BIOGRAPHICAL SKETCH

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NAME: Sonntag, Kai-Christian

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

POSITION TITLE: Assistant Professor of Psychiatry (Neuroscience)

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
Semmelweis University, Budapest, Hungary		1986-1988	Medicine
University of Heidelberg, Heidelberg, Germany	M.D.	1988-1993	Medicine
University of Heidelberg, Heidelberg, Germany	Ph.D.	1988-1994	Virology
Equivalent US Degree as approved by Center for Educational Documentation (03/06/1998)	M.D. Ph.D.		
University of Heidelberg, Heidelberg, Germany	Resident	1993-1994	Internal Medicine
University of Heidelberg, Heidelberg, Germany	Research Assistant	1994-1995	Virology
Transplantation Biology Research Center, Massachusetts General Hospital, HMS	Postdoctoral	1995-2000	Immunology
McLean Hospital, HMS	Instructor	2000-2005	Neurobiology

A. Personal Statement

I have a background in molecular and cellular biology in the fields of virology, transplantation immunology, stem cell biology, and neuroscience. My scientific interest is to understand the molecular and cellular mechanisms of neurodegenerative and neuropsychiatric disorders and to develop new therapeutic tools using gene and cell therapy approaches. My research is based on translational approaches that integrate the analysis of human material (postmortem and primary tissue), animal models of disease, and embryonic (ESC) or induced (iPSC) pluripotent stem cell and virus-mediated gene-engineering paradigms to study neuronal degeneration and dysfunction. My work has contributed, amongst others, to using ESC and iPSC as source for cell replacement therapy in Parkinson's disease (PD) or to study neurodegenerative processes *in vitro*, to determine the transcriptional regulation of neurons in context of neurodegenerative or neuropsychiatric disorders with a focus on miRNAs, and to understanding a role of bioenergetics dysfunction in brain aging and late-onset Alzheimer's disease (LOAD). It is my believe that neurological disorders are a consequence of holistic events, rather than caused by a (few) single factor(s) - pathogenesis is a consequence of one's individual genetic and epigenetic precondition, lifestyle, and the age-associated progressive dysfunction of cellular bioenergetics and metabolic events in combination with deregulated gene expression and signaling pathways. My studies as a leading academic senior scientist have involved many collaborations and the building of diverse teams positioning me well to conduct the proposed research on "Studying a role of bioenergetics in late-onset AD using an *in vitro* model of aging".

B. Positions and Honors

Positions and Employment

1989-1994 Graduate Student, Institute for Medical Virology, University of Heidelberg, Germany
1993-1994 Assistant Physician, Internal Medicine, University of Heidelberg, Heidelberg, Germany
1994-1995 Research Assistant, Institute for Medical Virology, University of Heidelberg, Germany,
1994-1995 Lecturer in Theoretical Virology, Institute for Virology, University of Heidelberg, Germany
1995-2000 Research Fellow, Transplantation Biology Research Center, Mass. Gen. Hosp., Boston, MA
2000-2004 Assistant Research Stem Cell Biologist, McLean Hospital, Belmont, MA

2000-2005 *Instructor* in Psychiatry, Harvard Medical School, Boston, MA
2004-2007 Associate Stem Cell Researcher, CNR, McLean Hospital, Belmont, MA
2005- *Assistant Professor* of Psychiatry (Neuroscience), Harvard Medical School, Boston, MA
2007- Independent Principal Investigator, McLean Hospital, Belmont, MA

Other Experience and Professional Memberships:

2002-2004 Chair, Neuroscience Seminar Series, McLean Hospital, Belmont, MA
2002- Editorial Board, *Journal of Translational Medicine*
2004-2007 Debuty Receiving Editor, *European Journal of Neuroscience*
2006- Editorial Board, *Journal of Visualized Experiments*
2007- Member, Steering Committee, McLean Hospital
2007-2011 Associate Editor, *Brain Research*
2008- Voting Member Partners Embryonic Stem Cell Research Oversight Committee (ESCRO)
2009-2016 Editorial Board, *Stem Cells*
2011- Voting Member Partners Institutional Biosafety Committee (PIBC)
2011- Editor, *Brain and Behavior*
2011- Editor, *ISRN Stem Cells*
2012 Invited Lecturer, Clinical Research Program, Massachusetts General Hospital
2015- Associate Editor, *World Journal of Stem Cells*
2015- Editorial Board, *Translational Medicine Communications*

