Greetings from the New ULF President

Some of you know that the ULF has been through a difficult year: first, the death of Ron Brazeal, former Executive Director; the death of Janet Read, the Office Manager; the death of Director Anne Marten; and then the death of Paula Brazeal, immediate past President on September 22. Additionally, the ULF offices were moved to a new address in DeKalb, IL, in early July. I know that you all join with me in a sincere word of appreciation to the Board of Directors and to Kirsten Kotlarchik, ULF Office Manager, for their diligent hard work during the move and in the transition of leadership. We are working our way through a rough time and a myriad of details.

Consequently, this is the first newsletter in more than a year. I trust you will enjoy catching up with your reading of all the enclosed. I want to emphasize how important each of you are to the ULF family. We exist to serve all who are afflicted by white matter diseases. Whether you are new or have been with the ULF for a long time, your participation and generosity are very important to all of us. The ULF derives all of its support from the generous giving of member families and friends. Perhaps the best gift you may offer in this holiday season is a special financial love gift to the ULF. Gifts in memory or in honor of loved ones are always most appreciated.

Our summer conferences over the years have been the way in which we communicate personally from our scientists and researchers the very latest in our fight to bring therapies and life saving measures to all our afflicted family members. Last summer we celebrated our 30th year. This coming summer, July 19 and 20 (Friday & Saturday), 2013 we will gather in DeKalb, IL, for a single meeting bringing together the latest in science and family support. Our thirty-first annual meeting will be dedicated to the memory of Paula Brazeal, as we remember her many years of service as ULF President.

Please watch our web site at ulf.org for ongoing information and important updates for conference registration. The registration deadline will be earlier this year in order to meet the demands of hotel deadlines and travel arrangements for conference presenters. Please plan now to attend. This will be a meeting not to be missed!

Peace and Joy to you in this New Year!

William Kintner, D.Min., Th.M.
ULF President
The 2011 ULF Scientific Meeting brought together a number of investigators and physicians, who presented their latest research findings on X-Linked adrenoleukodystrophy (X-ALD), Metachromatic leukodystrophy (MLD), Canavan disease and autosomal dominant leukodystrophy. The sessions covered a range of topics from basic science issues to clinical medicine. As always, the participants interacted informally to discuss common research interests and foster collaborations to help advance our understanding of these diseases.

**Bjorn van Geel, M.D., Ph.D.,** (Medical Center Alkmaar, Amsterdam) presented his recent findings on adrenomyeloneuropathy (AMN), a form of ALD that has onset after the second decade of life with prominent spastic paraparesis and adrenal insufficiency. In the Dutch cohort of 27 AMN patients studied over the course of 12.6 years, he found a much higher incidence of cerebral Demyelination (60%) than expected. The cerebral Demyelination had its onset from 5-25 years after spinal cord involvement became apparent and occurred in some patients at older ages, even after 60 years of age in 3 patients. This strikingly high incidence of cerebral involvement in the AMN group is disturbing, and indicates the need for more aggressive surveillance and treatment for AMN.

**Wolfgang Koehler, M.D.,** (Fachkrankenhaus Hubertusburg, Wermsdorf, Germany) presented his ongoing experience using hematopoietic stem cell therapy (HSCT) for adult ALD patients with cerebral Demyelination. Five patients, ages 32-48 years, have been treated long enough to analyze results so far (1-3 years). Three of the patients initially had AMN, whereas the other 2 were apparently normal prior to cerebral onset. Three patients showed stable clinical function and some showed improvement in MRI abnormalities. After transplantation, all 5 patients showed transient bladder dysfunction, and 4 patients had transient motor deterioration and transient organic psychiatric symptoms. He found that the pattern of brain involvement may impact survival after HSCT, i.e. men with parieto-occipital Demyelination had a better outcome than those with frontal predominance. Overall, the transplant response tends to be similar to that seen in childhood cerebral ALD. He emphasized the need to better define AMN patients with cerebral involvement at an early disease stage, and the need for conservative myeloablative therapy with reduced intensity conditioning to limit neurotoxicity.

