BIOGRAPHICAL SKETCH

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NAME: Nedergaard, Maiken

eRA COMMONS USER NAME (credential, e.g., agency login): mnedergaard

POSITION TITLE: Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Copenhagen	M.D.	1983	Medicine
University of Copenhagen	Ph.D.	1989	Neuroscience

A. Personal statement

The objective of my work is to understand the biological functions of astrocytes, their ability to interact with other cell types, and to use this knowledge to develop novel therapeutic strategies to treat, or perhaps cure, a variety of neurological diseases. In vivo explorations have radically challenged the classical dogma – that neurons are the sole substrate of higher brain function – and have led to a shift in paradigm by including astrocytes and other glial cells in higher cognitive functions. No current medications used in clinical medicine target glial cells – the most numerous cells in CNS. The premise for my work is that understanding the basic functions of glial cells offers extraordinary opportunities for combatting disease. We have identified a fundamentally novel pathway for interstitial solute clearance from the brain, consisting of a para-arterial cerebrospinal fluid (CSF) influx path and a para-venous interstitial fluid (ISF) clearance route, which are coupled through convective interstitial bulk flow supported by astrocytic AQP4 water channels. We designated it “the glymphatic system” based on its adoption of functions analogous to the peripheral lymphatic system and the dependence of CSF/ISF fluxes on astroglial AQP4. This brain- wide pathway acts as a unit to serve as the waste disposal system of large solutes and proteins, such as □-amyloid and tau, from CNS. We found that glymphatic activity is almost absent during wakefulness and proposed that the biological function of sleep is to clear the brain of the metabolic waste products of neural activity that accumulate during wakefulness. Also, the activity of the glymphatic system is reduced in old mice and more so in murine models of Alzheimer disease. One major obstacle slows advances in the field: the driving force responsible for CSF transport and its dependence on brain state remains to be defined. Not knowing what drives brain fluid transport constitutes a major bottleneck for progress. Data collected across multiple labs, combined with creation of fluid dynamic models that include all the complex factors that affect glymphatic transports, have not been developed. To address these issues, I am very excited to join forces with Drs. Kelley Karniadakis, and Thomas. Lack of methodology for studying brain fluid flow is the major barrier that impede development of fluid dynamics models.

1. Xie L, Kang H, Xu Q, Chen MJ, Liao Y, Thiyagarajan M, … Nedergaard M. (2013) Sleep Drives Metabolite Clearance from the Adult Brain. ***Science*** 342:373-7. PMC3880190
2. Nedergaard M. (2013) Garbage truck of the brain. ***Science*** 340:1529-30. PMC3749839
3. Rasmussen, M.K., Mestre, H., and Nedergaard, M**.** (2021). Fluid Transport in the Brain. ***Physiol. Rev.*** *[Online ahead of print]* PMID33949874
4. Nedergaard, M. and Goldman, S.A. (2020). Glymphatic failure as a final common pathway to dementia. ***Science*** *370*, 50-56. PMC8186542

Ongoing and recently completed projects that I would like to highlight include:

R01 AT011439
8/1/2021-5/31/2026
PI: Nedergaard
The glymphatic system at the crossroad of integrative health approaches in chronic pain

RF1 NS110049
PI: Nedergaard, Stevens, Lewis, Brunet, Sahay
9/15/2018-5/31/2023
Capillary hyperemia in white matter: Novel mechanistic insight and effect of hypertension and aging

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2014-present	Co-director, Center for Translational Neuromedicine, University of Copenhagen
2012-present	Elected member of Academia Europaea
2012-2016	Frank P. Smith Professor, University of Rochester, Rochester NY
2011-present	Elected member of the Royal Academy of Pharmacy of Spain
2008-present	Elected member of the *Royal Danish* Academy of *Sciences* and Letters
2007-present	Co-Director, Center for Translational Neuromedicine, Univ. of Rochester, Rochester, NY
2007-2012	Dean's Professor, University of Rochester, Rochester, NY
2003-present	Professor, Dept. of Neurology & Neurosurgery, University of Rochester, Rochester, NY
1994-2003	Professor of Cell Biology and Anatomy and Neurosurgery, New York Medical College
1993-1994	Associate Professor of Neurosurgery, Cornell University Medical College
1987-1993	Visiting follow, Assistant Professor, Dept. of Neurology, Cornell University Medical College
1984-1987	Fellow, Depts. of Physiology and Neuropathology, University of Copenhagen
1983-1984	Resident, Dept. of Neurology & Neurosurgery, Rigshospitalet, Copenhagen

Honors

2020	International Prize of Translational Neuroscience, Max Planck Society
2020	Thomas Willis Award, American Stroke Association
2018	Fernstrom Medical Prize, Lund University, Sweden
2015	Alzheimer Prize
2015	Newcomb Cleveland Prize, AAAS

