Christian Sheline, PhD
Associate Professor of Ophthalmology, and Neuroscience

Education

1996-1998 Postdoc, Washington University, St. Louis, MO
1989-2005 Postdoc, The Salk Institute, San Diego, CA
1984-1989 PhD, University of California, Los Angeles, CA
1979-1983 BA, Dartmouth College, Hanover, NH

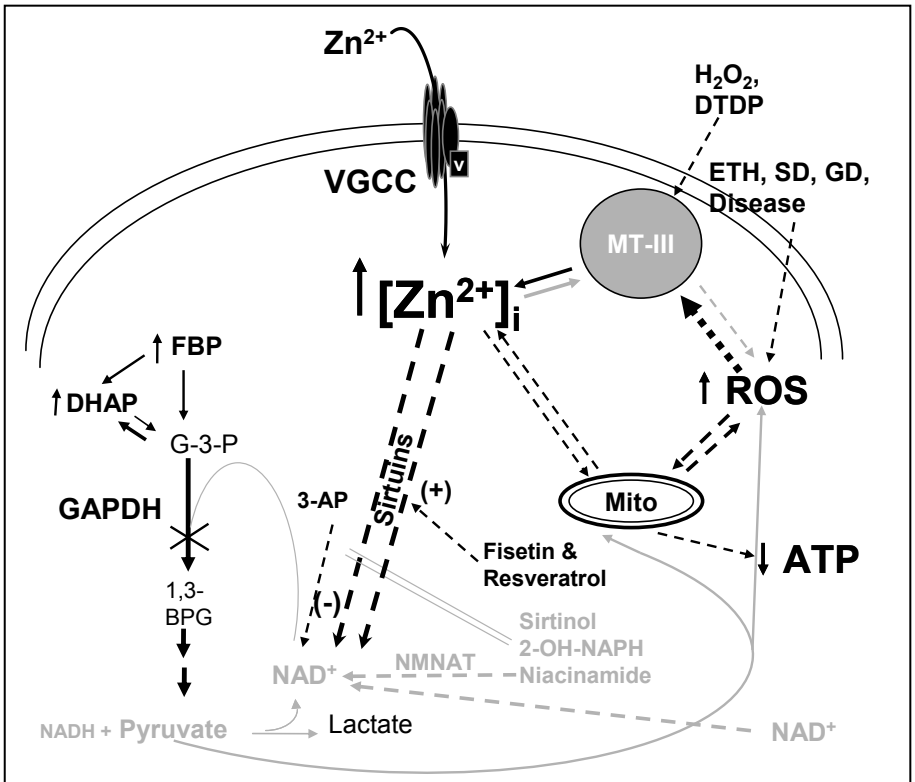
Positions

2008-present Associate Professor of Ophthalmology, and Neuroscience; Neuroscience Center, LSU Health Sciences Center, New Orleans, LA
2008 Research Associate Professor; Department of Neurology, Washington University, MO
2002-2008 Research Assistant Professor; Department of Neurology, Washington University, MO

Current Research

<u>Zn^{2+} neurotoxicity: role of NAD+ loss and glycolytic inhibition in vitro and in vivo.</u>

Zn^{2+} neurotoxicity has been shown to be involved in neuronal injury from global, focal, and retinal ischemias as well as head trauma, seizures, neuronal target deprivation, and hypoglycemia. Exogenous Zn^{2+} or Zn^{2+} released intracellularly because of oxidant conditions appear to have similar mechanisms of toxicity. NAD^+ is lost resulting in glycolytic inhibition, and compounds or genotypes which can attenuate the NAD^+ loss also attenuate glycolytic inhibition and neuronal death. Exogenous addition of NAD^+ restores intracellular NAD^+ as do, the conversion of pyruvate to lactate, and the synthesis of NAD^+ from nicotinamide by NMNAT1. The sirtuin family of NAD^+ dependent protein deacetylases appear to be involved as activators potentiate, and inhibitors attenuate death. We use in vitro culture of primary neurons as well as in vivo models of global, focal, and retinal ischemias and a model of target deprivation to study these processes. Techniques used include molecular biology to manipulate individual pathways by viral or transgenic means, biochemical measurements, and pharmacologic development of therapeutics.



SD means serum deprivation, GD means glucose deprivation, ROS means reactive oxygen species, ETH means ethacrynic acid (ROS generator), DTDP means dithiodipyridine (a thiol oxidizing agent), VGCC means voltage gated Ca^{2+} channel, MT-III means metallothionein III, G-3-P, FBP, and DHAP are glycolytic intermediates preceding GAPDH (glyceraldehyde-3 phosphate dehydrogenase), 3-AP means 3-acetylpyridine (inactivates NAD^+), sirtinol and 2-hydroxy naphthaldehyde are inhibitors, and fisetin and resveratrol are activators of the sirtuin pathway, Mito means mitchondria.

<u>Requirement for Zn^{2+} during tumor cell proliferation or neurogenesis in vitro and in vivo.</u>

Recent studies have demonstrated that tumor growth appears to be limited by the availability of Zn^{2+}. This result may be linked to the observed requirement of Zn^{2+} availability for robust

neurogenesis in the adult hippocampus. Different members of the ZIP family of transporters have been shown to be robustly over expressed in various tumors. Overexpressing ZIP's or the availability of extra Zn^{2+} potentiates tumor growth whereas knocking down their expression or Zn^{2+} chelation attenuates tumor growth. A similar situation occurs in adult hippocampus and expression of the ZnT3 zinc transporter and the availability of Zn^{2+}. We are studying tumor growth, ZIP knockdown, and Zn^{2+} chelation in vivo, and the mechanisms of this Zn^{2+} mediated affect in tumor growth as well as neurogenesis with particular attention on the kinase pathways shown to be activated by Zn^{2+} and those kinase pathways which are implicated in cell proliferation.

