OMB No. 3145-0279 (Expiration Date 10/31/2026)

NIH BIOGRAPHICAL SKETCH COMMON FORM

Name: Okun, Eitan

Persistent Identifier (PID) of the Senior/Key Person: https://orcid.org/0000-0001-8474-1487

Position Title: Head, the Paul Feder laboratory for Alzheimer disease research

Organization and Location: Bar ilan univeristy, Ramat Gan, Not Applicable, N/A, Israel

PROFESSIONAL PREPARATION

INSTITUTION AND LOCATION	DEGREE	Start Date	Completion Date	FIELD OF STUDY
National Institute on Aging, NIH, Baltimore, Maryland, United States	Postdoctoral Fellow	10/2007	10/2011	Neuroimmunology
Bar ilan univeristy, Ramat gan, Not Applicable, N/A, Israel	Doctor of Philosophy (PHD)	10/2004	10/2007	Immunology
Bar ilan univeristy, Ramat gan, Not Applicable, N/A, Israel	Master of Science (MS)	10/2003	10/2004	Immunology
Bar ilan univeristy, Ramat gan, Not Applicable, N/A, Israel	Bachelor of Science (BS)	10/2001	10/2003	Biology

Appointments and Positions

2012 - present	Head, the Paul Feder laboratory for Alzheimer disease research, Bar ilan univeristy, Ramat Gan, Not Applicable, N/A, Israel
2023 - present	Vice Dean for Research Resources Development , Mina and Everard Goodman Faculty of Life Sciences, Bar ilan university , Ramat Gan, Not Applicable, N/A, Israel
2020 - present	Full professor, Bar ilan univeristy, Ramat Gan, Not Applicable, N/A, Israel
2020 - present	Chair of the committee, Vivarium committee , Ramat Gan, Not Applicable, N/A, Israel
2020 - 2022	Committee member, Academic Staff Committee, Bar ilan university , Ramat Gan, Not Applicable, N/A, Israel
2016 - 2020	Associate professor, Bar Ilan University, Ramat Gan, Not Applicable, N/A, Israel
2013 - 2020	Committee member, Vivarium committee , Ramat Gan, Not Applicable, N/A, Israel
2012 - 2016	Senior Lecturer , Bar Ilan University, Ramat Gan, Not Applicable, N/A, Israel

Products

Products Closely Related to the Proposed Project

1. Illouz T, Madar R, Clague C, Griffioen KJ, Louzoun Y, Okun E. Unbiased classification of spatial strategies in the Barnes maze. Bioinformatics. 2016 Nov 1;32(21):3314-3320. PubMed PMID: 27378295.
2. Illouz T, Ascher LAB, Madar R, Okun E. Unbiased analysis of spatial learning strategies in a modified Barnes maze using convolutional neural networks. Sci Rep. 2024 Jul 10;14(1):15944. PubMed Central PMCID: PMC11237060.
3. Illouz T, Madar R, Okun E. A modified Barnes maze for an accurate assessment of spatial learning in mice. J Neurosci Methods. 2020 Mar 15;334:108579. PubMed PMID: 31926999.
4. Illouz T, Madar R, Louzoun Y, Griffioen KJ, Okun E. Unraveling cognitive traits using the Morris water maze unbiased strategy classification (MUST-C) algorithm. Brain Behav Immun. 2016 Feb;52:132-144. PubMed PMID: 26522398.

Other Significant Products Highlighting Contributions to Science

1. Ben-Zeev T, Hirsh T, Weiss I, Gornstein M, Okun E. The Effects of High-intensity Functional Training (HIFT) on Spatial Learning, Visual Pattern Separation and Attention Span in Adolescents. Front Behav Neurosci. 2020;14:577390. PubMed Central PMCID: PMC7521200.
2. Ben-Zeev T, Weiss I, Ashri S, Heled Y, Ketko I, Yanovich R, Okun E. Mild Physical Activity Does Not Improve Spatial Learning in a Virtual Environment. Front Behav Neurosci. 2020;14:584052. PubMed Central PMCID: PMC7705229.
3. Betzer O, Shilo M, Opochinsky R, Barnoy E, Motiei M, Okun E, Yadid G, Popovtzer R. The effect of nanoparticle size on the

ability to cross the blood-brain barrier: an in vivo study. Nanomedicine (Lond). 2017 Jul;12(13):1533-1546. PubMed PMID: 28621578.

4. Illouz T, Madar R, Griffioen K, Okun E. A protocol for quantitative analysis of murine and human amyloid-β(1-40) and (1-42). J Neurosci Methods. 2017 Nov 1;291:28-35. PubMed PMID: 28768163.

Certification:

I certify that the information provided is current, accurate, and complete. This includes but is not limited to information related to domestic and foreign appointments and positions.

I also certify that, at the time of submission, I am not a party to a malign foreign talent recruitment program.

Misrepresentations and/or omissions may be subject to prosecution and liability pursuant to, but not limited to, 18 U.S.C. §§ 287, 1001, 1031 and 31 U.S.C. §§ 3729-3733 and 3802.