**Stephan Kemp, Ph.D.,** (Academic Medical Center, Amsterdam) discussed his research to develop an improved mouse model for ALD. An ALD genetic knockout mouse (Abcd1−/−) was first generated more than 10 years ago. The mice had elevated very long-chain fatty acids (VLCFA) in various tissues, but did not have a neurologic phenotype until they were very old (>20 months). Even then, they resembled human AMN rather than the cerebral Demyelination seen in ALD boys. Based on subsequent human studies that pointed to increased VLCFA in brains of cerebral ALD compared to AMN, he reasoned that greater accumulation of VLCFA in the Abcd1−/− mice might result in an earlier ALD phenotype. He therefore generated ALD mice that also contained a “turned on” Elovl1 gene, which oversynthesizes VLCFA. These mice accumulated 2-fold more c26:0-lyso-PC in brain and 10-fold more C26:0 in adrenal glands compared to the previous ALD mice. Feeding the new ALD Mice a diet with excess VLCFA led to abnormal myelin unfolding and shredding on electron microscopy. The new ALD mice are being used now to investigate the role of VLCFA in Demyelination and adrenal disease.

**Marc Engelen, M.D.,** (Academic Medical Center, Amsterdam) presented results of a clinical trial of bezafibrate in AMN. Bezafibrate is a drug that reduces serum triglycerides and cholesterol, but it also reduces VLCFA (C26:0) accumulation in ALD fibroblasts by inhibiting the ELOVL1 enzyme that synthesizes VLCFA. He treated 10 AMN patients with 400 mg bezafibrate for 12 weeks, followed by 800 mg for a similar period. As expected, patients showed a reduction in triglycerides, a decrease in LDL cholesterol. However, C26:0 did not change, and C22:0 and C24:0 actually increased in plasma. In lymphocytes, there was no change in C26:0 or C26:0-lyso-PC in blood showed no change. This study illustrates the importance for thorough clinical evaluation of potentially promising drugs in ALD and other leukodystrophies.

**Keith Van Haren, M.D.,** (Stanford University) discussed the potential role of autoantibodies against myelin components in the initial steps in the inflammatory response in cerebral ALD. In ALD, VLCFA are elevated in myelin lipids, such as gangliosides and phosphatidylcholine, and are also bound to myelin proteins, such as proteolipid protein (PLP). These are potential antigens that may incite an inflammatory response typically seen in the brain of cerebral ALD patients. Using autoantibody arrays for lipid and acylated myelin proteins, he has developed a rapid screening method for detecting antibodies directed against lipids and proteins. He has detected IgG antibodies in the cerebral spinal fluid of ALD patients that target acylated peptide regions of PLP. Antibodies were also found to target some lipids, especially lyso-PE, C24:0, sulfatides and cerebrosides. The presence of autoantibodies against myelin components may be integral to the inflammatory reaction seen in the brain of ALD patients.
Patricia Musolino, M.D., Ph.D., (Massachusetts General Hospital) discussed the role of altered blood-brain barrier and perfusion abnormalities in cerebral demyelination of ALD. She noted that pathologic abnormalities in cerebral perfusion seem to precede the active demyelination. These perfusion abnormalities are regulated by the neurovascular unit in ALD, in which capillary pericytes that surround vessels proliferate and cluster, even in distal regions with no active demyelination. This process is also seen in Abcd1 KO mice that don’t have obvious symptoms. Pericytes (NG2-staining) are derived from the bone marrow and can differentiate into glial and mesenchymal cells, including phagocytic macrophages, which are important in angiogenesis. In brain, pericytes are located in pre-capillary arterioles and, following injury, can migrate along the vessels and relocate in the perivascular space, where they become macrophages when activated. In ALD brain, Dr. Musolino hypothesizes that abnormal accumulation of by-products in cells of the neurovascular unit (pericytes, endothelium, perivascularg macrocytes) alters the homeostasis of the brain parenchyma by allowing increased access of circulating homeostasis of the brain parenchyma by allowing increased access of circulating bone marrow-derived monocytes, triggering a pro-inflammatory state and leading to acceleration of myelin degeneration. It is possible that hematopoietic stem cell transplantation is able to stabilize Demyelination in ALD by replacing its bone marrow derived elements and restoring function of the neurovascular unit.

