

Novel mouse model : Selective cerebral white matter injury induced by combined hypoxia/ischemia and infection/inflammation

Contact Information

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Partnering goals (summary)

1. Understanding molecular mechanisms of white matter damage
2. Validation of novel targets of brain injury; discovery of new targets
3. Development of new therapies for CP and/or other neurological diseases
4. Elucidation of MOA for existing CNS drugs

Introduction/Business Opportunity

Dr. Deng's research is directly related to the biology of white matter pathology, a woefully understudied area. We believe that a pathway under investigation (Glu-PARP-AIF) is shared between many diseases with this specific neurological component, such as **periventricular leukomalacia, multiple sclerosis, transverse myelitis, spinal cord injury, subcortical stroke, pediatric leukodystrophies and lysosomal storage diseases.**

There is no therapy to improve or prevent neurological damage associated with these diseases. A significant barrier is the lack of reliable models to study the pathogenesis of the disease and to evaluate therapeutics. Presently, we lack a fundamental understanding of what goes wrong during brain development to cause the disorder, of the root causes for the common variants of cerebral palsy and why the brain fails to undergo repair. Building a better basic understanding of the events that lead to specific white matter brain damage in animal models is one of the first steps we must take if we hope to reduce the incidence of the condition and to develop therapeutic interventions.

Core Technology

Dr. Wenbin Deng's laboratory at UC Davis is the first to develop a *reliable mouse model of white matter brain damage*. In contrast to the majority of the brain injury/stroke models characterized by gray matter infarction with characteristic neuronal damage, the neuropathological hallmark of this model is selective white matter lesion with prominent oligodendroglial injury. Our model uniquely enables elucidation of molecular mechanisms of

white matter injury, including the role of such poorly understood but critical factors as activated microglia.

Initially, this model was developed to study periventricular leukomalacia. Although the etiology of PVL is multifactorial, a combination of perinatal hypoxia/ischemia with maternal intrauterine infection is thought to be its primary cause. We simulate the primary causes of the disease by the combination of the following factors, sequentially applied to mice at 7 days after birth:

1. surgical ligation of the proximal internal carotid artery with subsequent full animal recovery
2. hypoxia (1hr, 6% O₂),
3. injection of the endotoxin lipopolysaccharide.

An approved antibiotic and anti-inflammatory agent, minocycline, has been widely used off-label for CNS diseases including developing white matter damage, possibly by inhibiting microglial activation and reducing cell death. By using minocycline as a chemical tool in our model, we discovered several direct targets of action, including poly-(ADP-ribose) polymerase 1 (PARP-1), a nuclear enzyme that plays a critical role in multiple cellular and disease processes. Furthermore, our pilot data also indicated that the p38 mitogen activated protein kinase (MAPK) pathway appears to be a common signaling pathway for the inhibitory effects of minocycline on both inflammation and apoptosis. Derivatives of minocycline and other novel agents could be used in our model to ID new targets of microglial activation and cerebral white matter injury, as relevant to a number of neurological disorders.

Stage of Technology Development

Completed Milestones

1. Established the white matter brain damage model in immature mice
2. Established role of microglia activation in oligodendrocyte toxicity in primary co-culture systems of microglia, neurons and oligodendrocytes
3. Identified several minocycline targets by affinity chromatography and LC-MS/MS

Proposed milestones

1. To identify other targets of minocycline and/or other small molecules targeting CNS injury
2. To characterize the role of PARP-1, p38 MAPK and/or other target in the inflammation and apoptosis of oligodendrocytes triggered by activated microglia
3. Evaluate the function of novel targets in homozygous transgenic and knockout mice

Selected Publications

1. **Deng W**, Pleasure J, Pleasure D. (2008) Progress in periventricular leukomalacia (a review). *Arch Neurol*, in press.
2. **Deng W**, Neve RL, Rosenberg PA, Volpe JJ, Jensen FE. (2006) AMPA receptor composition and CREB regulate oligodendrocyte excitotoxicity. *JBC*, 281, 36004-36011.
3. **Deng W**, Wang H, Rosenberg PA, Volpe JJ, Jensen FE. (2004) Role of metabotropic glutamate receptors in oligodendrocyte excitotoxicity and oxidative stress. *PNAS* 101, 7751-7756.
4. **Deng W**, Rosenberg PA, Volpe JJ, Jensen FE. (2003) Calcium-permeable AMPA/kainate receptors mediate toxicity and preconditioning by oxygen-glucose deprivation in oligodendrocyte precursors. *PNAS* 100, 6801-6806.
5. Follett PL, **Deng W**, Dai W, Talos DM, Massillon L, Rosenberg PA, Volpe JJ, Jensen FE. (2004)

Glutamate receptor-mediated oligodendrocyte toxicity in periventricular leukomalacia: a protective role for topiramate. *J Neurosci* 24, 4412-4420.