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NIH BIOGRAPHICAL SKETCH SUPPLEMENT

Name: Okun, Eitan

Persistent Identifier (PID) of the Senior/Key Person: https://orcid.org/0000-0001-8474-1487

Position Title: Head, the Paul Feder laboratory for Alzheimer disease research

Organization and Location: Bar ilan univeristy, Ramat Gan, Not Applicable, N/A, Israel

Personal Statement

I am a neuroimmunologist with training in immunology and extensive experience in both basic and translational neuroscience. I completed my postdoctoral training at the National Institute on Aging (NIH), where I specialized in neuroimmunology, building on my doctoral training in immunology at Bar-Ilan University. My research program integrates adaptive immunity, aging biology, and neurodegeneration, positioning me well to lead projects focused on immune mechanisms that drive cognitive decline.

My laboratory investigates how immunity contributes to Alzheimer's disease (AD) and Down syndrome (DS) associated neuropathology. We combine immunological, cell sorting, RNA-seq, advanced imaging, molecular, and behavioral approaches in transgenic mouse models to define how immunity, brain pathology, biological sex, pregnancy, and meningeal immune niches influence disease progression. In parallel, we are developing immune-targeted and DNA vaccine-based strategies designed to delay or prevent cognitive decline, translating mechanistic insight into therapeutic innovation.

My team has advanced work on adaptive immune signatures in AD and DS, immune-brain interactions in aging, and mechanisms of fetomaternal communication and microchimerism that may shape long-term maternal brain health following pregnancies with a DS fetus. These studies integrate immunology, neurobiology, endocrinology, microchimerism, and maternal-fetal biology, supported by strong diverse international interdisciplinary collaborations and a research environment that fosters both mechanistic discovery and translational application.

As Principal Investigator and Vice Dean for Research Resources Development, I have extensive experience leading multidisciplinary teams, securing competitive funding, mentoring trainees, and building international collaborative research infrastructures. My scientific background, leadership experience, and ongoing work on adaptive immunity in neurodegeneration uniquely position me for success.

Honors

2011	Fellows Award for Research Excellence (FARE) Award, National Institute of Health (NIH)
2011	Young Researchers Award , European Society for Neurochemistry (ESN) / Israeli Society for Neurochemistry (ISN) societies

Contributions to Science

1. Dural ectopic lymphatic structures accumulate during aging and exhibit dysregulation in neurodegenerative diseases.

   Fruitman Davidi A, Shirenova S, Michaelovich D, Benedetti G, Shtrasberg H, Shoval I, Hauschner H, Oz G, Vardy K, Hirsh T, Madar R, Stern E.A, Rosenmann H, Biragyn A and Okun E, 2025

   The meninges serve as a critical interface between the peripheral immune system and the central nervous system, playing a crucial role in maintaining parenchymal homeostasis. Neurodegenerative disorders, such as amyloidosis and tauopathies, are marked by the accumulation of extracellular neurotoxic amyloid-β (Aβ) plaques and intracellular tau tangles, respectively, leading to neuronal cell death and cognitive decline. The role of the adaptive immune response in these pathologies remains under debate. Adaptive immune cells can manifest as ectopic lymphoid structures (ELS), which resemble secondary lymphoid organs, and form at sites of inflammation or pathology. While ELSs can support immune responses against infections or tumors, they may also have detrimental effects in certain pathological conditions. To explore whether meningeal ELS are implicated in aging and neurodegeneration, we analyzed the meninges of aged wild-type mice and mouse models of early-onset Alzheimer's disease, tauopathy, and Down syndrome-related neurodegenerative disorders. Our findings suggest that the accumulation of dural ELS varies according to age, brain pathology, and sex. Meningeal myeloid cells may contribute to the

initiation and maintenance of ELS during aging. These results demonstrate the potential contribution of meningeal ELS to healthy aging and neurodegenerative conditions, offering directions for future research.

2. CD8+ T cells exacerbate AD-like symptoms in mouse model of amyloidosis.

   Wang X, Campbell B, Bodogai M, McDevitt RA, Patrikeev A, Gusev F, Ragonnaud E, Kumaraswami KD, Shirenova S, Vardy K, Alameh MG, Weissman D, Ishikawa-Ankerhold H, Okun E, Rogaev E, Biragyn A. , 2024

   Alzheimer's disease (AD) is linked to toxic Aβ plaques in the brain and activation of innate responses. Recent findings however suggest that the disease may also depend on the adaptive immunity, as B cells exacerbate and CD8+ T cells limit AD-like pathology in mouse models of amyloidosis. Here, by artificially blocking or augmenting CD8+ T cells in the brain of 5xFAD mice, we provide evidence that AD-like pathology is promoted by pathogenic, proinflammatory cytokines and exhaustion markers expressing CXCR6+ CD39+CD73+/- CD8+ TRMlike cells. The CD8+ T cells appear to act by targeting disease associated microglia (DAM), as we find them in tight complexes with microglia around Aβ plaques in the brain of mice and humans with AD. We also report that these CD8+ T cells are induced by B cells in the periphery, further underscoring the pathogenic importance of the adaptive immunity in AD. We propose that CD8+ T cells and B cells should be considered as therapeutic targets for control of AD, as their ablation at the onset of AD is sufficient to decrease CD8+ T cells in the brain and block the amyloidosis-linked neurodegeneration.

