diagnosis of common and rare neurological diseases in Turkey. The translocation of NDAL to Koç University's Medical School in 2018, enabling a tighter interaction with specialist clinicians and hospitals, enhanced

the visibility and efficiency of NDAL, exponentially increasing the number of international collaborations and transnational consortia projects. Currently, the lab is the Turkish partner of Project MinE, the coordinator of the European EJP-ND Project PROSPAX on spastic ataxias, an active member of the ASAP/GP2 initiative on Parkinson's disease and was recently awarded an IDRC Research Grant on ALS-microbiome interaction, partnering with the University of Calgary, Canada and Israel's Weizmann Institute in Rehovot. NDAL is involved in many other consortia on neurodegenerative disease biology, like the RFC1 Consortium, Solve-RD Research Project and the Genesis Platform.

SUNA KIRAÇ MEMORIAL LECTURE
THE COMPLEX ARCHITECTURE OF ALS IN TURKEY

The last decade has seen an exponential progress in data output, based on advances in genetics, genomics and on large international collaborations. Consequently, our knowledge of the genetic factors behind ALS has improved in an unparalleled fashion and the scientific scenario of ALS has dramatically changed. Today, the disease is accepted to be part of a continuum with other neurological diseases and a crossroads between genetic, neurometabolic and environmental factors.

ALS genetic research has been largely focused on populations of European ancestry and attention has only recently shifted to other ethnicities. To the best of our knowledge, this is the largest and most systematic study performed in Turkey so far, a large country with a young population. As opposed to European countries in which family sizes steadily decreased in the last 50 years, Turkey still has a high birth rate with large kindreds and many offspring. Especially in the rural parts of the country, high consanguinity, consisting of mainly first cousin marriages is part of the culture and rather the rule than the exception. With its wealthy historical background and unique geographical position between three continents, the Anatolian Peninsula is a rich genetic pool with a high ethnic heterogeneity on one hand and inbred on the other.

A total of 2,320 ALS patients recruited from specialist centers across Turkey in the last 20 years were analysed within the scope of this study, adopting a combination of conventional and NGS approaches; 501 of these are familial cases (21.5%) and 1819 are sporadic patients (78.5%). The four major ALS genes, C9ORF72, SOD1, TARDBP, FUS contribute to 35% of fALS and 6% of sALS. Analysis of pathogenic exonic variants obtained from WES and WGS data increases these numbers to 45% in fALS and 10% in sALS.

Apart from classical ALS genes, WES revealed variants in rare genes associated with diverse motor neuron phenotypes with upper or lower motor neuron predominance pointing to a great heterogeneity with presently 53 genes identified in the ALS cohort under study. Locus and allelic heterogeneities, genetic pleiotropy, variable penetrance, genetic discordance, and oligogenic etiology contribute to the complex genetic landscape of ALS in Turkey. Moreover, the variability and fluidity of observed phenotypes, not only in ALS, but among all neurodegenerative diseases warrant a rethinking of the traditional disease taxonomy. Under the surface of the disparate clinical, syndromic, and diagnostic classification, hide not only shared genes and phenotypes, but also common mechanisms and pathways.

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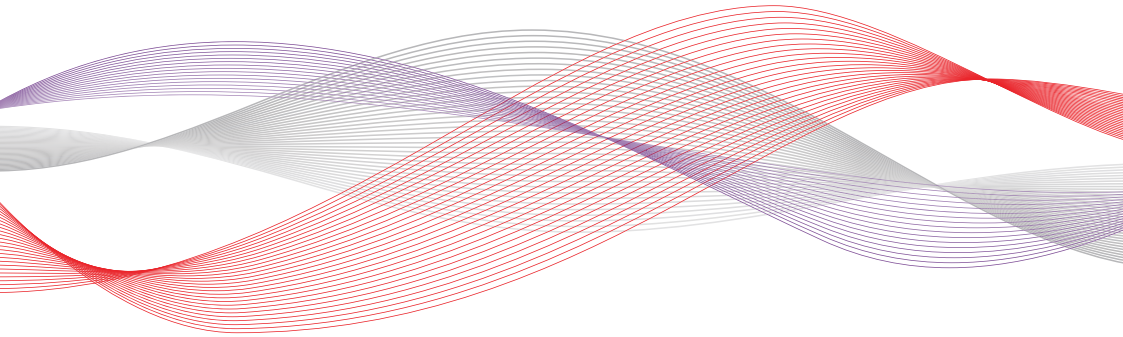

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