BIOGRAPHICAL SKETCH

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 combating disease. We have recently 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 beta-amyloid and tau, from CNS.

We found that glymphatic activity is strongly suppressed 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. I am particularly excited about Dr. Hablitz’ work on the circadian regulation of the glymphatic system and believe her studies will provide a long needed bridge between the circadian regulation of sleep with the basic biological need to sleep. I will provide Dr. Hablitz all possible support to pursue the project while working in my lab and look forward to working with her once she establishes her own independent lab.

a) Iliff JJ, Wang M, Liao Y, Plogg BA, Peng W, Gunderson GA, Benveniste H, Vates GE, Deane R, Goldman SA, Nagelhus EA, Nedergaard M. (2012) A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β. ***Sci Transl Med*** 4:147ra111. PMC3551275
b) Xie L, Kang H, Xu Q, Chen MJ, Liao Y, Thiyagarajan M, O’Donnell J, Christensen DJ, Nicholson C, Iliff JJ, Takano T, Deane R, Nedergaard M. (2013) Sleep Drives Metabolite Clearance from the Adult Brain. ***Science*** 342(6156):373-7. PMC3880190
c) Wang M, Ding F, Deng S, Guo X, Wang W, Iliff JJ, Nedergaard M. Focal Solute Trapping and Global Glymphatic Pathway Impairment in a Murine Model of Multiple Microinfarcts. **J Neurosci.** 2017 37(11):2870-2877. PMC5354332
d) Lundgaard I, Wang W, Eberhardt A, Vinitsky HS, Reeves BC, Peng S, Lou N, Hussain R, Nedergaard M Beneficial effects of low alcohol exposure, but adverse effects of high alcohol intake on glymphatic function. **Sci Rep**. 2018 8(1):2246. PMC5797082

B. Positions and Honors

1983-1984 Resident, Dept. of Neurology & Neurosurgery, Rigshospitalet, Copenhagen
1984-1987 Fellow, Depts. of Physiology and Neuropathology, University of Copenhagen
1987-1993 Researcher, Dept. of Neurology, Cornell University Medical College
1993-1994 Associate Professor of Neurosurgery, Cornell University Medical College

1994-2003	Professor of Cell Biology and Anatomy and Neurosurgery, New York Medical College
2003-Present	Professor, Dept. of Neurosurgery, University of Rochester, Rochester, NY
2007-2012	Dean's Professor, University of Rochester, Rochester, NY
2007-present	Co-Director, Center for Translational Neuromedicine, Univ. of Rochester, Rochester, NY
2008-present	Elected member of the Royal Danish Academy of Sciences and Letters
2011-present	Elected member of the Royal Academy of Pharmacy of Spain
2012-2016	Frank P. Smith Professor, University of Rochester, Rochester NY
2012-present	Elected member of Academia Europaea
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. ***Nature 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, Han X, Smith Y, 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 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, 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 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, Xu Q, Wyatt J, Pilcher W, Ojemann JG, Ransom BR, Goldman SA, Nedergaard M. (2009) Uniquely hominid features of adult human astrocytes. ***J. Neuroscience*** 29:3276-3287. PMC2819812
c) Oberheim NA, Goldman SA, Nedergaard M. (2012) Heterogeneity of astrocytic form and function. ***Methods Mol Biol*** 814:23-45. PMC3506190
d) Han X, Chen M, Wang F, Windrem M, Wang S, Schanz S, Xu Q, Oberheim NA, Bekar L, Betstadt S, Silva AJ, Takano T, Goldman SA, Nedergaard M. (2013) Forebrain Engraftment by Human Glial Progenitor Cells Enhances Synaptic Plasticity and Learning in Adult Mice. ***Cell Stem Cell*** 12(3):342-53. PMC3700554

