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BIOGRAPHICAL SKETCH

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NAME: Steven A. Goldman M.D., Ph.D

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

POSITION TITLE: URMC Distinguished Professor of Neurology and Co-Director, Center for Translational Neuromedicine, University of Rochester Medical Center

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Pennsylvania	B.A., Honors	1978	Biology, Psychology
Rockefeller University	Ph.D.	1983	Neurobiology
Cornell University Medical College	M.D.	1984	Medicine
NY Hospital-Cornell & Memorial Sloan-Kettering	Residency	1988	Medicine/Neurology

A. Personal Statement

Role on T32: Mentor

I look forward to serving as a mentor for Trainees in our Department's long-standing T32 in Experimental Therapeutics. This T32 has created an inclusive, supportive environment for Trainees to acquire the sound research methodologies necessary to pursue their individual career goals. I also welcome the opportunity to mentor young investigators and to integrate them into our research in ways that yield skills, credentials, and experience applicable to the next steps of their career. I have mentored several dozen postdoctoral fellows, MD-PhD students and graduate students at Cornell and Rockefeller as well as Rochester; most have gone on to careers in academic medicine.

I am a cell biologist and clinical neurologist, with interests in neural stem cell biology, adult gliogenesis and neurogenesis, and cell-based treatment of neurodegenerative and myelin disorders. My translational interests are in establishing the use of glial progenitor cells as reagents for treating primary disorders of glia, including progressive multiple sclerosis (MS), the hereditary leukodystrophies, and Huntington disease. My research also includes the use of disease-specific human embryonic stem cell- and induced pluripotent stem cell-derived glial progenitors, in establishing in vitro and in vivo models of neurological disease. The latter effort includes the establishment of human glial chimeric mice as tools for defining astrocytic and oligodendrocytic contributions to both the neurodegenerative and neuropsychiatric disorders. Clinically, I am trained as a stroke neurologist and neuro-oncologist, and have served as chairman of the Department of Neurology at the University of Rochester. I have also served on over 2 dozen NIH and FDA panels, including a recent 4-year term on the Cell, Tissue and Gene Therapy Advisory Committee of the FDA. Besides my appointment at Rochester, I have a secondary appointment as Professor of Neuroscience at the University of Copenhagen in Denmark.

B. Positions and Honors

Professional Experience

1984-85	Intern in Medicine, New York Hospital-Cornell Univ. Medical Center, NY, NY
1985-87	Resident in Neurology, NY Hospital-Cornell and Memorial Sloan-Kettering Cancer Ctr, NY, NY
1987-88	Chief Resident in Neurology, New York Hospital-Cornell Univ. Medical Center, NY
1988-2001	Assistant, Associate and full Professor of Neurology & Neuroscience, Cornell U. Med. Col., NY
1988-2001	Assistant, Associate and Senior Attending Neurologist, NY Hospital-Cornell Med. Ctr, NY, NY
2001-2003	Nathan Cummings Professor of Neurology & Neuroscience, Cornell Univ. Medical College, NY
2008-2011	Founding program director in Neuro-oncology, Univ. Rochester Medical Center
2008-2012	Chairman, Dept. of Neurology, Univ. Rochester Medical Center
2008-2012	Neurologist-in-Chief, Strong Memorial and Highland Hospitals, Rochester, NY
2003-2013	Adjunct Professor of Neurology, Weill Medical College of Cornell University, NY, NY
2003-present	Attending Neurologist, Univ. of Rochester Medical Center (URMC)/Strong Memorial Hospital
2003-present	Professor of Neurology (*primary*); Professor of Neurosurgery (*secondary*), URMC