Aurora Pujol, M.D., Ph.D., (L’Hospitalet de Uobrhat, Barcelona, Spain) reported on her studies that have implicated the role of oxidative damage and reactive oxygen species (ROS) in ALD. By measuring biochemical markers of oxidative stress, she has found evidence for early oxidative damage in the ALD mouse brain and spinal cord, even before any clinical phenotype is seen. In cultured ALD cells, C26:0 accumulation results in elevations in oxidative markers, pointing to VLCFA as causative for the oxidative stress. This was associated with reduced NADH and ATP levels, suggesting that the oxidative damage leads to bioenergetic failure and general metabolic dysregulation. Importantly, antioxidants prevented C26:0-mediated ROS generation in ALD fibroblasts. In ALD mice, a mixture of antioxidants decreased oxidized proteins in spinal cord, improved NADH levels, reversed axonal degeneration and improved locomotor disability. These animal studies showed proof of concept that oxidative stress is a major causative factor underlying axonal degeneration. She will begin a small pilot clinical trial of antioxidants in AMN patients later this year. She cautioned that the doses of antioxidants given to the mice were unusually high and may be associated with harmful toxic effects in man.

Inderjit Singh, Ph.D., (Medical University of South Carolina) discussed potential drugs for inhibiting the inflammatory reaction in the brains of patients with cerebral ALD. Previous studies suggested that lovastatin and phenylacetate lower VLCFA levels in cultured cells for ALD patients, and they also might inhibit the cerebral inflammatory reaction. Lovastatin helps protect neurodegeneration in several animal models of brain degeneration, perhaps mediated by a reduction in isoprenoid metabolism rather than cholesterol synthesis. Cultured oligodendrocytes and astrocytes both respond to VLCFA accumulation, but in different ways; astrocytes produce inflammatory molecules (i.e. cytokines, iNOS, 5-lipoxygenase), whereas oligodendrocytes die. Histone deacetylase inhibitors, such as phenylacetate and SAHA, also help preserve white matter in animal models. Like phenylacetate, SAHA increases gene expression of Abcd2 and Abcd3 in cultured ALD fibroblasts, which is associated with increased fatty acid oxidation and decreased levels of VLCFA. It also inhibits proinflammatory cytokines and oxidative stress in Abcd1/2 silenced mouse astrocytes. SAHA is an experimental drug that is currently being studied for other diseases in humans. These promising drugs may ultimately be beneficial in patients with ALD, but need further study.

Gerry Raymond, M.D., (Kennedy Krieger Institute, Baltimore) summarized efforts from the Kennedy Krieger Institute and Johns Hopkins to develop methods for newborn screening of ALD. He noted that there was a need to identify affected patients as early as possible since some presymptomatic ALD boys already show elevations in ACTH by 2 years of age, indicating the pres-ence of adrenal gland dysfunction which can be the initial symptom of this disease. Together with Ann Moser, B.A., (Kennedy Krieger Institute) and Walter Hubbard, Ph.D., (Johns Hopkins School of Medicine), newborn blood spots from 16 known ALD mails were found to have 10-fold elevations in C26:0-lyso-PC as a screening test for ALD infants. In a pilot feasibility study, they screened 4,688 newborns in Maryland over a 1-year period and found no false positive infants. Research is underway to help newborn screening labs save time and effort by combining the ALD test with the standard acylcarnitine measurements.