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) Nedergaard, M. (2013) Neuroscience. Garbage Truck of the Brain. ***Science*** 340(6140):1529-30. PMC3749839
b) Kress BT, Iliff JJ, Xia M, Wang M, Wei H, Zeppenfeld D, Xie L, Kang H, Xu Q, Liew J, Plog BA, Ding F, Deane R, Nedergaard M. (2014) Impairment of paravascular clearance pathways in the aging brain. ***Ann Neurol***. 76(6):845-61. PMC4245362
c) Iliff JJ, Chen MJ, Plog BA, Zeppenfeld DM, Soltero M, Yang L, Singh I, Deane R, Nedergaard M. (2014) Impairment of glymphatic pathway function promotes tau pathology after traumatic brain injury. ***J Neurosci***. 34(49):16180-93. PMC4252540
d) Iliff JJ, Lee H, Yu M, Feng T, Logan J, Nedergaard M, Benveniste H. (2013) Brain-wide pathway for waste clearance captured by contrast-enhanced MRI. ***J Clin Invest*** 123(3):1299-309. PMC3582150

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 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, Li P, Xu Q, Liu QS, Goldman SA, 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, Oberheim N, Lou N, Zielke HR, Kang 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, Goldman SA, Csiszar A, 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, Lovatt D, Williams E, Takano T, Schnermann J, Bakos R, Nedergaard M. (2007) 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) Wang M, Iliff J, Liao Y, Chen MJ, Shinseki M, Venkataraman V, Nedergaard M. (2012) Cognitive deficits and delayed neuronal loss in a mouse model of multiple microinfarcts. ***J. Neurosci*** 32:17948-60. PMC3541041
b) Rangroo Thrane V, Thrane AS, Wang F, Cotrina ML, Smith NA, Chen M, Xu Q, Kang N, Fujita T, Nagelhus EA, Nedergaard M. (2013) Ammonia triggers neuronal disinhibition and seizures by impairing astrocyte potassium buffering. ***Nature Med*** 19(12):1643-8. PMC3899396
c) Plog BA, Dashnaw ML, Hitomi E, Peng W, Liao Y, Lou N, Deane R, Nedergaard M. (2015) Biomarkers of traumatic injury are transported from brain to blood via the glymphatic system. ***J Neurosci***.14:518-26. PMC4293408
d) Lundgaard I, Li B, Xie L, Kang H, Sanggaard S, Haswell JDR, Sun W, Goldman S, Blekot S, Nielsen M, Takano T, Deane R, Nedergaard M. (2015) Direct neuronal glucose uptake heralds activity-dependent increases in cerebral metabolism ***Nat Commun***. *6:6807.* PMC4410436

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/maiken.nedergaard.1/bibliograpahy/41151089/public/?sort=date&direction=ascending

D. Current Research Support

University of Rochester

Stein Innovation Award (Nedergaard) 1/1/18-12/31/20
Research to Prevent Blindness Role: PI
The goal of this project is to definitively establish the existence of a hitherto undescribed ocular fluid transport system, to assess the nature and casual role of its dysfunction in glaucoma, and to use the biological insight provided in that effort to identify venues for therapeutic intervention.

Adelson Medical Research Foundation (Nedergaard) 10/1/17-9/30/19
Repairing the injured nervous system by harnessing glymphatic clearance Role: PI
This project will enable the first systematic evaluation of the glymphatic system as a potential therapeutic target in repair and functional recovery after TBI.

RF1AG057575 (Nedergaard) 9/15/17-6/30/22
NIH Role: PI
Age and AD related bottlenecks in glymphatic-lymphatic waste transport
The goal of this project is to create a complete map of the glymphatic-lymphatic connections in young, middle aged, and old wildtype and APP/PS1 mice to identify age and AD related bottlenecks in the clearance of amyloid-β and tau.

RF1AG053991 (Benveniste, Nedergaard) 8/1/16-6/30/21
NIH Role: Co-PI
Characterizing the glymphatic peri-vascular connectome and its disruption in AD
This project aims to characterize the glymphatic peri-vascular connectome and its disruption in rat models of Alzheimer disease based on MRI imaging using OMT modelling.

W81XWH-16-1-0555 (Nedergaard) 9/15/16-9/14/19
DOD/ARMY Role: PI
Is Failure of Glymphatic Tau Clearance a Critical Pathophysiological Event in CTE?
The proposed studies will test the hypothesis that a diagnostic test of glymphatic function early after TBI can identify subjects at risk for developing chronic traumatic encephalopathy (CTE). The proposal will also provide insight into which mechanisms suppress glymphatic clearance after TBI and thereby contribute to the accelerated accumulation of phosphorylated tau post-TBI.