2003-present Chief, Division of Cell and Gene Therapy, Dept. Neurology, Univ. of Rochester Medical Center
2003-present Dean Zutes Chair in Biology of the Aging Brain, University of Rochester
2007-present Co-Director, Center for Translational Neuromedicine, Univ. Rochester Medical Center
2013-present URMC Distinguished Professor of Neurology and Neuroscience, Rochester, NY
2013-present Adjunct Professor, Lab of Molecular Embryology, The Rockefeller University, NYC, NY
2014-present Professor of Neuroscience and Center Co-Director, University of Copenhagen (*part-time*)
2015-present Consultant Neurologist, Copenhagen University Hospital (Rigshospitalet), Denmark (*part-time*)

Honors and Awards

Academia Europae (European Acad., *elected 2015*)
Novo Nordisk Foundation Laureate Award, 2014
Presidential Lectureship, Amer. Acad. Neurol., 2010
Association of American Physicians (*elected 2007*)
Jacob Javits Neurosci. Invest. Award (NIH), 2002-9
Presidential plenary lect., Amer. Neurol. Assc., 2005
American Soc. Clinical Investigation (*elected 2001*)
Berlex Fellow in Regenerative Medicine, 2004-2006
American Neurological Association *(elected 1995)*
Irma T. Hirschl Career Scientist Award, 1993-97
FIRST award, NIH/NINDS, 1992-97
Human Frontiers Scientific Pgm. Awd., 1998-2001
Mathers Charitable Fdn. Award, 1988-97; 2007-9
Cornell Scholar in Biomed. Science, 1988-1991
Clinical Invest. Develop. Awd., NIH, 1988-93
Medical Scientist Training Pgm., USPHS, 1978-84
Phi Beta Kappa, University of Pennsylvania, 1978
Mayor's Scholar, City of Philadelphia, 1974-78
Senatorial Scholar, Pennsylvania, 1974-78
Benj. Franklin Scholar, U. Pennsylvania, 1974-8

C. Contributions to science

1. Discovery of adult neurogenesis and establishment of link between angiogenesis and neurogenesis
As a graduate student with Fernando Nottebohm at Rockefeller, I discovered neuronal production in the adult songbird brain, and found that newly generated neurons arose from persistent subependymal progenitor cells. At the time, this was the first example of ventricular zone-derived neuronal production, migration and differentiation in an adult vertebrate brain. This work was followed up by a large number of groups, and led to the discovery of persistent neurogenesis in the adult rodent brain, and of persistent neural stem cells in the forebrain. After my medical training and residency, I returned to this work independently, and subsequently established an in vitro model for assessing ventricular zone neurogenesis, the first of its kind, and used that model to establish the role of angiogenesis and endothelial cytokines in directing neuronal production from resident neural stem cells. The concept of angiogenic control of neuronal recruitment has proven operative in the adult mammalian brain as well, and has since been followed up by a number of groups.

a. Goldman SA, Nottebohm F. (1983) Neuronal production, migration and differentiation in a vocal control nucleus of the adult female canary brain. Proc. Natl. Acad. Sci. 80:2390-2394, PMC393826
b. Goldman SA. et al. (1992) In vitro neurogenesis by precursors from adult avian brain. J. Neurosci.12:2532-41.
c. Louissaint A, Rao S, Leventhal C, Goldman SA (2002) Coordinated interaction of neurogenesis and angiogenesis in the adult songbird brain. Neuron 34:945-960. (*see editorial*: Neuron 34:856-58).
d. Goldman SA, Chen Z. (2011) Perivascular instruction of cell genesis and fate in adult brain. Nature Neuroscience 14:1382-89. PMC3655803

2. Discovery and isolation of persistent neural stem and progenitor cells from the human brain
On the basis of my work in the songbird brain, I studied the adult rodent and the human ventricular subependyma in culture, and identified persistent neural stem and neuronal progenitor cells in the human brain as well. At the time, these were the first reports of persistent neuronal progenitor cells capable of renewed neurogenesis in adult human brain tissue. In subsequent studies, I used promoter-based GFP-driven fluorescence-activated cell sorting to isolate these cells from both the human ventricular zone and hippocampus. This work comprised the first isolation of adult human neuronal progenitors, as well as the first use of FACS to separate cells from brain tissue, a technique that we first established using fetal human brain tissue, and then applied to adult tissue as well; FACS of brain tissues has since become a widely used technique in cellular neurobiology.