Ad hoc reviewer: Acta Neuropathologica, American Journal of Physiology, Alzheimer's & Dementia, Behavioral Brain Research, BioEssays, Biotechnology Journal, BioMed Research International, BMC Biotechnology, BMC Neuroscience, BMC Stem Cell Research and Therapy, BRAIN, Brain Research, Brain Research Bulletin, Cancer Therapy, Cell Death and Disease, Cell and Tissue Research, Cell Transplantation, Cellular and Molecular Life Sciences, Cerebral Cortex, Current Aging Science (Bentham), Developmental Dynamics, EMBO, European Journal of Neuroscience, Experimental Cell Research, Experimental Neurology, Expert Opinion in Drug Discovery, Expert Opinion on Investigational Drugs, FASEBJ, FEBS, Future Neurology, Frontiers Genes, Human Molecular Genetics, International Journal of Developmental Neuroscience, International Journal of Neuropsychopharmacology, International Journal of Molecular Sciences, International Journal of Pharmaceutical Medicine, ISRN Stem Cells, Journal of Biomaterials and Tissue Engineering, Journal of Clinical Investigation, Journal of Experimental Medicine, Journal of Neuroscience, Journal of Neuroscience Methods, Journal of Neurodegeneration and Regeneration, Journal of Neuroscience Research, Journal of Neurotrauma, Journal of Neurotransmission, Journal of Translational Medicine, Movement Disorders, Molecular Genetics and Genomics, Molecular Therapy, Molecular and Cellular Therapies, Molecular Biology Reports, Molecular Medicine Reports, MDPI Open Access, Methods Neurobiology of Aging, Neurobiology of Disease, Neuropsychopharmacology, NeuroMolecular Medicine, Neuroscience Letters, Neurotherapeutics, PNAS, PLoS One, PLoS Genetics, Progress in Neuro-Psychopharmacology & Biological Psychiatry, Restorative Neurology and Neuroscience, Regenerative Medicine, Scientific Reports, Stem Cells, Stem Cell and Cloning, Stem Cells and Development, Stem Cells International, Stem Cell Research, Stem Cell Reports, Stem Cell Research and Therapy, Tissue Engineering, Transplantation, World Journal Stem Cells, Xenotransplantation. *Ad hoc grant reviewer:* Alzheimer's Association, Alzheimer's Society/UK, Austrian Science Fund, Biotechnology and Biological Research Council/UK, Dystonia Medical Research Foundation, European Research Council, Israel Science Foundation, Medical Research Council/UK, National Sciences and Engineering Research Council of Canada, New Jersey Commission on Science and Technology/AIBS, New York Stem Cell Research Program/AIBS, Parkinson's Disease Society/UK, USAMRMC/AIBS, US-Israel Binational Science Foundation, Wings for Life.

Honors:

1994 Doctoral Thesis, "summa cum laude"
1995 Best Thesis Award, Foundation for Molecular Biology in Heidelberg (GFMB)
1995-1997 Fellowship Grant, German Society of Science (DFG)
1999 Travel Award, Keystone Symposium
2004 Best Abstract Award, The Cell Transplantation Society, 7th Intl Congress, Boston
2008 Best Abstract Award, Angel Fund Junior Investigator, Sporadic Neurodegeneration/Biosymposia
2010 Guest Editor, Special Issue "RNA Mechanisms in CNS Systems and Disorders", *Brain Research*
2011 Poster Award, NINDS, NIMH, NIDA 5th Annual Julius Axelrod Lecture
2012 Partners in Excellence Team Award for service at PHS/PIBC
2013 PHS Sustainable Champion Award
2013 McLean Green Leadership Award

