A New Framework for Targeting Neurodegenerative Disorders

Contributed by Stephen Ginsberg, PhD

Stephen Ginsberg, PhD, is a Research Scientist in the Center for Dementia Research and an Associate Professor in the NYUGSOM Department of Psychiatry, Department of Neuroscience and Physiology, and the NYU Neuroscience Institute. Broadly speaking, the focus of the Ginsberg laboratory is to delineate cellular and molecular mechanisms underlying neurodevelopmental and neurodegenerative disorders. His most recent work, described in an article featured on the cover of the January issue of Trends in Pharmacological Sciences, suggests that stressor-induced dysfunctions in protein-protein interaction networks may be targeted via structures called epichaperomes. Here Dr. Ginsberg provides an overview of this line of research.

Most diseases, including neurodegenerative disorders such as Alzheimer’s disease (AD) and cancer have a complex etiology in which internal and external stressors negatively impact, directly or indirectly, on specific cells, tissues, organs, and ultimately organisms.

Proteins, akin to individuals, do not function in isolation. They interact with, impact on, and are impacted by other proteins. They often behave in systems, termed protein–protein interaction (PPI) networks, with redundancies that have inherent adaptability capabilities. This translates all too often into a drug failing to produce a desired effect, especially in disease states (e.g., cancer) where treatments are effectively evaded through cellular plasticity.

We hypothesize that the disease network – a map of how individual or a combination of stressors alter cellular PPIs, and in turn perturb the system – is a target for therapeutic intervention. A paradigm shift in developing therapies is needed that requires movement from the unitary protein approach to the goal of targeting context-specific PPI network dysfunctions for disease control.
Epichaperomes are oligomeric structures composed of tightly bound chaperones, cochaperones, and other factors. Not to be confused with chaperones, which are abundantly expressed in all cells and across normal and disease conditions, epichaperomes are principally localized to diseased cells and tissues. Functionally, epichaperomes are also distinct from chaperones. They act as scaffolds for remodeling PPIs at the proteome-wide level rather than serving as folders of proteins in protein synthesis and degradation pathways. The more epichaperomes are present in cells and tissues, the higher the number of proteins that are negatively impacted upon, and in turn the higher the severity of perturbation to the complex network of molecular interactions.

Epichaperomes form in neurodegenerative disorders in cells and tissues exposed to maladaptive stressor conditions that are associated with disease. For example, epichaperomes were detected in postmortem human AD brains but not age-matched subjects with no cognitive impairment, in APP duplication-expressing iPSC-derived neurons but not wild-type iPSC-derived neurons, in iPSC-derived neuron/astrocyte spheroids exposed to toxic human tau oligomers, and in PS19 transgenic mouse brains but not wild-type littermates.

Pharmacological disruption of epichaperomes in neurodegenerative models resulted in reversal of the phenotype to pre-stressor levels. For example, introduction of human tau into N2a cells led to epichaperomes that rewired the connectivity of proteins in synaptic protein networks. Also, delivery of a small-molecule epichaperome disruptor termed PU-AD reverted pathologic effects on synaptic protein pathways to the pre-tau stressor state. Therefore, disassembling epichaperomes, scaffolding platforms that enable pathologic rewiring of PPI networks, may restore PPI networks to a pre-stressor state, and has emerged as an approach to target context-specific disease PPI networks in neurodegenerative disorders and cancers.

Thus, we propose a new framework based upon disrupting epichaperomes, pathological entities that enable dysfunctional rewiring of PPI networks, as a mechanism to revert context-specific PPI network dysfunction to a normative state. Advances in the understanding of controlling dysfunctional PPIs may lead to a better model for detecting and treating complex diseases early in their pathogenetic state, including neurodegenerative disorders and cancer. Therefore, targeting stressor-induced PPI network dysfunctions via epichaperomes may be amenable to a precision medicine approach.