a. Kirschenbaum B, Nedergaard M, Barami K, Fraser RA, Goldman SA (1994) In vitro neuronal production and differentiation by precursor cells derived from adult human forebrain. Cerebral Cortex 4: 576-89.
b. Wang S, Wu H, Jiang J,… Goldman SA (1998) Isolation of neuronal precursors by sorting embryonic forebrain transfected with GFP regulated by the T alpha1 tubulin promoter. Nature Biotechnology 16: 196-201.
c. Roy N, Wang S,… Okano H, Nedergaard M, Goldman SA (2000) In vitro neurogenesis by progenitor cells isolated from the adult human hippocampus. Nature Medicine 6:271-77. (cover and editorial).

d. Keyoung H, Roy N,… Okano H, Goldman SA (2001). High-yield selection and extraction of two promoter-defined phenotypes of neural stem cells from the fetal human brain. Nature Biotechnology 19:843-50.

3. Induction of neuronal production in the adult mammalian brain, and its application as a therapeutic strategy in Huntington's Disease

Having defined both the phenomenology and the cellular interactions mediating neuronal addition into the adult avian forebrain, I next identified how to recapitulate that process in the adult mammalian brain. By transducing the adult rodent forebrain ventricular wall with adenovirally-delivered BDNF, as a neurotrophic and neuronal differentiation agent, and Noggin, to suppress BMP-driven glial differentiation, my group achieved the first induction of functionally-integrated new neurons from endogenous neural stem cells, and did so in an otherwise non-neurogenic region of brain, the adult striatum. We then used longer-term AAV expression vectors to sustain neuronal recruitment over many months, and applied that methodology to mouse models of Huntington disease, in which striatal neurons are typically lost. We found that BDNF/noggin-induced striatal neurons could be produced in sufficient numbers to significantly delay disease progression and lengthen survival, and that the newly generated neurons fully integrated both anatomically and physiologically into the extant neural network. We have advanced this strategy in proof-of-concept studies intended to develop a gene therapeutic strategy for inducing striatal neuronal replacement in Huntington disease, which we would nor like to complement with our parallel strategy to replace diseased with healthy glia in the Huntington environment.

a. Cho SR, Benraiss A, …Goldman SA (2007) Induction of neostriatal neurogenesis slows disease progression in a transgenic murine model of Huntington Disease. J. Clin. Invest., 117: 2889-2902. PMC1978427
b. Benraiss A,...Nedergaard M, Goldman SA (2013) Sustained mobilization of endogenous neural progenitors delays disease progression in a transgenic model of Huntington's disease. Cell Stem Cell 12:787-99.
c. Benraiss A,…Nedergaard M, Goldman SA (2016) Human glia can both induce and rescue aspects of phenotype in Huntington Disease. Nature Commun. 7:11758. PMC4899632
d. Osipovitch, M.,…Windrem, M., Goldman, S.A. hESC-based human glial chimeras reveal glial differentiation defects in Huntington Disease. Cell Stem Cell, 2018, doi: https://doi.org/10.1016/j.stem.2018.11.010.

