BIOGRAPHICAL SKETCH

NAME: Kostas Vekrellis

POSITION TITLE: Research Director, Biomedical Research Foundation Academy of Athens, Greece

EDUCATION/TRAINING

INSTITUTION AND LOCATION	degree / qualification	Completion Date	FIELD OF STUDY
University College London, London, UK BSc.	BSc (Hons)	1993	Neuroscience
University College London, London, UK Ph.D.	PhD	1997	Neuroscience
Research Fellow in Neurobiology, Harvard University, USA	Postdoctoral Fellow	2000	Neurodegeneration

A. Personal Statement

My research focuses on unraveling the molecular mechanisms underlying neurodegeneration in synucleinopathies, particularly Parkinson's Disease (PD). These disorders are characterized by the misfolding and aggregation of proteins such as α-synuclein (AS) in vulnerable brain regions, leading to progressive neuronal dysfunction. Given the high conservation of protein homeostasis pathways across species, my work employs diverse model systems—from mammalian cell cultures to murine models—to investigate the origins of pathological aggregation and its propagation.

A key emphasis of my research is understanding how amyloidogenic proteins like AS spread between neurons and identifying strategies to enhance their clearance. My lab utilizes *in vivo* and *in vitro* models of protein misfolding diseases to dissect these mechanisms, with a particular focus on extracellular aggregate clearance. To this end, we are trying to identify enzymatic activities in the extracellular space that can bind and degrade AS aggregates. It is possible that such dysfunctional enzymes might contribute to the built up of toxic AS species in the Interstitial Fluid. We have developed innovative *in vivo* approaches, including microdialysis, to monitor protein misfolding and aggregation dynamics in real time within the living brain. We have pioneered techniques to isolate small extracellular vesicles (exosomes) from brain tissue, enabling us to study their role in pathology dissemination.

The ultimate goal of our work is to translate these findings into novel therapeutic strategies for synucleinopathies and related disorders. To bridge the gap between bench and bedside, I collaborate closely with clinicians, ensuring our discoveries accelerate drug development and improve patient outcomes. By integrating basic science with translational applications, I aim to contribute meaningfully to the fight against neurodegenerative diseases.

B. Positions and Honors

2000-2001	Instructor in Neurology, Harvard Medical School
2002-2008	Lecturer, Biomedical Research Foundation, Academy of Athens, BRFAA
2009-2015	Assistant Professor, Biomedical Research Foundation, Academy of Athens, BRFAA
2015-2021	Associate Professor, Biomedical Research Foundation, Academy of Athens, BRFAA
2021-	Professor, Biomedical Research Foundation, Academy of Athens, BRFAA
2015-2022	Visiting Professor, University of Oxford, Medical School, Dept. Of Experimental Medicine, Radcliffe Dept. of Medicine

Honors

1993.	Prize for Best Neuroscience Finalist by the Board of Examiners of the University of London
1993-1997	The Naito Scholarship, Eisai Pharmaceuticals Inc, Japan
1997-1999	Edward R. and Anne G. Lefler Fellowship for postdoctoral research in Neurobiology, Harvard Medical School

C. Research Support (related)

1 The Michael J Fox Foundation. VALIDATION OF KLK6 AS A NEW THERAPEUTIC TARGET FOR PARKINSON'S DISEASE. 2023-2025. Co-PI €200000

2. European Commission H2020 (2020-2025). Innovative Medicines Initiative IMI2 IDENTIFICATION OF DRUGGABLE TARGETS MODULATING MISFOLDED PROTEINS IN ALZHEIMER'S AND PARKINSON'S DISEASES: PI €360000

4. European Union Research-Create-Innovate Grant, GSRT, GREECE, BIOLUMINPD. 2018-2023. DEVELOPMENT OF METHODOLOGIES FOR DIFFERENTIAL DIAGNOSIS OF PARKINSON'S DISEASE. PI. €200.000

5. European Union Research-Create-Innovate, GSRT, GREECE, AlphaSyn. 2018-2023. DEVELOPMENT OF NOVEL INHIBITORS TO ALPHA SYNUCLEIN AGGREGATION.: PI €175.000

6. The Alzheimer's Association. 2021-2023. TARGETING KLK6 FOR THE TREATMENT OF ALZHEIMER'S DISEASE, Co-I 200000

7. Greece 2.0, National Recovery and resilience Plan. Brain Precision: GENETIC BASIS OF PARKINSON'S AND ALZHEIMER'S DISEASE. Development of biomarkers and therapeutic strategies.2022-2026. PI € 320.0000

D. Bibliography (related and selected)

1 Emmanouilidou E, Melachroinou K, Roumeliotis T, Garbis SD, Ntzouni M, Margaritis LH, Stefanis L, **Vekrellis K.** Cell-produced alpha-synuclein is secreted in a calcium-dependent manner by exosomes and impacts neuronal survival. J Neurosci.2010 (20):6838-51.

2. Emmanouilidou E, Minakaki G, Keramioti MV, Xylaki M, Balafas E, Chrysanthou- Piterou M, Kloukina I, **Vekrellis K**. GABA transmission via ATP-dependent K+ channels regulate α-synuclein secretion in mouse striatum. Brain. 2016;139(Pt 3):871-90.

3. Karampetsou M, Ardah MT, Semitekolou M, Polissidis A, Samiotaki M, Kalomoiri M, Majbour N, Xanthou G, El-Agnaf OMA, **Vekrellis K.** Phosphorylated exogenous alpha-synuclein fibrils exacerbate pathology and induce neuronal dysfunction in mice. Sci Rep. 2017 28;7(1):16533.