Alexandre LeBeaut, (Bluebird Bio, Cambridge, MA) presented and exciting update on gene therapy for cerebral ALD, pioneered by Dr. Patrick Aubourg of Paris. Like other ALD patients suitable for bone marrow transplantation, all ALD patients were treated in the earliest stages of cerebral Demyelination. Their hematopoietic stem cells were harvested from bone marrow, transfected with Lentivirus carrying the normal ABCD1 gene and subsequently transfused back into them. The overall experience with gene therapy of ALD is still limited. To date, Dr. Aubourg has treated 4 patients, who have been subsequently followed for 9 to 57 months post treatment. All 3 patients with enough time in follow up have stable MRI scores. No serious adverse side effects or graft-versus-host disease developed. Additional patients will need to be treated to judge the efficacy of gene therapy. Current plans are to enroll 12 early childhood-onset cerebral ALD patients in a Phase 2/3 clinical study, which will be conducted at 3 sites (Paris, Boston and Los Angeles).
Gustavo Maegawa, M.D., Ph.D., (Johns Hopkins University) addressed the value of certain small molecules as drugs for the treatment of metabolic brain diseases caused by lysosomal enzyme deficiencies. These molecules are more likely to cross the blood brain barrier and enhance enzyme activity by acting as molecular chaperones. In some instances, it is only necessary to increase function of a mutant enzyme by a small amount to have a major impact on clinical symptoms. Dr. Maegawa has developed methods to screen for thousands of potential drugs for GM2 gangliosidosis using high throughput assays and has identified and FDA-approved anti-malarial drug that can increase activity of the mutant enzyme. The drug binds to the mutant enzyme in the cytosol where it assists proper folding and is then dissociated from the enzyme when it travels to the lysosomes. Newer approaches for small molecule screening takes advantage of intact cells from the patient to take up the molecule and metabolize it to an active agent. These cell-based assays do not require the small molecule to work on a known molecular target - for example, the mutant enzyme - and thereby expands the repertoire of available targets and simultaneously generates initial cytotoxicity data. In Metachromatic leukodystrophy (MLD) and Krabbe disease, there are common mutations that increase the likelihood that multiple patients may respond to a small molecule drug. He is screening small molecules for potential use in MLD and Krabbe disease.

Guangping Gao, Ph.D., (University of Massachusetts Medical School) reported on efforts to explore gene therapy for Canavan disease. This disease is caused by deficiency of aspartoacylase (ASPA), an enzyme that metabolizes N-acetylaspartic acid (NAA) in the brain. The challenge for gene therapy is to replace ASPA in the entire brain. Initial studies to replace the ASPA gene in Canavan Patients by injecting the ASPA gene directly into the brain showed no significant clinical response. Dr. Gao has been investigating AAV viral vectors and has found striking differences in various AAV strains with respect to delivery of the ASPA gene. Using the Canavan mouse as recipient, he found the AAV.rh10 is the most effective AAV vector for transducing brain and spinal cord. The Canavan mouse normally dies at 25 days of age, but animals treated with AAV.rh10 carrying the ASPA gene survive long term. The Vector crosses the blood-brain barrier and transfects the entire brain. Mice injected at day 2 of life, and even later on day 14, showed reduced motor disability, improved gait, vision and NAA excretion in urine. The neuropathology was also prevented or mitigated by gene therapy.

Reuben Matalon, M.D., Ph.D., (University of Texas Medical Branch, Galveston) raised the possibility of enzyme replacement therapy for Canavan disease. Dr. Ron Viola, Ph.D., (Toledo, OH) has produced recombinant ASA and administered it to Canavan mice via an intrathecal route. It retained catalytic activity and resulted in reduction of NAA levels in brain. Additional animal studies will need to be done to fully evaluate intrathecal ASPA, but these initial studies raise the possibility that Canavan disease may be treatable in this fashion. The advantage of enzyme replacement therapy over other modalities is based on emerging experience with other metabolic diseases, which suggest that it is superior to intravenous enzyme therapy for treating brain diseases.

