Workshop Objectives: To better understand the molecular and cellular pathophysiology of Wilson disease, and to improve upon current diagnostics and therapeutics for disorders of copper metabolism

Meeting Organizers: Michael Schilsky (Cornell U), Sihoun Hahn (University of Washington), Danilo Tagle (NINDS), and Kimberly Symonds (WDA)

Thursday, November 2, 2006

7:30-8:00 a.m. Registration/Continental Breakfast

8:00-8:15 a.m. Welcome/Introduction from NINDS and ORD: Meeting Organizers
Welcome from NINDS and ORD: Drs. Story Landis and Steve Groft
Statement of workshop goals: Meeting Organizers

8:15-10:00 a.m. Session I: Copper metabolism
Session Chair: Dennis Thiele (Michigan)
Overview of Copper Transport into Cells: - Dennis Thiele (Michigan)
Structure, function and regulation of Cu transporting ATPases in normal cells and during Inflammation – Michael Petris (Missouri)
Mechanism of action and function of copper chaperones – Tom O'Halloran (Northwestern)
XIAP: Linking Copper Metabolism to the Cell Death Machinery – Colin Duckett (Michigan)

General discussion (30 minutes)

1) What is the cellular role of copper in cellular metabolism?
2) How is copper homeostasis maintained?
3) What do we know about the cellular role of ATP7B?
4) What other players are involved in copper transport? What is the role of COMMD1?

10:00-10:15 a.m. Break

10:15-12:00 a.m. Session II: Molecular Genetics of ATP7B and Wilson disease
Session chair: Diane Cox (U Alberta Canada)
Gene discovery and mutations: Diane Cox (U Alberta, Canada)
Genotype/Phenotype correlation:
Evidence for correlation – Peter Ferenczi (U Vienna, Austria)
Evidence indicating no correlation - Hartmut Schmidt (Berlin, Germany)
Proteomic Analysis of Copper metabolism – **Han Roelofsen (University Hospital Groningen, Netherlands)**
The structure and function of nucleotide binding domain of ATP7B gene: **Svetlana Lutsenko (OHSU)**
Proteomics as a strategy for studying hepatic Wilson disease: **Bibudhendra Sarkar (U Toronto)**
NMR Spectroscopy of ATP7B – **Oleg Dmitriev (Canada)**

**General discussion (30 minutes)**

1) Is there a strict phenotype-genotype correlation? What contributes to the wide clinical spectrum?
2) Are modifier genes or environmental factors major contributors to this heterogeneity?
3) What are the major interacting proteins and what are their roles in regulating copper metabolism?
4) Can proteomic and metabolomic approaches be useful tools for biomarker discovery in WD?

12:00-1:00 p.m. **Lunch**

1:00-3:00 p.m. **Session III: Copper Metabolism and other Neurodegenerative disorders**
Session Chair: **Sharon Cooperman (NICHD)**

Aceruloplasminemia – **Zena Harris (Hopkins)**
Amyotrophic lateral Sclerosis - **TBD**
Freiderich’s Ataxia – **Robert Wilson (U Penn)**
Alzheimer’s disease – **Jack Rogers (Harvard)**
Prion - **Nibaldo C. Inestrosa (Chile)**
Copper Deficient Myeloneuropathy – **Julie Rowin (U Illinois)**
Menkes – **Steve Kaler (NICHD)**

**General discussion (30 minutes)**

1) What key role do copper transporters and metal chaperones play in the nervous system? What is the roles do these molecules play in the development of neurodegenerative diseases?
2) What is the interplay between copper deposition and the neurodegenerative disorder aceruloplasminemia resulting in abnormal iron accumulation within the central nervous system?
3) Does APP and PrP normally act as copper reductases?
4) What role does the copper binding domain play in neuroprotection?
5) How does copper lead to Aβ aggregation or in induction of PrP misfolding?
6) What is the cellular mechanism involved in the formation of these aggregates in the presence of copper?
7) What have we learned from these other copper-related diseases that will be useful in understanding WD and vice-versa?