4. Establishment of human glial progenitors as cellular vectors for therapeutic remyelination

In the course of isolating neural progenitor cells from the human brain, my group reported the first isolation of mitotic human oligodendrocyte progenitor cells (now designated glial progenitor cells, or GPCs) from the adult forebrain. We found that these cells retained multilineage competence, and could act as somatic stem cells, but were restricted to glial fate in vivo. In subsequent work, we compared the myelination competence of fetal and adult human GPCs as cellular vectors for remyelinating demyelinated and hypomyelinated brain, and established fetal GPCs as an optimal vector for therapeutic remyelination. We subsequently reported the first phenotypic rescue of a mouse model of leukodystrophy using the transplantation of fetal human tissue-derived GPCs into early postnatal mice. On that basis, I obtained funding from NY State for a multicenter consortium whose goal is to establish a clinical trial of human GPCs in progressive multiple sclerosis; IND-enabling studies are now underway for that effort, following a pre-IND meeting in 2014. Anticipating the need for more abundant sources of cells, we then established a now-standard protocol for producing GPCs and their derived glia from pluripotential stem cells, the latter including both embryonic stem cells and induced pluripotent cells. Using these cells, we achieved the complete in vivo myelination and restored survival of congenitally hypomyelinated mice, the first such rescue of a lethal genetic disorder using human iPS cell-derived neural or glial cells.

a. Nunes M, Roy N,...Nedergaard M, Goldman SA (2003) Identification and isolation of multipotent neural progenitors from subcortical white matter of adult human brain. Nature Medicine 9:239-47 (cover).
b. Windrem MS,... Roy N, Goldman SA (2004) Fetal and adult human oligodendrocyte progenitor cell isolates myelinate the congenitally dysmyelinated brain. Nature Medicine 10: 93-7.
c. Windrem MS, Goldman SA (2008) Neonatal chimerization with human glial progenitor cells can both remyelinate and rescue the otherwise lethally hypomyelinated shiverer mouse. Cell Stem Cell 2: 553–565. PMC3358921
d. Wang S,…Windrem MS, Goldman SA. (2013) Human iPS cell-derived oligodendrocyte progenitor cells can myelinate and rescue a mouse model of congenital hypomyelination. Cell Stem Cell 12:252-264.

5. Development of human ESC and iPSC technologies and transplanted chimeras as model systems for assessing contributions – especially glial - to cognition and disease

In the setting of our studies of cell-based remyelination, we discovered that when mouse brains were neonatally engrafted with human GPCs, that the human cells outcompeted their mouse counterparts, resulting

in the progressive replacement of host GPCs with human cells. As astrocytic turnover progressed, these brains then became progressively colonized with human astrocytes. When established in hypomyelinated shiverer mice, the host oligodendrocytes were replaced by human cells as well, so that in these mice most glia were ultimately replaced by human cells. Importantly, in earlier studies, my long-time collaborator Maiken Nedergaard and I had reported that astrocytes are intimately involved in establishing synaptic plasticity, and that human astrocytes in particular are larger, more structurally complex and pleomorphic than mouse astroglia. Putting these observations together, we surmised that human glial chimeric mice might exhibit facilitated synaptic plasticity. We found that this was the case, in that human glial chimeras exhibited more sustained hippocampal long-term potentiation, and performed significantly better on cognitive testing than untransplanted and allografted mice. This work demonstrated the critical role of glia in information processing, and the greater capabilities of human astrocytes in that regard. Furthermore, by establishing human glial chimeras with patient-derived iPS cell-derived glial progenitors, we can now produce chimeric mice in which virtually all glia are derived from single patients, allowing us to assess the specific contributions of glia to neurological disease, especially in those neuropsychiatric and neurodegenerative disorders for which the relative contributions of glia and neurons to disease have not been well defined.

In addition, we can use these human glial chimeras to study infectious agents specific to human glia, which had not previously been amenable to study for lack of effective in vivo models. To that end, we established the first mouse model for JC virus, the human gliotropic virus that causes progressive multifocal leukoencephalopathy, and discovered that this virus, long thought to be an oligodendrocytic pathogen, targets primarily astrocytes, with oligodendrocytic death and myelin loss a late event. This discovery has changed current concepts in neurovirology, of how to potentially target and treat polyoma viral infections of the brain.

a. Han X, 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 12:342-53. PMC3700554
b. Windrem M, Wang S, Goldman SA (2014) A competitive advantage by neonatally engrafted human glial progenitors yields mice whose brains are chimeric for human glia. J. Neuroscience. 34:16153-61.
c. Kondo Y, Windrem M, Gorelik L, Goldman SA (2014) JC virus-infected human glial chimeric mice reveal PML to be an astrocytic disease. J. Clin. Invest. 124:5323-36 (cover; featured story, JCI Impact).
d. Windrem M, Osipovitch M, Tesar P, Goldman SA. (2017) Human glial chimeras reveal a causal contribution of glial pathology to juvenile-onset schizophrenia. Cell Stem Cell 21:195-208.