R01NS100366 (Nedergaard) 9/30/16-6/30/21
NIH/NINDS/NIA Role: PI
Para-Vascular Basis of Small Vessel Disease
This award seeks to determine the role of the 'glymphatic system' in small vessel disease (SVD) - a common type of dementia. The goal is to understand how dysfunction of the glymphatic system contributes to myelin loss and dementia in SVD.

R01AG048769 (Nedergaard, Benveniste) 9/1/14-5/31/19
NIH/NIA Role: PI
Glymphatic function in a transgenic rat model of Alzheimer's disease
This project will test the hypothesis that age-related decline in glymphatic clearance precedes and contributes to cognitive decline and amylodosis in wild type rats and in a transgenic rat model of Alzheimer's disease.

P01HD076892 (Nedergaard) 9/20/14-7/31/19
NIH (University of Wisconsin sub) Role: PI/Project Lead
Alexander's accentuation by failure of glymphatic clearance
The goal of this project is to provide fundamentally new insights into the role of glymphatic GFAP clearance on reactive gliosis and Rosenthal fiber burden and thereby define novel targets for treatment of this grave disease.

R01MH099578 (Nedergaard, Goldman) 3/5/13-2/28/18 (NCE 2/28/19)
NIH/NIMH Role: Co-PI
A humanized mouse model of astrocytic pathology in schizophrenia
The goal of this project is to define the disease-specific effects, gene expression patterns, and paracrine toxicities of schizophrenic hiPS-derived astrocytes relative to normal hiPSC-derived glia.

University of Copenhagen (part-time appointment)

Novo Nordisk Foundation 1/1/2014-12/31/2020
Emerging Roles of Astrocytes in Health and Disease Role: PI
The goal of this project is to study basic cellular properties including Ca2+ signaling in mouse and human astrocytes.

Lundbeck Foundation 4/1/17-12/31/21
Astrocytic modulation of arousal and pain Role: PI
The goal of this project is to establish the role of astrocytes in chronic pain.

Completed Research Support

R01NS078304 (Nedergaard) 1/15/12-12/31/2016 (12/31/17 NCE)
NIH/NINDS Role: PI
The glymphatic system, a new concept in glia biology
The overall objective of this project is to define the function of astroglia fluid transport in clearance of metabolic waste.

R01NS075177 (Nedergaard) 2/1/12-1/31/17
NIH/NINDS Role: PI
ATP as the instigator of inflammatory responses to spinal cord injury
The overall objective of this project is to define targets for development of novel therapeutic to treat acute spinal cord injury.

R01NS078167 (Nedergaard) 5/15/12-2/28/17
NIH/NINDS Role: PI
Failure of metabolite clearance in a model of multi-lacunar infarcts
The overall objective of this project is to test the hypothesis that cognitive decline associated with vascular dementia is in part attributable to the failure of glymphatic pathway function.

R21HD0808573 (Nedergaard, Benveniste) 7/1/14-6/30/16
NIH (Stony Brook Univ. sub) Role: PI
Metabolic Profiling of Neonatal Anesthesia Toxicity
These proposed studies attempt to develop a clinically relevant diagnostic test to assess anesthesia induced neurotoxicity in the young brain.

R25NS065748 (Nedergaard) 3/4/09-2/28/14
NIH/NINDS Role: PI
Molecular Neurosurgery Training Program (NEUROTRAP)
The overall goal of this project is to provide a unique multidisciplinary translational neuroscience research experience for Neurosurgeons in training.

SMA-1344466 (Nedergaard) 9/15/13-8/31/15
NSF Role: PI
EAGER: Collaborative Research: Non-Local Cortical Computation and Enhanced Learning with Astrocytes
The goal of this project is to explore the hypothesis that enhanced learning is a consequence of increased spatial integration of synapses, providing a new communications route between synapses.

R01 NS038073 (Nedergaard) 07/01/07-06/30/12 *(unfunded extension)*
NIH/NINDS Role: PI
Astrocyte Dysfunction in Epilepsy
The overall objective of this project is to investigate the mechanisms controlling astrocytic calcium signaling.

P01NS042803 (Messing) 9/20/08-6/30/13
NIH/NINDS- University of Wisconsin subcontract Role: PI
Alexander Disease: Cellular and Molecular Mechanisms
The overall objective of this project is to investigate the cellular pathology that accompanies GFAP accumulation.