Quasar Padiath, MBBS, Ph.D., (University of Pittsburgh) has been investigating Autosomal Dominant Leukodystrophy (ADLD), a disease that appears during the 4th or 5th decade of life, and is usually fatal within 20 years. Patients often demonstrate autonomic dysfunction followed by loss of fine motor control. Dr. Padiath found that the affected patients have a duplication of the LMNB1 gene. He has identified 9 families with ADLD. The duplications in some families differ slightly and therefore have occurred independently. In one patient studied postmortem, lamin B1 protein was elevated in the brain. This protein is located just beneath the nuclear membrane and functions as part of the nuclear lamina structure that supports the nuclear envelope and anchors nuclear pore complexes. Over expression of this gene causes nuclear blebbing. Lamin B1 may be involved in epigenetic chromatin modifications, specific histone methylation and acetylation patterns, and Pol II-mediated transcription of genes. Although lamin B1 is a member of a larger family of lamins, which are associated with at least 12 distinct diseases (Laminopathies), it is unclear how duplication of LMNB1 results in late-onset white matter disease. Transgenic mice that over express lamin B1 develop motor abnormalities by 18 months of age. Studies in transgenic mice are in progress to identify the critical brain cell types that are most important in ADLD leukodystrophy.

2012 PROPOSED BY-LAWS ELECTION RESULTS:

The ULF Scientific Meeting took place on July 12, 2012 in conjunction with the Family Conference. The meeting brought together scientists and physicians from the United States, Canada and Europe to discuss their latest research results on leukodystrophies and share ideas about their treatment. The Meeting focused on 1) new leukodystrophies and the genes that cause them; 2) new understanding of established leukodystrophies; and 3) novel approaches to therapy.

New Diseases and Genes
Adeline Vanderver, M.D. (Children’s Hospital National Medical Center, Washington DC) discussed a new algorithm for classification of the leukodystrophies. The impetus for this reclassification was the discovery of new white matter diseases over the past several years and the need to update our working knowledge of the leukodystrophies as new pathogenic mechanisms are discovered. The classification is meant to be particularly useful for epidemiologic comparisons of disease incidence and distribution. It also provides guidance for the practicing neurologist and other physicians when facing a bewildering array of leukodystrophies that now includes dozens of diseases. One aspect that was emphasized is the lack of neuropathological information about many of the hypomyelinating leukodystrophies.

Genevieve Bernard, M.D., MSc, FRCPC (McGill University, Montreal, Canada) reported on a novel group of white matter diseases caused by genetic defects in RNA polymerase III (Pol III). These leukodystrophies have been discovered over the past several years and have some overlapping clinical features, which have been used to name them: 1) Leukodystrophy with oligodontia, 2) Ataxia, delayed dentition and hypomyelination, 3) Tremor ataxia with central hypomyelination (TACH), and 4) Hypomyelination, hypodontia, hypergonadotropic hypogonadism (4H disease). Recently, Dr. Bernard’s genetic linkage studies on TACH led to the identification of mutations in the RNA polymerase gene POLR3A. Due to some overlapping symptoms between TACH and some of the other leukodystrophies, she screened additional families and found POLR3A mutations in patients with 4H disease and some patients with hypomyelination and a thin corpus callosum. Because the POLR3A protein interacts with another protein, POLR3B, to generate an active RNA polymerase, Dr. Bernard screened additional hypomyelinating patients and identified families with mutations in POLR3B. RNA polymerase POL III transcribes small RNAs such as trRNA and microRNAs. Disrupted expression of these RNAs is thought to be responsible for the abnormal myelin integrity and alterations in dentition seen in patients.

William Rizzo, M.D. (University of Nebraska Medical Center, Omaha) described a new form of leukodystrophy that is associated with ichthyosis (dry scaly skin), seizures, intellectual impairment and spastic quadriplegia. The disease resembles Sjögren-Larsson syndrome. Patients from two unrelated families were identified. One 5-year-old boy with severe seizures had an MRI that showed white matter disease and brain atrophy. A second family had two affected boys who died by 2 years of age. The disease is caused by mutations in the ELOVL4 gene, which codes for an elongating enzyme that is essential for synthesizing fatty acids longer than 26-carbons. These unusual fatty acids are prominent in the membranes of the skin, where they are necessary for the cutaneous water barrier, and in myelin and retinal phospholipids. Deficiency of the fatty acids is responsible for the symptoms seen in patients. An Elovl4 knockout mouse shows ichthyosis and dies from dehydration on the first day of life, but exhibits no neurologic symptoms. There is no proven therapy for ELOVL4 deficiency in humans, but the ichthyosis could theoretically respond to topical very long-chain fatty acids. Unfortunately, these fatty acids probably do not enter the brain sufficiently to have an impact on the neurologic disease.