4. **Vekrellis K,** Xilouri M, Emmanouilidou E, Rideout HJ, Stefanis L. Pathological roles of α-synuclein in neurological disorders. Lancet Neurol. 2011, 10(11):1015-25

5. Stefanis L, Emmanouilidou E, Pantazopoulou M, Kirik D, **Vekrellis K**, Tofaris GK. How is alpha-synuclein cleared from the cell? J Neurochem. 2019 Sep;150(5):577-590.

E. Contributions to Science

Our *in vivo* and *in vitro* studies demonstrate that soluble oligomeric and monomeric α-synuclein (AS) species are released, in part, via externalized membrane vesicles exhibiting exosome-like characteristics. These findings support the hypothesis that toxic protein aggregates are packaged into extracellular vehicles (EVs) as a mechanism of intercellular communication, enabling their transfer to neighboring cells. Consequently, factors regulating AS extracellular levels and secretion represent potential therapeutic targets.

Using *in vivo* approaches, we identified the serine protease kallikrein-6 (KLK6) as a major AS-degrading enzyme. Viral overexpression of KLK6 was non-toxic *in vivo* and, importantly, reduced phosphorylated S129 AS levels in the striatum and substantia nigra pars compacta (SNpc) of Parkinson's disease (PD) model mice highlighting its therapeutic potential.

Our lab was the first to demonstrate that AS can be physiologically secreted via exosomes and confirmed the presence of extracellular AS in rodent and human brain interstitial fluid using microdialysis. We are investigating the role of exosomes in AS pathology transmission and neuronal homeostasis by analyzing exosomes from various sources for their ability to seed AS aggregation and propagate neurodegeneration *in vivo* and *in vitro*. *We have also identified proteases on EVs that actively degrade extracellular AS, positioning them as promising therapeutic candidates.* Similar to prion protein (PrP) aggregation, fibrillar AS assemblies template the aggregation of endogenous AS, facilitating pathological spread *in vivo*. We have provided *in vivo* evidence that AS phosphorylation modulates its brain localization and species distribution, influencing its propagation. Ongoing work focuses on characterizing the structural properties of pathological AS responsible for cell-to-cell transmission.

6. Pampalakis G, Sykioti VS, Ximerakis M, Stefanakou-Kalakou I, Melki R, **Vekrellis K**, Sotiropoulou G. KLK6 proteolysis is implicated in the turnover and uptake of extracellular alpha-synuclein species. Oncotarget. 2017.
7. Melachroinou K, Divolis G, Tsafaras G, Karampetsou M, Fortis S, Kriebardis AG, Samiotaki M, **Vekrellis K.** Endogenous Alpha-Synuclein is Essential for the Transfer of Pathology by Exosome-Enriched Extracellular Vesicles, Following Inoculation with Preformed Fibrils in vivo. Aging Dis. 2023 A doi: 10.14336/AD.2023.0614.6.
8. Pantazopoulou M, Lamprokostopoulou A, Karampela DS, Alexaki A, Delis A, Coens A, Samiotaki M, Kriebardis AG, Melki R, **Vekrellis K.** Differential intracellular trafficking of extracellular vesicles in microglia and astrocytes. Cell Mol Life Sci. 2023.
9. Sandau US, Magaña SM, Costa J, Nolan JP, Ikezu T, Vella LJ, Jackson HK, Moreira LR, Palacio PL, Hill AF, Quinn JF, Van Keuren-Jensen KR, McFarland TJ, Palade J, Sribnick EA, Su H, **Vekrellis K**, Falcón-Perez JM, Nieuwland R, Saugstad JA; International Society for Extracellular Vesicles Cerebrospinal Fluid Task Force. Recommendations for reproducibility of cerebrospinal fluid extracellular vesicle studies. J Extracell Vesicles. 2024, 3(1): e12397.
10. Papadopoulos VE, Nikolopoulou G, Antoniadou I, Emmanouilidou E, Sardi SP, Stefanis L, **Vekrellis K.** Modulation of β-glucocerebrosidase increases α-synuclein secretion and exosome release in mouse models of Parkinson's disease. Hum Mol Genet. 2018;27(10):1696-1710
11. Karampetsou M, Sykioti VS, Leandrou E, Melachroinou K, Lambiris A, Giannelos A, Emmanouilidou E, **Vekrellis K.** Intrastriatal Administration of Exosome- Associated Pathological Alpha-Synuclein Is Not Sufficient by Itself to Cause Pathology Transmission. Front Neurosci. 2020.
12. Pediaditakis I, Kodella KR, Manatakis DV, Le CY, Hinojosa CD, Tien-Street W, Manolakos ES, **Vekrellis K**, Hamilton GA, Ewart L, Rubin LL, Karalis K. Modeling alpha-synuclein pathology in a human brain-chip to assess blood-brain barrier disruptionNat Commun. 2021 Oct 8;12(1):5907

F. **Patents:** Invention Disclosure: Vekrellis K OBI application number 200601000538, Greece. generation of an inducible human neuroblastoma cell line expressing various forms of alpha-synuclein as a model for Parkinson's disease.

Biogen-Idec, USA (2159 356PC01 PCT Application) use of an anti-α-synuclein antibody to diagnose an elevated level of α-synuclein in the brain.

Full list of bibliographic references:
https://pubmed.ncbi.nlm.nih.gov/?term=Vekrellis+K&cauthor_id=22014436