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

University of Rochester

R01NS110776 Goldman (PI) 04/01/2019-03/31/2024
Transcriptional determinants of the fate trajectories of single human glial progenitor cells in response to demyelination in vivo
The goal of this work is to identify the basis for the loss of progenitor cell competence that accompanies the terminal failure to remyelinate that characterizes longstanding MS.
Role: Principal Investigator

R01MH104701 Goldman (PI) 09/01/2014-08/31/2019
An iPSC-based humanized mouse model of dysmyelination in schizophrenia
The goal of this project is to establish human glial chimeric mice whose brains are comprised of OPCs derived from schizophrenic patients, and to use these mice as platforms from which to study the anatomic, behavioral and genomic effects of schizophrenic oligodendroglia and myelin, in real-time and in vivo, in adult animals.
Role: Principal Investigator

R01NS100366 Nedergaard (PI) 09/01/2016-06/30/2021
Paravascular basis of small vessel disease
This project aims to diagnose early Alzheimer disease and predict progression via a biomarker that captures ‘glymphatic’ pathway transport on a systems level.
Role: Co-Investigator

Adelson Medical Research Foundation Goldman (PI) 10/01/2017-09/30/2019
Project 1: mIRNA based cooperative transformation of resident glial progenitor cells by glioma stem cells

Project 2: Neurogenesis from resident human glial progenitor cells
Project 3: iPSC glial progenitor cell-based modeling and treatment of pediatric leukodystrophy
This grant includes three individual projects; together all three of the projects reflect our strong bias towards collaboratively advancing the best science possible, in the service of developing well-grounded, translationally-informative, and clinically feasible strategies for brain repair.
Role: Principal Investigator

Oscine Corporation Goldman (PI) 11/01/2018-08/31/2021
Commercial development of human glial progenitor cell-based therapeutics
The goal of this project is to establish methods for producing GLP/GMP-compliant human ESC-derived glial progenitor cells for clinical use, and to validate the release and safety-toxicology criteria required for clinical progression.
Role: Principal Investigator

University of Copenhagen *(part-time appointment)*
Lundbeck Foundation Goldman (PI) 02/01/2017-01/31/2022
The glial contribution to frontotemporal dementia
To define the glial contribution to frontotemporal dementia
Role: Principal Investigator

Novo Nordisk Foundation Laureate Award Goldman (PI) 06/01/2014-05/31/2021
Glial progenitor cell-based treatment and modeling of neuropsychiatric disease
To define cell-based methods for modeling and treating neuropsychiatric disorders
Role: Principal Investigator

Recently completed support
A-4184 Goldman (PI) 09/01/2016-12/31/2018
CHDI Foundation, Inc.,
Contribution of mHTT-expressing glia to Huntington pathogenesis and therapeutic targeting thereof
The goal of this project is to assess the role of mutant Huntington-expressing glia in the initiation and progression of neuropathology in Huntington's disease.
Role: Principal Investigator

R01MH099578 Goldman and Nedergaard (Co-PIs) 03/01/2013-02/28/2019
A humanized mouse model of astrocytic pathology in schizophrenia
The goal of this project is to establish a humanized astroglial mouse model of schizophrenia.
Role: Co-Principal Investigator

ALS Association Goldman (PI) 10/01/2015-09/30/2018
A human glial chimeric model of C9orf72 frontotemporal dementia (FTD)-ALS complex
The goal of this project is to define the contribution of glial progenitor cell pathology to C9orf72 ALS and FTD, and to use that information to identify new glial targets for disease treatment.
Role: Principal Investigator