**Kudos**

Karya Ottey, PhD, the Director of Compliance at NKI over the past six years, has been named Director of the NYS Office of Mental Health (OMH) Human Research Protection Program (HRPP). This is a newly created position responsible for protecting the rights and welfare of research participants at all OMH institutions. The HRPP will oversee Institutional Review Board (IRB) activities as well as research compliance, education, and quality assurance at NKI, New York State Psychiatric Institute (NYSPI), and all affiliated OMH sites. Karya will remain based at NKI and will continue to provide guidance to the NKI compliance team. This promotion recognizes the remarkable accomplishments that Karya has achieved in structuring compliance at NKI.
Laura Trubenbach has been named Acting Director of Human Resources at NKI. Laura started her state career 25 years ago at Helen Hayes Hospital and most recently worked for the Office of Development Disabilities in the Hudson Valley Offices before coming to NKI. She has worked in both the Human Resources Office and the Business Office for the last 15 years. This promotion recognizes the contributions that Laura has made in Human Resources over the years and her vision to rebuild and rebrand our Human Resource Department.

**GRANTS RECEIVED**

**National Institute of Neurological Disorders and Stroke**

Dr. Helen Scharfman (Dementia Research) received a Javits Neuroscience Investigator Award, issued as an R37 grant, for her project titled “Mossy cells in temporal lobe epilepsy.”

**FROM AROUND THE INSTITUTE**

The work of Dr. Ralph Nixon, Director of NKI’s Center for Dementia Research, was highlighted in a recent *Newsweek* article titled “New Alzheimer’s Drug Brings Hope—and Tough Choices for Patients, Caregivers.”

NKI’s DLAR (Department of Laboratory Animal Resources) participated in the 2023 International Laboratory Animal Technician Week, branded “Technicians Bring the Magic”. This annual celebration of the American Association of Laboratory Animal Science (AALAS) recognizes laboratory animal technicians for their contributions as essential members of the research team. The hard work and dedication of all members the NKI DLAR staff were recognized with a free lunch, certificates, and goodie bags provided by the Employee Assistance Program.
John Orczyk (first author), Yoshi Kajikawa (corresponding author), Annie Barczak, and Noelle O’Connell (Translational Neuroscience, C-BIN) published this paper in the Journal of Neurophysiology.


Pasquale D’Acunzo, Efrat Levy, and colleagues at NKI (Dementia Research; Neurochemistry) and NYU just published this open access paper in the *Journal of Extracellular Vesicles*.


Lila Davachi (Clinical Research) coauthored this article published recently in *Psychological Science*.

Renee Hartig (Translational Neuroscience Laboratories, C-BIN) is a coauthor of this review published in the open access journal *Current Research in Neurobiology*. The article appears in a special issue titled “A Global Outlook on Non-Human Primates in Neuroscience Research,” of which Dr. Hartig is one of the editors.


Balapal Basavarajappa and Shivakumar Subbanna (Dementia Research) published this new open access review in *Cells*. The article is part of a special Issue on “New Advances in Synaptic Dysfunctions and Plasticity”.


Dr. Basavarajappa notes, “Evidence suggests that FASD pathogenesis involves altering a set of molecules involved in neurotransmission, myelination, and neuroinflammation, and these studies identify several immediate and long-lasting changes using many molecular approaches that are essential for synaptic plasticity and cognitive function. In this article, we discuss the substantial research progress in different aspects of synaptic and molecular changes that can shed light on the mechanism of synaptic dysfunction in FASD, which can offer potential synaptic targets for the many neurobehavioral abnormalities observed in FASD.”

Vilma Gabbay (senior author) and Emily Stern (Clinical Research) coauthored this open access paper appearing in *NeuroImage: Clinical*.


Anzalee Khan (first author), Jean-Pierre Lindenmayer, and Matt Hoptman (Manhattan Schizophrenia Research Program; Clinical Research) are coauthors of this paper appearing in *Schizophrenia Research*.


Aidong Yuan and Ralph Nixon (Dementia Research) published this open access review in a special issue of *Brain Research Bulletin* on “Cytoskeletal proteins in health and neurodegenerative disease”.

Robert Smith (Neurochemistry) is co-principal author and Russell Tobe (Clinical Evaluation Center) is a coauthor of this paper published recently in the *Journal of Autism and Developmental Disorders*.