Zn^{2+} plays a role during □-cell death in diabetes which is also caused by NAD+ loss in vitro and in vivo.

Zn^{2+} is highly abundant in the secretory vesicles of pancreatic β-cells both bound to insulin and free. We showed that Zn^{2+} chelation, reduced Zn^{2+} in the diet, and pyruvate or nicotinamide reduce β -cell death and diabetic incidence in animal models of type-1 diabetes. We also showed that restoration of NAD^+ levels or sirtuin inhibition attenuated β -cell death in vitro. We use in vitro and in vivo models of diabetes together with molecular and transgenic techniques to modify NAD^+ and Zn^{2+} levels, or the sirtuin pathway to determine the molecular mechanisms involved in □-cell death to develop novel therapeutics for diabetes.

Research Interests and Goals

Molecular mechanisms of the requirement for zinc in tumor proliferation and neurogenesis, zinc neurotoxicity in injuries and neurodegeneration, and zinc toxicity in β-cells leading to diabetes.

Awards/Recognitions/Lectures

2007 to 2008	Alzheimer's Disease Research Center small pilot grant
2006 to 2011	NIDDK R01 grant 073446
2002 to 2007	NINDS R01 grant 30337
1996-97	NIH postdoctoral training grant
1993-94	NIH postdoctoral training grant
1989 to 1996	Member California Task force against AIDS
1990-92	California Universitywide Task force on AIDS postdoctoral grant 525247.
1/86 to 1/89	NIH predoctoral training grant in Genetics GM07104
1988	Special Faculty Award, UCLA Department of Biology.

Key Recent Papers

Sheline, C.T., Shi, C., Takata. T., Zhu, J., Xhang, W., Sheline, P.J., and Cai, A.L. (2009) NOD Mice Demonstrated Toxic β-cell Zn^{2+} Staining; Pyruvate Attenuated □-Cell Death and Diabetic Incidence In Vivo. PNAS, in submission.

Sheline, C.T., Shi, C., and Cai, A.L. (2009) Oxidative Neuronal Injuries and Target Deprivation: Role of Zn^{2+}, NAD^+, and the Sirtuin Pathway. American J. Physiol., in submission.

Cai, A.L., Zipfel, G.J., and **Sheline, C.T.** (2006) Zinc Neurotoxicity Is Dependent on Intracellular NAD^+ Levels and the Sirtuin Pathway. European Journal of Neuroscience 24: 2169-2176.

Sheline, C.T., and Ling Wei (2006) Free Radical Mediated Toxicity May Be Caused By Inhibition of Mitochondrial Dehydrogenases In Vitro and In Vivo. Neurosci. 140: 235-246.

Sheline, C.T., and Dennis W. Choi (2004) Copper-Mediated Toxicity May Be Caused By Inhibition of Mitochondrial Dehydrogenases In Vitro and In Vivo. Ann. Neuro. 55: 645-53.

Sheline, C. T., Takata, T., Ying, H., Canzoniero, L.M. T., Yang, A., Yu, S.P., and Choi, D.W. (2004) Potassium Attenuates Zinc-Induced Death of Cultured Cortical Astrocytes. Glia 46:18-27.

Sheline, C.T., Wang, H., Cai, A.-L., Dawson, V.L., and Dennis W. Choi (2003) Involvement of Poly-ADP Ribosyl Polymerase-1 in Fast But Not Slow Zinc Neurotoxicity. Eur. J. Neurosci **18**:1402-9.

Sheline C. T., Ying H. S., Ling C. S., Canzoniero L. M. T., Choi D. W. (2002) Depolarization-Induced ^{65}Zinc Influx into Cultured Cortical Neurons. Neurobiol. Dis. **10:**41-53.

Sheline C. T., Behrens M. M., Choi D. W. (2000) Zinc-induced cortical neuronal death: contribution of energy failure attributable to loss of NAD(+) and inhibition of glycolysis. Journal of Neuroscience **20**(9): 3139-46.

Okamoto, H., **Sheline, C.T.**, Corden, J.L., Jones, K.A., Peterlin, B.M. (1996) Trans-activation by human immunodeficiency virus tat protein requires the c-terminal domain of RNA polymerase II. PNAS **93**(21):11575-9.

Sheline, C. T., Sheridan, P.L., Cannon, D., Voz, M.L., Pazin, M.J., Kadonaga, J.T., Jones K.A. (1995) Activation of the HIV-1 enhancer by the LEF-1 HMG protein on nucleosome-assembled DNA in vitro. Genes and Development **9**(17):2090-104.

Funding

"Type-1 Diabetes: Zn^{2+} Potentiated □-Cell Death By Sirtuin-Mediated NAD^{+} Loss"
Agency: NIH/NIDDK-PI;
Type: R01 DK 073446-02;
Period: 8/01/06-4/30/11;
This R01 is aimed at understanding the role of Zn^{2+}, NAD^{+} loss, and sirtuins in pancreatic β-cell loss using cell lines and in vivo models of type-1 diabetes.