C. Contribution to Science

1. As a M.D. Ph.D. student, I studied the molecular compositions of *Chilo Iridescent Virus Type 6* (CIV) and *Molluscum Contagiosum Virus Type I* (MCV). CIV has agricultural importance as it infects the rice stem borer *Chilo suppressalis* (Lepidoptera), and MCV is a species of the *poxvirus* family that causes *Molluscum contagiosum* in humans. I have identified several genes that are important in the replication and host interactions of these viruses. This scientific work has contributed to understanding the molecular evolution and biology of large DNA viruses, which has implications on translating virus systems to biomedical and socio-economical applications, e.g., as biological insecticide (CIV) or in the treatment of diseases caused by *poxviruses*.
    a. **Sonntag, K.-C.,** Schnitzler, P., Koonin, E., and Darai, G. **(1994).** Chilo Iridescent Virus Encodes a Putative Helicase Belonging to a Distinct Family within the „DEAD/H" Superfamily; Implications for the Evolution of Large DNA Viruses. *Virus Genes* 8 (2), 151-158. PMID: 8073636.
    b. **Sonntag, K.-C.,** Schnitzler, P., Janssen, W., and Darai, G. **(1994).** Identification of the Primary Structure and the Coding Capacity of the Genome of Insect Iridescent Virus Type 6 Between the Genome Coordinates 0.310 and 0.347 (7990 bp). *J. Intervirol.* 37 (5), 287-297. PMID: 7698884.
    c. **Sonntag, K.-C.,** Clauer, U., Bugert, J. J., Schnitzler, P., and Darai, G. **(1995).** Identification and Properties of the Genes Encoding the Poly-A Polymerase, a Small (22kDa), and the Largest Subunit (147kDa) of the DNA-Dependent RNA Polymerase of Molluscum Contagiosum Virus Type 1. *Virology* 210, 471-478. PMID: 7618282.
    d. **Sonntag, K.-C.,** and Darai, G. **(1996).** Evolution of Viral DNA-Dependent RNA Polymerases. *Virus Genes* 11:2/3, 271-285. PMID: 8828152.
2. As a research fellow in the *Transplantation Biology Research Center*, Massachusetts General Hospital, Harvard Medical School, I aimed to induce transplantation tolerance to solid kidney grafts in a large animal miniature swine model using a lentivirus-mediated gene-engineering approach. I developed a strategy to transduce autologous bone marrow stem cells from recipient animals with lentiviruses that express allogeneic MHC Class II genes, which are matched to subsequent allogeneic kidney grafts. I could show that this regimen conveys full immune-tolerance to the grafts without using immune-suppressive drugs. I was also interested in understanding a role of the Fas/FasL system in the induction of tolerance, which I initially studied in NK cells and later in ESC as potential source for cell therapeutic applications. I found that FasL does not induce tolerance in both cell systems. These studies have contributed to understanding the mechanisms of graft rejection and developing strategies to induce immune-tolerance to solid and cell transplants.
    a. **Sonntag, K.-C.,** Haller, G.W., Giauffret D., Germana S., Reeves, S.A., Levy, J., Sachs, D.H., and LeGuern, C. **(2000).** Regulated Expression of an MHC Class II Gene from a Promotor-Inducible Retrovirus. *Human Gene Therapy* 11;Sept. 20;11 (14):1961-1969. PMID: 11020796.
    b. **Sonntag, K.-C.**, Emery, D.W., Yasumoto, A., Haller, G.W., Germana, S., Sablinski, T., Shimizu, A., Yamada, K., Shimada, H., Arn, S., Sachs, D.H., and LeGuern, C. **(2001).** Tolerance to Solid Organ Transplants through Transfer of MHC Class II Genes. *J. Clinical Investigation.* Jan.1; 107 (1): 65-71. PMID: 11134181, PMC198548.
    c. Matter-Reissmann, B.U.*, **Sonntag, K.-C.***, Gilli, U.O., LeGuern, C. and Seebach, J.D. **(2004)**. Human Fas-Ligand Expression on Porcine Endothelial Cells Does Not Protect Against Xenogeneic Natural Killer Cytotoxity. *both authors contributed equally. *Xenotransplantation* 11(1): 43-52. PMID: 14962292.
    d. Brunlid, G., Pruszak, J., Holmes, B., Isacson, O., **Sonntag, K.-C., (2007).** Immature and neurally differentiated mouse ES cells do not express a functional Fas/FasL system. *Stem Cells* 25(9):2257-2268. Epub 2007 Jul 5. PMID: 17615270.
3. Since 2000, I have developed cell systems and gene-engineering approaches in neurobiology, such as developing ESC systems for neurogenesis as a tool to study neurodegeneration, and as a source for cell therapy, with an emphasis on generating dopamine (DA) cell types for the treatment of PD. I also studied the molecular mechanisms in Huntington's disease (HD) demonstrating a general dysfunction of the ubiquitin proteasome system in neurons and skin fibroblasts from HD patients. My work provided major contributions to developing the ESC paradigm as therapeutic strategy for PD, and a deeper understanding of the molecular mechanisms in degenerating neurons in general.