3. HCAR1-Mediated l-Lactate Signaling Suppresses Microglial Phagocytosis.

   Nicola R, Madar R and Okun E, 2022

   Microglia, the primary brain-resident immune cells, protect the brain from various harmful pathogens, insulting and maintaining its homeostasis by phagocytosing extracellular particles. How microglia are metabolically regulated by their microenvironment remains largely elusive. Here, we investigated how extracellular lactate, which is abundant in the brain and dynamically changes in pathological states, affects microglial phagocytotic ability. We show that l-lactate reduces microglia phagocytic capacity in a Hydroxycarboxylic Acid Receptor 1 but not Monocarboxylate transporter 1-dependent manner. Our findings point to a potential role for extracellular lactate in suppressing the phagocytic activity of microglial cells in homeostasis and inflammatory conditions.

4. Early diagnosis and treatment of Alzheimer's disease by targeting toxic soluble Aβ oligomers.

   Habashi M, Vutla S, Tripathi K, Senapati S, Chauhan PS, Haviv-Chesner A, Richman M, Mohand SA, Dumulon-Perreault V, Mulamreddy R, Okun E, Chill JH, Guérin B, Lubell WD, Rahimipour S. , 2022

   Transient soluble oligomers of amyloid-β (Aβ) are toxic and accumulate early prior to insoluble plaque formation and cognitive impairment in Alzheimer's disease (AD).Synthetic cyclic D,L-α-peptides self-assemble into cross β-sheet nanotubes, react with early Aβ species, and inhibit Aβ aggregation and toxicity in stoichiometric concentrations, in vitro. Employing a semicarbazide as an aza-glycine residue with an extra hydrogen-bond donor to tune nanotube assembly and amyloid engagement,[azaGly]-1 inhibited Aβ aggregation and toxicity at substoichiometric concentrations. High-resolution NMR studies revealed dynamic interactions between [azaGly]-1 and Aβ42 residues F19 and F20, which are pivotal for early dimerization and aggregation. In an AD mouse model, brain positron emission tomography (PET) imaging using stable Cu-labeled (aza)peptide tracers gave unprecedented early amyloid detection in 44-d pre-symptomatic animals. No tracer accumulation was detected in the cortex and hippocampus of 44-d-old 5xFAD mice; instead, intense PET signal was observed in the thalamus, from where Aβ oligomers may spread to other brain parts with disease progression. Compared with standard C-labeled Pittsburgh compound-B (C-PIB),which binds specifically fibrillar Aβ plaques, Cu-labeled (aza)peptide gave superior contrast and uptake in young mouse brain correlating with Aβ oligomer levels. Effectively crossing the blood–brain barrier (BBB), peptide 1 and [azaGly]-1 reduced Aβ oligomer levels, prolonged lifespan of AD transgenic Caenorhabditis elegans, and abated memory and behavioral deficits in nematode and murine AD models. Cyclic (aza)peptides offer novel promise for early AD diagnosis and therapy.

5. Maternal antibodies facilitate Amyloid-β clearance by activating Fc-receptor-Syk-mediated phagocytosis.

   Illouz T, Nicola R, Ben-Shuhan L, Madar R, Biragyn R and Okun E, 2021

   Maternal antibodies (MAbs) protect against infections in immunologically-immature neonates. Maternally transferred immunity may also be harnessed to target diseases associated with endogenous protein misfolding and aggregation, such as Alzheimer's disease(AD) and AD-pathology in Down syndrome (DS). While familial early-onset AD (fEOAD) is associated with autosomal dominant mutations in the APP, PSEN1,2 genes, promoting cere-bral Amyloid-β (Aβ) deposition, DS features

a life-long over expression of the APP andDYRK1A genes, leading to a cognitive decline mediated by Aβ overproduction and tau hyper-phosphorylation. Although no prenatal screening for fEOAD-related mutations is in clinical practice, DS can be diagnosed in utero. We hypothesized that anti-Aβ MAbs might promote the removal of early Aβ accumulation in the central nervous system of human APP-expressing mice. To this end, a DNA-vaccine expressing Aβ1-11 was delivered to wild-type female mice, followed by mating with 5xFAD males, which exhibit early Aβ plaque formation. MAbs reduce the offspring's cortical Aβ levels 4 months after antibodies were undetectable, along with alleviating short-term memory deficits. MAbs elicit a long-term shift in microglial phenotype in a mechanism involving activation of the FcγR1/Syk/Cofilin pathway. These data suggest that maternal immunization can alleviate cognitive decline mediated by early Aβdeposition, as occurs in EOAD and DS.

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