2005 PROGRAM

8:00 a.m. **Registration and Continental Breakfast, Atrium (Room 1-65), William T. Young Library**

8:30 a.m. **Welcome by Dr. Lee T. Todd, Jr., President, University of Kentucky - Auditorium (Room 1-62), William T. Young Library**

8:35 a.m. **Welcome by Dr. Wendy Baldwin, Executive Vice President for Research, University of Kentucky**

8:40 a.m. **Introductory Remarks - Dr. D. Allan Butterfield, Department of Chemistry, University of Kentucky**

8:45 a.m. **Dr. Barry Halliwell, National University of Singapore**
"Oxidative Stress and Neurodegenerative Disease: Distinguishing Fact from Fiction"

Neurodegenerative diseases have three common features: mitochondrial dysfunction, increased oxidative damage and accumulation of abnormal proteins. All three are intimately related, with failure of the clearance mechanism for abnormal proteins often being a primary event. It is important to study these events in human post-mortem material (although the conclusions drawn are necessarily limited) and in animal models; studies on cultured neurons may give artifactual results. This will be illustrated by studies of dopamine toxicity and GSH levels.

9:30 a.m. **Question and Answer Session**

9:40 a.m. **Dr. Irwin Fridovich, Duke University**
"The Biology of Superoxide and a Novel Activity for the Cu,Zn SOD"

In addition to its very efficient catalysis of the dismutation of superoxide, SOD1 catalyzes the bicarbonate-dependent peroxidation of diverse substrates. The mechanism of the peroxidations can be depicted by reactions (a)-(d). (a) E-Cu(II) + H_2O_2 ↔ E-Cu(I) + $2H^+$ + $O_2^{\cdot-}$; (b) E-Cu(I) + H_2O_2 ↔ E-Cu(I)O + H_2O; (c) E-Cu(I)O $\overset{H^+}{\Longleftrightarrow}$ E-Cu(II)OH ↔ E-Cu(III) + OH^-. The bound oxidant produced by reaction (b), and shown in several possible forms in reactions (c), then oxidized CO_2 to $CO_3^{\cdot-}$ as shown in reaction (d). (d) E-Cu(II)OH + CO_2 ↔ E-Cu(II) + OH^- + $CO_2^{\cdot+}$ $\Longleftrightarrow$ H^+ + $CO_3^{\cdot-}$. Surprisingly it is CO_2, and not HCO_3^-, that becomes oxidized to the $CO_3^{\cdot-}$; that then diffuses from the active site and oxidizes diverse substrates in bulk solution. $CO_3^{\cdot-}$ has a standard redox potential of +1.7 V and could be more damaging in the biological milieu than $HO^{\cdot}$; since it is a more selective oxidant. Whether or not it is produced in significant amounts in cells remains to be demonstrated.

10:25 a.m. **Question and Answer Session**

10:35 a.m. **Dr. Earl R. Stadtman, National Institutes of Health**
"Roles of Bicarbonate Buffer, Apoptosis, and Carbon/Nitrogen Deficiency on Metal-Catalyzed Oxidation of Proteins and Lipids"

The possibility that loss of apoptotic capacity contributes to age- and disease-related oxidation of proteins is suggested by studies showing that inhibition of apoptosis in acute promyelocytic cells leads to a substantial increase in the level of oxidized proteins. Metal-catalyzed oxidation of LDL is greatly stimulated by the presence of bicarbonate/CO_2 buffers at physiological pH. Replicative senescence in *E. coli* induced by either carbon or nitrogen starvation leads to substantial increases in the levels of oxidized proteins.

11:20 a.m. **Question and Answer Session**

11:30 a.m. **Lunch and Poster Session, Room CP-137, Chemistry-Physics Building**

1:00 p.m. **Dr. William R. Markesbery, University of Kentucky**
"Oxidative Damage in the Brain in Alzheimer's Disease: Can Reducing the Damage Help in Prevention?"

Oxidative damage in the brain of patients with advanced Alzheimer's disease (AD) involves lipids, carbohydrates, proteins, and DNA. More recently, increased lipid peroxidation, protein oxidation, DNA and RNA oxidation have been found in autopsied patients with amnestic Mild Cognitive Impairment, the earliest detectable form of AD, which suggests that oxidative damage is involved early in the pathogenesis of the disease. Prevention is the key to AD and because oxidative damage is present early in the disease, antioxidant therapy has the potential of slowing or preventing the onset. It is important to use antioxidants and other neuroprotective therapy early in individuals at high risk for AD before the neurodegenerative changes occur.

1:45 p.m. **Question and Answer Session**

1:55 p.m. **Dr. J. Timothy Greenamyre, University of Pittsburgh**
"Convergent Pathways to Parkinson's Disease"

Rarely, Parkinson's disease (PD) may be caused by single gene mutations or environmental exposures, but most cases are likely related to individual genetic susceptibilities and a lifetime of environmental exposures. About one dozen genetic loci have been described and more than half of these genes have been identified. Despite the multiple genes and potential environmental causes of PD, there is increasing evidence that a limited set of pathogenic mechanisms is involved, including protein aggregation and mitochondrial dysfunction, both of which may be related by oxidative stress.

2:40 p.m. **Question and Answer Session**

2:50 p.m. **Dr. Don W. Cleveland, University of California, San Diego**
"Motor Neuron Growth and Death: Neurofilaments, SOD1 and Lou Gehrig"

ALS is characterized by premature death of motor neurons. Mutation in superoxide dismutase (SOD1) causes an inherited form through an acquired toxicity unrelated to dismutase activity. This provokes mutant-mediated damage to mitochondria only within affected tissue, which in turn triggers caspase mediated cell death. Toxicity is non-cell autonomous, requiring mutant SOD1 action on axonal elements including neurofilaments, but also requiring action within astrocytes and microglia, supporting therapy development through stem cell replacement of non-neuronal cells.

3:35 p.m. **Question and Answer Session**

3:45 p.m. **Closing Remarks - Dr. D. Allan Butterfield, Department of Chemistry, University of Kentucky**

(http://www.chem.uky.edu/seminars/naff/welcome.html)

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Thirty-First Annual
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established in the memory of
Anna S. Naff

Oxidative Stress in Aging and Age-Related Neurodegenerative Disorders

SPEAKERS

Barry Halliwell
Irwin Fridovich
Earl R. Stadtman
William R. Markesbery
J. Timothy Greenamyre
Don W. Cleveland

Friday, April 15, 2005

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