a. **Sonntag, K.-C.,** Simantov, R., Kim, K.-S., and Isacson, O. **(2004)**. Temporarily Induced *Nurr1* Can Induce a Non-Neuronal Dopaminergic Cell Type in ES Cell Differentiation. *Europ. J. Neuroscience.* 19(5):1141-52. [cover]. PMID: 15016073, PMC2614072, NIHMS81758.
b. Seo, H., **Sonntag, K.-C.,** and Isacson, O. **(2004)**. Generalized Brain and Skin Proteasome Inhibition in Huntington's Disease. *Ann. Neurol.* 56, 319-28. PMID: 15349858.
c. Krichevsky, A.M.*, **Sonntag, K.-C.*,** Isacson, O., Kosik, K.S. **(2006).** Specific microRNAs modulate ES cell-derived neurogenesis. *Both authors contributed equally. *Stem Cells* 24:857-864. PMID: 16357340, PMC2605651, NIHMS81626.
d. **Sonntag, K.-C.,** Pruszak, J., Yoshizaki, T., van Arensbergen, J., Sanchez-Pernaute, R., Isacson, O. **(2007)**. Enhanced yield of neuroepithelial precursors and midbrain-like dopaminergic neurons from human embryonic stem cells using the BMP antagonist Noggin. *Stem Cells.* 25:411-418. [cover]. PMID: 17038668, PMC2667240, NIHMS81986.

4. During my scientific work, I have created a large bank of lentivirus vectors that have been used in my own and collaborative studies. One of the applications is the use of viruses that cell-specifically and constitutively or conditionally express dopamine (Dr) and adrenergic (Adra2a) receptors in rat models of development and psychological conditions. In particular, our work could demonstrate that specific expression of *Drd1a* on excitatory output neurons in the prelimbic prefrontal cortex of adult rats induces anxiety-, addictive- and impulsive-like behaviors. This virus system has also been used in a recent study demonstrating that D1 and D2 receptors don't form heteromers. These combined approaches of lentivirus-mediated gene-engineering with behavioral animal models provide important information on our understanding of the molecular and behavioral mechanisms in development and psychiatric disorders, and have implications for the use of psychopharmacological treatments, and in particular, in juveniles and adolescents.
    a. Brenhouse, H.C., **Sonntag, K.-C.,** Andersen, S.L., **(2008).** Transient D1 dopamine receptor expression on prefrontal cortex projection neurons: Relationship to enhanced motivational salience of drug cues in adolescence. *J. Neuroscience* 28(10):2375-2382. PMID: 18322084.
    b. **Sonntag, K.C.,** Brenhouse, H.C., Freund, N., Thompson, B.S., Puhl, M., Andersen, S.L. **(2014)**. Viral over-expression of D1 dopamine receptors in the prefrontal cortex increase high-risk behaviors in adults: Comparison with adolescents. *Psychopharmacology* 231(8):1615-26, Jan. 10 [Epub ahead of print]. PMID: 24408208
    c. Frederick, A.L., Yano, H., Trifilieff, P., Vishwasrao, H., Biezonski, D., Mészáros, J., Sibley, D.R., Kellendonk, C., **Sonntag, K.-C.,** Graham, D.L., Colbran, R.J., Stanwood, G.D., Javitch, J. **(2015)**. Evidence against dopamine D1/D2 receptor heteromers. *Mol. Psych.* 20(11):1373-85 Jan. 6 [Epub ahead of print]. PMID: 25560761
    d. Brenhouse, H.C., Thompson, B.S., **Sonntag, K.-C.,** Andersen, S.L. **(2015)**. Extinction and reinstatement to cocaine-associated cues in male and female juvenile rats and the role of D1 dopamine receptor. *Neuropharmacology* 95:22-28. Mar 4 [Epub ahead of print] PMID: 25749358

5. In my current research, I investigate factors and mechanisms governing neuronal dysfunction in aging and neurological disorders, based on the concept that normal brain aging and the pathogeneses of sporadic diseases are most likely not a consequence of a (few) single or 'disease-specific' factor(s) alone, rather they are driven by holistic events that include one's individual genetic and epigenetic condition, progression of aging, and lifestyle. My work stems from the understanding that cell development and function depend on a strictly organized network orchestrating intracellular and environmental factors that include bioenergetics and metabolic processes, regulatory mechanisms of gene expression levels, and the effects of specific factors and signaling pathways providing a temporal, positional and molecular framework to achieve normal cell function. Progressive dysfunction and deregulation of these factors and cellular events are major contributors to malfunction and ultimately lead to disease development. One of my focus has been on miRNAs, which are post-transcriptional regulators of gene expression. Notably, our studies on laser-microdissected postmortem DA neurons in PD have identified a novel mechanism in neurons, mediated by miR-126, to regulate growth factor activities and vulnerability to neurotoxic insult. In addition, current research efforts are focused on understanding a role of dysfunctional bioenergetics in LOAD studying patient-derived fibroblasts, iPSC, and induced neurons (iN). These studies provide new insight into the function and dysfunction of human neurons in psychiatric and neurodegenerative disorders and have identified mechanisms and molecules that can be translated to the development of therapeutic intervention.