C. Contributions to Science

I. Neuroglia signaling

It was a surprise to most when we and other groups showed that astrocytes can transmit Ca^{2+} signals to neurons, because astrocytes traditionally were regarded as the brain's housekeeping cells. Later studies from several labs, including ours, extended this observation by documenting that astrocytes can regulate the activity of hippocampal neurons. These discoveries laid the foundation for a new line of work – the field of neuro-glia signaling – that has its own journal, *Gordon Conference*, and is included as a section in most neuroscience textbooks. Emerging evidence from many lines of work now place astrocytes at the center stage of complex processes, such as sleep, working memory and epilepsy, that just a decade ago were regarded as purely neuronal. Using 2-photon in vivo imaging, among other modalities, we showed that astrocytes in awake mice are activated in response to sensory stimulation, mediate functional hyperemia, are highly responsive to norepinephrine, and that astrocytes differ in the adult brain from those in the developing brain with regard to responses to glutamate.

a. Nedergaard M. (1994) Direct signaling from astrocytes to neurons in cultures of mammalian brain cells. ***Science*** 263:1768-1771. PMID8134839
b. Kang J, Jiang L, Goldman SA, Nedergaard M. (1998) Astrocyte-mediated potentiation of inhibitory synaptic transmission. ***Nat. Neurosci*** 1:683-692. PMID10196584
c. Takano T, Tian GF, Peng W, Lou N, Libionka W, Han X, Nedergaard M. (2006) Astrocyte-mediated control of cerebral blood flow. ***Nat. Neurosci*** 9:260-267. PMID16388306
d. Sun W, McConnell E, Pare JF, Xu Q, Chen M, Lovatt D, … Nedergaard M. (2013) Glutamate-dependent neuroglial calcium signaling differs between young and adult brain. ***Science*** 339:197-200. PMC3569008

II. Evolutionary aspects of astrocytes

Defining what is unique about the human brain has always been central to the study of higher cognitive brain function. Since the proportional representation, size, complexity, and diversity of astrocytes have expanded during evolution, one of the hypotheses underlying my work is that astrocytes in the hominoid brain, in addition to their well-described housekeeping functions, also participate in more complex neural functions than in other species. In collaboration with Steve Goldman, we engrafted neonatal mice with human glia progenitors and demonstrated that a large proportion differentiated into mature protoplasmic astrocytes that maintained their size and complexity. The humanized chimeric mice were faster learners, demonstrating that human astrocytes can enhance the cognitive performance of mice in the absence of human neurons. Humanized chimeric mice offer great promise to the exploration of the role of astrocytes in several complex psychiatric diseases by implantation of glia progenitor cells, generated from IPS cells harvested from patients suffering from for example schizophrenia.

a. Oberheim NA, Wang X, Goldman SA, Nedergaard M. (2006) Astrocytic complexity distinguishes the human brain. ***Trends Neurosci*** 29:547-53. PMID16938356
b. Oberheim N, Takano T, Han X, He W, Lin J, Wang F, …Nedergaard M. (2009) Uniquely hominid features of adult human astrocytes. ***J. Neuroscience*** 29:3276-3287. PMC2819812
c. Han X, Chen M, Wang F, Windrem M, Wang S, Shanz S. … Nedergaard M. (2013) Forebrain Engraftment by Human Glial Progenitor Cells Enhances Synaptic Plasticity and Learning in Adult Mice. ***Cell Stem Cell*** 12:342-53. PMC3700554
d. Windrem MS, Osipovitch M, Liu Z, Bates J, Chandler-Militello D, Zou L, … Nedergaard M, Goldman, SA (2017). Human iPSC Glial Mouse Chimeras Reveal Glial Contributions to Schizophrenia. ***Cell Stem Cell*** *21*:195-208. PMC5576346

III. The Glymphatic System

Lymphatic circulation is essential in peripheral tissue and organs for the removal of metabolic waste products; but the brain, in spite of having the highest metabolic activity of all tissues, is uniquely devoid of a conventional lymphatic system. We identified a fundamentally novel pathway for interstitial solute clearance from the brain consisting of a para-arterial cerebrospinal fluid (CSF) influx path and a para-venous interstitial fluid (ISF) clearance route, which are coupled through convective interstitial bulk flow supported by astrocytic AQP4 water channels. We designated it “the glymphatic system” based on its adoption of functions analogous to the peripheral lymphatic system and the dependence of CSF/ISF fluxes on astroglial AQP4. This brain wide pathway acts as a unit to serve as the waste disposal system of large solutes and proteins, such as β-amyloid and tau, from CNS. In collaboration with Dr. Helene Benveniste, we have expanded the analysis to imaging of the glymphatic system using MRI/PET. We have also shown that normal aging, or traumatic brain injury, is linked to a dramatic suppression of glymphatic clearance of β-amyloid and tau, possibly explaining why these conditions are linked to neurodegenerative diseases. Finally, we showed that glymphatic activity is strongly suppressed during wakefulness. We propose that one of the biological functions of sleep is to clear the brain of the metabolic waste products of neural activity that accumulate during wakefulness.