6. **Deng W**, Yue Q, Rosenberg PA, Volpe JJ, Jensen FE. (2006) Oligodendrocyte excitotoxicity determined by local glutamate accumulation and mitochondrial function. *J Neurochem* 98, 213-222.
7. **Deng W**, Poretz RD. (2003) Oligodendroglia in developmental neurotoxicity. *Neurotoxicology* 24, 161-178 (featured with cover illustration).
8. **Deng W**, Poretz RD. (2002) Protein kinase C activation is required for the lead-induced inhibition of proliferation and differentiation of cultured oligodendroglial progenitor cells. *Brain Res* 929, 87-95.
9. **Deng W**, Poretz RD. (2001) Chronic dietary lead exposure affects galactolipid metabolic enzymes in the developing rat brain. *Toxicol Appl Pharmacol* 172, 98-107.
10. **Deng W**, McKinnon RD, Poretz RD. (2001) Lead exposure delays the differentiation of oligodendroglial progenitors in vitro. *Toxicol Appl Pharmacol* 174, 235-244.
11. **Deng W**, Poretz RD. (2001) Lead alters the developmental profile of galactolipid metabolic enzymes in cultured oligodendrocyte lineage cells. *Neurotoxicology* 22, 429-437.
12. Poretz RD, Yang A, **Deng W**, Manowitz P. (2000) The interaction of lead exposure and arylsulfatase A genotype affects sulfatide catabolism in human fibroblasts. *Neurotoxicology* 21, 379-388.
13. **Deng W**, Feng Y. (1997) Effect of dl-n-butylphthalide on brain edema in rats subjected to focal cerebral ischemia. *Chin Med Sci J (Engl.)* 12, 102-106.

Abstracts (recent)

- Y. SHEN, S. CROCKETT, G. P. KAUR, **W. DENG**. Microglial activation in a mouse model of periventricular leukomalacia. 37th Annual Meeting of Society for Neuroscience, San Diego, 2007.
- G. P. KAUR, Y. SHEN, **W. DENG**. Microglial PARP-1 is responsible for triggering toxicity to oligodendroglia. 37th Annual Meeting of Society for Neuroscience, San Diego, 2007
- L. M. MAHAKIAN, G. P. KAUR, **W. DENG**. SIRT1 and SIRT2 are developmentally regulated in the oligodendrocyte lineage. 37th Annual Meeting of Society for Neuroscience, San Diego, 2007.
- S. N. STATT, G. P. KAUR, **W. DENG**. PARP-1 mediates AMPA receptor dependent toxicity to developing oligodendrocytes. 37th Annual Meeting of Society for Neuroscience, San Diego, 2007.
- D. B. SELIP, A. LI, D. M. TALOS, **W. DENG**, J. J. VOLPE, F. E. JENSEN. Protective effect of group I metabotropic glutamate receptor agonists in a rat model of periventricular leukomalacia. 37th Annual Meeting of Society for Neuroscience, San Diego, 2007.
- Deng W**, Park CJ, Rosenberg PA, Volpe JJ, Jensen FE. Developmental Regulation of Bcl-2 in the Oligodendroglial Lineage. 36th Annual Meeting of Society for Neuroscience, Atlanta, 2006.
- Deng W**, Rosenberg PA, Volpe JJ, Jensen FE. AMPA Receptor Subunit Composition and CREB Regulate Oligodendrocyte Excitotoxicity. 35nd Annual Meeting of Society for Neuroscience, Washington, D.C., 2005.
- Deng W**, Rosenberg PA, Volpe JJ, Jensen FE. Oligodendrocyte Excitotoxicity Determined by Glutamate Diffusion and the AMPA Receptor Subunit GluR2. 34nd Annual Meeting of Society for Neuroscience, San Diego, 2004.
- Deng W**, Massillon LJ, Follett PL, Rosenberg PA, Volpe JJ, Jensen FE. Activation of Group I mGluRs Attenuates Oligodendrocyte Excitotoxicity and Oxidative Stress. 33nd Annual Meeting of Society for Neuroscience, New Orleans, 2003.
- Deng W**, Rosenberg PA, Volpe JJ, Jensen FE. AMPA/kainate Receptor-mediated Excitotoxicity Induced by Oxygen-glucose Deprivation in Cultured Oligodendrocyte Lineage Cells. 32nd Annual Meeting of Society for Neuroscience, Orlando, 2002.
- Jensen FE, **Deng W**, Rosenberg PA, Volpe JJ, Dai W. Protective Effect of Pyrroloquinoline Quinone on Oligodendroglial Excitotoxicity *In Vitro*. Soc Neurosci Abs, 2002.