Sang Han Lee (Biomedical Imaging & Neuromodulation) coauthored this article recently published in *Infant Behavior & Development*.


Nunzio Pomara (Geriatric Psychiatry) is a coauthor of this open access perspective paper in *Clinical Neuropsychiatry*.


**INFO UPDATE**

In 2020, the National Library of Medicine launched the NIH Preprint Pilot to explore how inclusion of preprints in PubMed Central (PMC) and PubMed, could accelerate the discoverability and maximize the impact of NIH-supported research. Now the pilot project is expanding into a new phase. Coinciding with the designation of 2023 as the Year of Open Science, this second phase will run for a year and encompass all preprints reporting on NIH-funded research and posted to an eligible preprint server on or after January 1, 2023. (Participating preprint servers are bioRxiv, medRxiv, arXiv, and Research Square.) For more details and documentation, see this [NCBI Insights post](https://www.ncbi.nlm.nih.gov/biobrefer/).

A new and improved version of the Science Experts Network Curriculum Vitae (SciENcv) has been rolled out. SciENcv is an electronic system that helps you assemble professional information needed to apply for federal grant applications. Check out [this announcement](https://www.ncbi.nlm.nih.gov/biobrefer/) for more information and [upcoming workshops](https://www.ncbi.nlm.nih.gov/biobrefer/).

In January, the new NIH Policy for Data Management and Sharing went into effect. This [toolkit page](https://www.nlm.nih.gov/bsd/dataSharing/hot_topics.html) from the Network of the National Library of Medicine compiles a number of resources related to the new policy. These include links to a [checklist for researchers](https://www.nlm.nih.gov/bsd/dataSharing/hot_topics.html), [sample plans](https://www.nlm.nih.gov/bsd/dataSharing/hot_topics.html), and the free [Data Management Plan Tool](https://www.nlm.nih.gov/bsd/dataSharing/hot_topics.html) (DMPTool).
The American Psychiatric Association has launched LaSaludMental.org, a website hosting culturally informed and evidence based Spanish language resources for patients and psychiatrists. The content hosted on the new site includes informational text, quizzes, expert Q&A in both print and video formats, infographics, printable handouts, animated explainer videos, and more. For more background about LaSaludMental.org, see this article in Psychiatric News.

Recent Developments in Scientific Publishing

The state of the art in publishing continues to evolve at a rapid pace, catalyzed by issues such as public access, peer review, and artificial intelligence. Here are a few recent developments:


- “Journal seeks to upend scientific publishing by only reviewing—not accepting—manuscripts” (Science. 2022 Oct 28;378(6618):346)

- “Nonhuman “Authors” and Implications for the Integrity of Scientific Publication and Medical Knowledge” (JAMA. 2023 Jan 31)

- “Science journals ban listing of ChatGPT as co-author on papers” (The Guardian)

DEPARTMENT OF WONDER

2022 in Review

The wheels of science keep turning, and each year brings a range of progress in biomedicine. For a sampling of advances, check out these research highlights:

- Human Health Advances
- Promising Medical Findings
- Basic Research Insights

Or download the PDF compilation of NIH Research Highlights.

We all need a bit of joy now and then.

The NKI librarian is always available to assist with literature searching, citation searching (Web of Science, Scopus), bibliographic reference management, and the like. When you have any information needs, or questions about available resources, don’t hesitate to turn to us.

The library offers a comfortable, quiet space for reading, work, and small meetings. To use the library’s Wi-Fi network, ask the library staff for the password.