a. Kress BT, Iliff JJ, Xia M, Wang M, Wei H, Zeppenfeld D, … Nedergaard M. (2014) Impairment of paravascular clearance pathways in the aging brain. ***Ann Neurol.*** 76:845-61. PMC4245362
b. Hablitz LM, Vinitsky HS, Sun Q, Staeger FF, Sigurdsson B, Mortensen KN, … Nedergaard, M. (2019). Increased glymphatic influx is correlated with high EEG delta power and low heart rate in mice under anesthesia. Sci Adv *5:*eaav5447. PMC6392807
c. Hablitz LM, Pla V, Giannetto M, Vinitsky HS, Staeger FF, Metcalfe T, … Nedergaard, M. (2020). Circadian control of brain glymphatic and lymphatic fluid flow. ***Nat Commun.*** *11:*4411. PMC7468152
d. Mestre H, Du T, Sweeney AM, Liu G, Samson AJ, Peng W, … Nedergaard M. (2020). Cerebrospinal fluid influx drives acute ischemic tissue swelling. ***Science*** *367:eaax7171*. PMC7375109

IV. Neurological diseases as primary gliopathies: a reassessment of neurocentrism

Since almost all symptoms of neurological diseases reflect neuronal dysfunction, it is not surprising that our understanding of the contribution of astrocytes to most diseases is poorly developed. We use several models of CNS diseases, in combination with physiological measurements, transcriptome analysis, and diverse manipulations, to better define the role of astrocytes in disease pathogenesis. The aim of this work is to define new targets for medical interventions.

a. Wang X, Arcuino G, Takano T, Lin J, Peng WG, Wan P, … Nedergaard M. (2004) P2X7 receptor inhibition improves recovery after spinal cord injury. ***Nat. Med*** 10:821-7. PMID15258577
b. Tian GF, Azmi H, Takano T, Xu Q, Peng W, Lin J, … Nedergaard M. (2005) An astrocytic basis of epilepsy. ***Nat. Med*** 11:973-981. PMC1850946
c. Ballabh P, Xu H, Braun A, Smith K, Rivera A, Lou N, Ungvari Z, … Nedergaard M. (2007) Angiogenic inhibition reduces germinal matrix hemorrhage. ***Nat. Med*** 13:477-85. PMID17401377
d. Bekar L, Libionka W, Tian GF, Xu Q, Torres A, Wang X, … Nedergaard M. (2008) Adenosine is crucial for deep brain stimulation-mediated attenuation of tremor. ***Nat. Med*** 14:75-80. PMID18157140

V. Developing and/or improving 2-photon imaging and rodent model of disease

An integral part of my work is improving our experimental approaches. Ongoing development includes expansion of the capacities of 2-photon imaging (e.g. depth, speed, spatial resolution, 3rd order harmonic), use of new fluorescent tracers (near infrared), and combination of 2-photon imaging with other optical techniques (e.g. bioluminescence, intrinsic optical signal detection, photolysis, optogenetics). My efforts are also continuously devoted to developing more relevant rodent models of CNS diseases, including: (1) lacunar strokes, which are epidemic among the older populations: in ages between 60–70 years, about 87% have subcortical white matter lesions, (2) traumatic brain injury not confounded by anaesthesia, surgery, or fixation of the skull, and (3) the first experimental model of ammonia toxicity – a common complication of inborn metabolic disorders – that is not complicated by hepatic failure.

a. Thrane RV, Thrane AS, Wang F, Cotrina ML, Smith NA, Chen M, … Nedergaard M. (2013) Ammonia triggers neuronal disinhibition and seizures by impairing astrocyte potassium buffering. ***Nat. Med*** 19:1643-8. PMC3899396
b. Plog BA, Dashnaw ML, Hitomi E, Peng W, Liao Y, Lou N, … Nedergaard M. (2015) Biomarkers of traumatic injury are transported from brain to blood via the glymphatic system. ***J Neurosci.***14:518-26. PMC4293408
c. Lundgaard I, Li B, Xie L, Kang H, Sanggaard S, Haswell JDR, … Nedergaard M. (2015) Direct neuronal glucose uptake heralds activity-dependent increases in cerebral metabolism ***Nat Commun***. *6:6807.* PMC4410436
d. Wang X, Lou N, Eberhardt A, Yang Y, Kusk P, Xu Q, ... Nedergaard M. (2020). An ocular glymphatic clearance system removes beta-amyloid from the rodent eye. ***Sci Transl Med.*** *12*:536. PMC7356596

Complete List of Published Work in MyBibliography: Cited >68,700 times, H-factor 139, Google Scholar 2022

http://www.ncbi.nlm.nih.gov/sites/myncbi/maiken.nedergaard.1/bibliograpahy/41151089/public/?sort=date&direction=ascending