a. Simunovic, F., Yi, M., Wang, Y., Macey, L., Brown, L.T., Krichevsky, A.M., Andersen, S.L., Stephens, R., Benes, F., **Sonntag, K.-C. (2009)**. Gene expression profiling of substantia nigra dopamine neurons: Further insights into Parkinson disease pathology. *Brain* Jul;132(Pt 7):1795-809. *Epub 2008 Dec 3.* PMID: 19052140, PMC2724914.
b. Aguila, J.C., Blak, A., van Arensbergen, J., Sousa, A., Vázquez, N., Aduriz, A., Lopez Mato, M.P., Hedlund, E., **Sonntag, K.-C.,** Sanchez Pernaute, R. **(2014)**. Selection based on FOXA2 is not sufficient to enrich for dopamine neurons from human pluripotent stem cells. *Stem Cells Transl. Med.* 3(9):1032-42. July 14 [Epub ahead of print] PMID: 25024431
c. Kim, W., Noh, H., Lee, Y., Jeon, J., Shanmugavadivu, A., McPhie, D.L., Kim, K.-W., Cohen, B.M., Seo, H., **Sonntag, K.-C. (2016)**. miR-126 regulates growth factor activities and vulnerability to toxic insult in neurons. *Mol. Neurobiol.* Jan;53(1):95-108, Nov. 19 [Epub ahead of print] PMID 25407931; Featured in *World Biomedical Frontiers*: http://biomedfrontiers.org/alzheimer-2015-5-9/
d. **Sonntag, K.-C.,** Ryu, W.-I., Healy, R.A., Siegel, A.J., McPhie, D.L., Forester, B., Cohen, B.M. **(2017)**. Late-onset Alzheimer's disease is associated with inherent changes in bioenergetics profiles. *Sci. Rep.* 7;(1);14038; Oct. 25. PMID: 29070876.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40339362/?sort=date&direction=ascending

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

Ongoing Research Support

McLean Hospital, internal funds (Sonntag, Cohen) 04/01/16 - 03/31/19
"Bioenergetics in Alzheimer's disease",
This project aims to study bioenergetic changes in fibroblasts, and neurons and astrocytes differentiated from AD patients'-derived induced pluripotent stem cells (iPSC), or induced neurons (iNs).
Role: Investigator

Completed Research Support within last three years

R01MH091114 (Andersen, Sonntag, MPI) 04/01/11 - 03/31/16
NIMH/NIH
"Developmental mechanisms underlying risky behaviors"
This project will investigate the role of D1 dopamine receptors on impulsivity and its modulation by pharmacological treatment using a multifaceted approach that includes behavior, virus-mediated gene-engineering, laser microdissection and gene and miRNA expression profiling.
Role: Co-PI

R01 DA015403 (Andersen, PI) 01/01/10 - 10/01/14
NIDA/NIH
"Early Drug Exposure and Drug Reward Mechanisms"
This proposal will test the hypothesis that pre-pubertal exposure to methylphenidate (MPH) alters drug responsiveness to cocaine later in life. The studies aim to determine 1) To what extent low cortical dopamine levels increase drug-seeking behavior, 2) The enduring effects of MPH exposure on females, 3) How MPH, working thru the D3 dopamine receptor, changes dopamine release, and 4) Whether MPH exposure reduces D1 expression on glutamatergic neurons.
Role: Co-Investigator

DA026485-01 (Andersen, PI) 12/01/10 - 10/01/14
NIDA /NIH
"Sensitive periods, development, and substance abuse"
The major goals of this project are to determine the mechanisms of vulnerability in young animals at risk for developing a substance abuse disorder.
Role: Co-Investigator

Ageing and Alzheimer's Disease (Sonntag, Cohen) 10/01/11 – 07/01/14
Department Research Support, Shervert H. Frazier Research Institute
This project aims to analyze a function of miRNAs in neurons and in patient-derived fibroblasts in AD.
Role: Co-PI