You can link to the NKI Library’s website from myNKI. The Library site includes quick links to the NYU Health Sciences Library and to the New York State Library, as well as links to NKI’s own library resources (journal finder, online catalog, etc.).
EVENTS AND SEMINARS

Community Space Discussion

Everyone is invited to participate in a virtual community discussion on

*The Imposter Syndrome*

Wednesday, March 1st at noon

Zoom link details:
https://us02web.zoom.us/j/88933310864?pwd=WIXluZjZaYjkzRFgzcHdjEtoa1ZTQT09
Meeting ID: 889 3331 0864  
Passcode: 794399

*Sponsored by the Community Building Committee*

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Center for Biomedical Imaging and Neuromodulation Science Series

Held on Mondays at 11 am via Zoom

https://childmind.zoom.us/j/2142826575?pwd=dX1SeDRCaW9RNRWhR2Z3Y0dPQkw4UT09

Richard Bethlehem, PhD  
University of Cambridge  
*Brain Charts for the Human Lifespan*  
February 27th

Pierre Bellec, PhD  
University of Montreal  
March 13th

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Center for Dementia Research  
Neuroscience Seminar Series

Held on Thursdays in the NKI conference room

Kim Green, PhD  
University of California, Irvine  
*Exploring the roles of microglia in the healthy and Alzheimer’s disease brain*  
February 16th, 10 am

Martin Picard, PhD  
Columbia University  
*Mitochondrial Psychobiology*  
March 2nd

Zhenyu Yue, PhD  
Icahn School of Medicine at Mount Sinai  
*A Selective Eater that Protects Brain*  
March 16th

Yadong Huang, PhD  
UCSF Gladstone Institute, San Francisco  
*ApoE4 and Alzheimer’s Disease: Molecular Mechanisms and Therapeutic Strategies*  
April 20th
Statewide Grand Rounds

**Aging, Physiological Changes, and Mental Health**

**Presenters**

Guerman Ermolenko, MD  
Clinical Director, Capital District Psychiatric Center

Elizabeth J. Santos, MD, MPH  
University of Rochester  
School of Medicine & Dentistry

Wednesday, February 15th  
1:00 – 2:15 pm

The New York State Office of Mental Health (OMH) regularly hosts an interactive video broadcast covering the latest research, technology, and treatment implementation in the fields of psychiatry and psychology. These programs are recorded, and the archived Statewide Grand Rounds programs can be viewed on the OMH website.

Atlantic Council

Sam Neymotin (Biomedical Imaging & Neuromodulation) participated in a webinar panel of the Atlantic Council’s GeoTech Center on artificial intelligence (AI) and healthcare. Dr. Neymotin provided insight into the application of AI to process data and recognize patterns in biomedical imaging related to brain neuron excitability, known as oscillations, that can be used to monitor and alleviate the effects of conditions such as schizophrenia and epilepsy. He appears approximately 38 minutes into the video recording found here.

NKI ON THE ROAD

Drs. Jean-Pierre Lindenmayer and Anzalee Khan will present a poster at the 19th Annual Scientific Meeting of the International Society for CNS Clinical Trials and Methodology (ISCTM) scheduled for February 15-17 in Washington, DC. The poster title is “Using AI-Driven Platform to Detect Negative Symptoms of Schizophrenia Through Facial and Acoustic Analysis.”

Dr. Marilena Lekas (Social Solutions & Services) is participating in a four-part roundtable discussion series on mental health stigma. The series is sponsored by the New York State Office of Mental Health and Behavioral Health News. View the website for more details and session recordings.

Department of Psychiatry Grand Rounds

Dr. Ricardo Osorio Suarez (Clinical Research) gave the NYU Department of Psychiatry Grand Rounds on January 12th. His presentation topic was “Slow-Wave Sleep (SWS): From the Neuron to the Clinic”.

And on February 9th, Dr. Katlyn Nemani (Clinical Research) presented Grand Rounds on “Response to COVID-19 Infection and Vaccination in People with Schizophrenia”.

[9]
Below is a list of references that have been added to the NKI publications database since the previous update. The full database contains over 7,100 items dating back to 1995 and can be searched from the myNKI website.


Roetzer-Pejrimovska T, Kiesel B, Nenning KH, Klughammer J, Rajchl M, Bock C et al. LINKING HISTOLOGICAL GLIOBLASTOMA PHENOTYPES TO TRANSCRIPTIONAL SUBTYPES AND PROGNOSIS USING DEEP LEARNING. Neuro-Oncology 24[Suppl. 7], vii118-vii119. 2022. [Abstract]