New Understanding of Established Leukodystrophies
There is great interest in the application of stem cells for understanding and treating genetic diseases of all types. In an effort to gain insight into the neurologic abnormalities in X-linked adrenoleukodystrophy (X-ALD), Joseph Hacia, Ph.D. (University of Southern California, Los Angeles) has made pluripotent stem cells (or iPS cells) from X-ALD patients using their cultured skin fibroblasts. These iPS cells have the potential to differentiate into oligodendrocytes and other brain cells that are affected in X-ALD. Dr. Hacia defined the gene expression profile in the normal and X-ALD iPS cells and their corresponding fibroblasts using microarray analysis and characterized their lipid abnormalities. As expected, the iPS cells differed considerably from their progenitor fibroblasts with respect to gene expression profiles. Surprisingly, the iPS cells from X-ALD patients did not accumulate C26:0 fatty acid, which is the biochemical hallmark of this disease, but did show abnormal expression of several genes involved in peroxisome function and neuro-inflammation. Future studies will be focused on investigating X-ALD oligodendrocytes produced from these cells. These iPS cells are a unique cellular tool for investigating the molecular and biochemical features of this leukodystrophy.
Women who are carriers for the X-ALD gene are at risk for developing neurologic symptoms in adulthood. **Marc Engelen, M.D.** (Academic Medical Center, Amsterdam) reported on a prospective study to characterize the clinical and biochemical features of carrier women. He studied 46 women who ranged in age from 22-76 years (mean 48 years). A subgroup of the women had some degree of urinary incontinence (21/46), gait disorder (22/46) and sensory complaints (15/46) that tended to increase with age. Overall, 74% of all adult carrier women had neurologic symptoms of some type, and 88% of those greater than 60 years old were symptomatic. Evoked studies (NCV, BAER, SSEP) done on the women were frequently abnormal, but were no more sensitive for detecting clinical involvement than neurologic examination alone. It has been assumed that symptomatic carrier women developed symptoms because they had a preponderance of cells expressing the mutant X-chromosome with the X-ALD gene. Indeed, Dr. Engelen found a good correlation between the skewing of X-chromosome inactivation in cultured skin fibroblasts and C26:0 accumulation, but this did not hold for clinical symptoms, suggesting that the relative proportion of active X-chromosomes expressing the mutant X-ALD gene in fibroblasts does not explain the expression of neurologic symptoms in female carriers.

A perplexing issue for X-ALD is why some patients develop the childhood cerebral form of the disease (CCALD), whereas other patients escape this severe form and later develop the more common spastic paraparesis of adrenomyeloneuropathy (AMN) without cerebral demyelination. **Keith Van Haren, M.D.** (Stanford University, Palo Alto), drawing upon studies in multiple sclerosis showing low vitamin D levels as a risk factor for demyelination, wondered whether vitamin D deficiency might be involved in X-ALD. In collaboration with **Gerald Raymond, M.D.** (Kennedy Krieger Institute, Baltimore), a pilot retrospective analysis was performed in 8 presymptomatic patients who later developed CCALD and 8 age-matched control patients who did not convert to CCALD. Plasma vitamin D levels were controlled for seasonal variation and all patients were taking Lorenzo's oil. The mean vitamin D level was significantly lower in patients who converted to CCALD compared to the controls who did not; this finding was associated with a 76% reduction in risk for conversion. This pilot study will need to be replicated using more patients, but it raises the question about whether vitamin D, which has known effects on innate and adaptive immunity, might be a risk factor in X-ALD. For example, low vitamin D levels have been associated with relapsing multiple sclerosis and other auto-inflammatory diseases.