Follett PL, Massillon LJ, **Deng W**, Rosenberg PA, Volpe JJ, Jensen FE. PQQ Attenuates Hypoxic/Ischemic White Matter Injury in the Immature Rat Brain. Soc Neurosci Abs, 2002.

Deng W, Poretz RD. Lead Affects the Enzymes of Galactolipid Metabolism and Cell Fate of Oligodendrocyte Lineage Cells. 40th Annual Meeting of Society of Toxicology, San Francisco, 2001.

Deng W, Poretz RD. Lead Exposure Alters the Developmental Expression of Galactolipids and CNPase in Oligodendrocytes. 39th Annual Meeting of Society of Toxicology, Philadelphia, 2000.

Deng W, Poretz RD. The Effect of Chronic Dietary Lead Exposure on Galactolipid Metabolism in Rats. 38th Annual Meeting of Society of Toxicology, New Orleans, 1999.

Deng W, Chen X, Poretz RD. Inherited Susceptibility to Lead-induced Neurotoxicity-A Hypothesis. Gordon Conference in Glycolipids, Italy, 2000.

Poretz RD, Yang A, **Deng W**. Genetic polymorphisms of Arylsulfatase A and Inherited Susceptibility to Lead-induced Neurotoxicity. Gordon Conference in Mechanisms of Toxicity, Rhode Island, 1998.

Research Support (as PI)

- National Multiple Sclerosis Society (NMSS), "Mechanisms of Microglial Activation Underlying EAE", Role: P.I., 2007-2010, Active.
- NIH/NIEHS R01ES015988, "Oligodendrocytes, Glutamate Receptors, and Neurotoxicity", Role: P.I., 2007-2012, Direct Cost: \$400,000/year, Active.
- NIH/NINDS R01NS059043, "Glutamate Receptors in Hypoxic-ischemic Injury to Developing Oligodendrocytes", Role: P.I., 2008-2013, Direct Cost: \$225,000/year, Active.
- UC Davis Children's Miracle Network (CMN) Junior Faculty Research Grant, "Microglial Activation in Periventricular Leukomalacia", Role: P.I., 2007-2009.
- University of California TSR&TP New Investigator Grant, "Oligodendroglia and Lead Toxicity" Role: P.I., 2007-2009, Active.
- Alternatives Research & Development Foundation (ARDF) Grant, "The Potential of ES-derived Oligodendrocytes for Assessment of Neurotoxicity", Role: P.I., 2007-2008, Active.
- Roche Foundation for Anemia Research (RoFAR) Grant, "Protective Effects of Erythropoietin against Hypoxic-ischemic Injury to Developing Oligodendrocytes", Role: P.I., 2008-2010, Active.
- The Johns Hopkins Center for Alternatives to Animal Testing (CAAT) Research Grant, "Oligodendroglial Lineage Cells Derived from Embryonic Stem Cells for Testing Developmental Neurotoxicity", Role: P.I., 2008-2011, Active.
- Shriners Hospital for Children (SHC) Research Grant, "mGluR Modulation of Developing Cerebral White Matter Injury", Role: P.I., 2008-2011, Active.
- UC Davis-California Institute for Regenerative Medicine (CIRM) Institutional Training Grant (Meyers, Director; Pleasure and Tarantal, Co-Directors), Role: Mentor of Postdoctoral Fellow S. Meeusen, 2006-2007.
- United Cerebral Palsy Research and Educational Foundation (UCPREF), Role: P.I., "Metabotropic Glutamate Receptors in Hypoxic-Ischemic Oligodendrocyte Injury", 2005-2007, completed.
- National Research Service Award (NRSA), Role: P.I., "Molecular Mechanisms of Excitotoxic Oligodendrocyte Degeneration", 2002-2005, completed.
- William Randolph Hearst Fund, Role: P.I., "Hypoxic-Ischemic Injury to Developing Oligodendrocytes", 2003-2005, completed.