3:00 -3:15 p.m. **Coffee Break**

3:15-5:30 p.m. **Session IV: Epidemiology and Diagnoses of Wilson Disease**
Session chair: **Sihoun Hahn (University of Washington)**
Population screening for Wilson disease in Japan: **Tsugutoshi Aoki (Toho U, Japan)**/Dr. Shimizu
European Population screening for Wilson’s disease – **Hartmut Schmidt (Berlin, Germany)**
Population Screening for Wilson disease in the US – **Sihoun Hahn (University of Washington)**
Challenges in pathological diagnosis: **Milton Finegold (Texas Children's Hospital)**
Biochemical test and it's pitfall in current diagnostic algorithm: **Anil Dhawan (King’s College, London)**
Applied molecular testing – **Matthew Ferber (Mayo Clinic)**

**General discussion (30 minutes)**

1) Is there a different clinical course of WD in different population groups? What is the mutation spectrum in these populations?
2) What contributes to a different clinical spectrum even within a family sharing the same mutations?
3) What is the best diagnostic algorithm? What are the pitfalls in making the diagnosis? – copper contamination in drinking water, ceruloplasmin levels?
4) How can molecular testing be incorporated into the clinical arena?
5) What are the limitations of clinical testing by direct DNA sequencing? How can we predict the function of unknown alterations?

5:30-6:30 p.m. **Poster Presentations:**

7:00 p.m. **Reception hosted by the Wilson’s Disease Association**

**Friday, November 3, 2006**

7:30-8:00 a.m. Registration/Continental Breakfast

Toxic milk mouse – **Julian Mercer (Deakin U, Australia)**
Knockout mouse - **Svetlana Lutsenko (OHSU)**
Canine copper toxicosis – **George Brewer (Michigan)**

8:00-9:45 a.m. **Session V: Animal Models for studying Wilson disease**

Chair: **Stuart Tanner (Children’s Hospital, Sheffield, UK)**

Rodent models: **Stuart Tanner (Children’s Hospital, Sheffield, UK)**

Long-Evans Cinnamon rat - **Diane Cox (U Alberta Canada)**

**General discussion (30 minutes)**

1) How faithful are the animal models in replicating the human disease? What are their limitations?
2) How can these animals be used best for studying copper transport mechanisms and homeostasis?
3) What insights have we learned from the various treatment strategies employed in these animal models? – cell transplantation, gene transfer, copper chelating compounds
4) Are the efficacy results from the animal work predictive of human trials?

9:45-10:00 a.m. **Break**

10:00-12:00 a.m. **Session VI: Clinical Spectrum of Wilson disease**

Session chair: **Eve Roberts (U Toronto)**
Adult clinical spectrum: **Irmin Sternlieb** or **Michael Schilsky (NY)**
Pediatric considerations: **Eve Roberts (U Toronto)**
Age of onset and prognosis in Wilson disease - **Wolfgang Stremmel (U Heidelberg, Germany)**
Neurological and psychiatric aspects of WD: **John Fink (Michigan)**

General discussion (30 minutes)

1) What is the long term prognosis on living donor liver transplant for WD?

2) Why do some patients manifest neurologic symptoms while others do not?

3) What are the clinical overlaps of WD with other copper-related neurological disorders? What are the implications of these in terms of pathomechanisms?

4) What useful instruments are currently being used or should be used for documenting the disease manifestations, such as neurological scales, psychiatric/psychological testing, imaging techniques, etc.? Are these useful for following treatment or prediction of outcome?

5) What can diagnostic testing yield with respect to analysis of neuro/psychiatric disease?

12:00-1:00 p.m. **Lunch**

1:00-2:30 p.m. **Session VII Treatment Strategies for Wilson disease**
Session chair: **Michael Schilsky (Cornell, NY)**

Chelators (Penicillamine, Trientine, Tetrathiomolybdate)- **Fred Askari (Michigan)**
Zinc therapy- **George Brewer (Michigan)**
Liver transplantation – **Michael Schilsky (NY)**

2) What side effects can accompany treatment with drugs – joint pains, neurological problems that affect mental abilities, problems with blood clotting, allergic reactions, etc.?

Cell transplantation – **Sanjeev Gupta (NY)**
Gene therapy/repair –
Jayunta Roy
Chowdhury(NY)

General discussion (30 minutes)

1) What are the challenges in treatment of WD?

3) Why does neurological worsening persist in some cases?

4) What complications and long term outcome can be expected from current treatment strategies?

5) What are the treatment options for primarily neurologic cases? Are there other approaches that can improve their quality of life?(rehabilitation, botox, etc.)

2:30-4:00 p.m. **Summary and Future Directions**

- Research resources
- Pathogenic mechanisms
- Animal models
• Diagnostic and clinical measures
• Treatment strategies and practices
• Future research priorities and collaborations

Meeting Adjourns