Animal models of leukodystrophies are critical for understanding pathogenesis and developing new treatments. The Abcd1 knockout mouse model for X-ALD shows a late onset phenotype resembling AMN, but not the early cerebral demyelination typically seen in X-ALD boys (CCALD). In at attempt to induce cerebral disease in mice, **Stephan Kemp, Ph.D.** (Academic Medical Center, Amsterdam) generated mice that have two genetic defects: knockout of Abcd1 and overexpression of Elovl1, an enzyme that synthesizes very long-chain fatty acids. The double mutant mice accumulate much more C26:0 in their tissues than the Abcd1-/ mice alone. By generating double mutant mice that selectively accumulate C26:0 in oligodendrocytes or astrocytes, he found that the astrocyte-altered mice developed behavior abnormalities at 3 months and exhibited activated microglial cells in their brain, a feature of CCALD in X-ALD males. The oligodendrocyte-altered mice exhibited neurologic symptoms at an even younger age (9-13 weeks) with grossly abnormal motor testing. These double mutant mice need further characterization, but they should be a much better animal model for X-ALD and will be important for preclinical therapeutic studies.

To gain insight into the lipid abnormalities associated with brain demyelination in X-ALD, **Ann Moser, B.A.** (Kennedy Krieger Institute, Baltimore) reported on detailed measurements of lipids in regions of demyelinating brain and distant areas. Brain regions were identified by histological examination and ex vivo MRI. Using LC-mass spectrometry, she found that several lipids containing very long-chain fatty acids were elevated in demyelinating regions, including lyso-PC, lyso-PAF, ceramides, sphingomyelin and gangliosides. Consistent with a process of increased oxidative stress. These studies indicate that lipid abnormalities are a major precursor for the demyelination that occurs in X-ALD.

**Albee Messing, V.M.D., Ph.D.** (Waisman Institute, University of Wisconsin, Madison) reported on studies to discover a biomarker to monitor future therapy for Alexander disease (AD). This disease is a dominant leukodystrophy caused by de novo mutations in the gene for glial fibrillary acidic protein (GFAP). GFAP has been reported to be elevated in urine of patients and AD mouse models. Since this protein may have toxic properties, GFAP reduction is a goal for AD therapy. Dr. Messing therefore measured GFAP in CSF samples from 11 patients and plasmas from 41 patients. CSF GFAP was elevated in most AD patients (mean 6000 vs 250 in controls), whereas plasma GFAP tended to be elevated but showed much overlap with the normal range. Efforts are continuing to use GFAP from biological specimens as a therapeutic monitor and search for additional biomarkers for AD.
New Therapies for Leukodystrophies

Ali Fatemi, M.D. (Kennedy Krieger Institute, Baltimore) discussed the potential for glial precursor cells to be used for therapy of the leukodystrophies. These cells have the ability to differentiate into pro-oligodendrocytes and mature oligodendrocytes. All precursor cells, however, do not behave the same. Glial restricted precursor (GRP) cells, when injected into the brains of animals, have the ability to migrate to more distant sites within the brain, whereas migration of other oligodendrocyte progenitor cells is more restricted. Human oligodendrocyte progenitor cells and GRPs both completely remyelinate the brain in the Shiverer mouse model of leukodystrophy, and precursor cells injected into ventricles of MLD mice result in decreased microglial activation and sulfatide deposits in brain associated with improved motor potentials. The transplantation of GRPs or oligodendrocyte precursor cells may be most useful in hypomyelinating syndromes with primary myelin deficiencies. These animal studies indicate that cell-based therapy for the leukodystrophies is very promising; however caution must be raised for humans because there is one report of brain tumor formation after stem cell transplantation in a young boy.

Jacqui Hawkins, Ph.D. (Washington University, St. Louis) described her studies to develop therapy for the Twitcher mouse, which is a model for Krabbe disease. Like humans, the mice have galactocerebrosidase deficiency and accumulate psychosine in their brains. Twitcher mice develop tremors at 21 days of age and die of progressive neurodegeneration by approximately 40 days of age. A number of therapeutic approaches have been tried including enzyme replacement therapy (ERT), bone marrow transplantation (BMT), substrate reduction therapy (SRT), gene therapy (GT) and anti-inflammatory drugs. SRT and anti-inflammatory drugs each seem to extend lifespan to about 55 days of age, while treatment with ERT, BMT and GT results in a 70-day lifespan. Dr. Hawkins reported that BMT in combination with GT using AAV2/5 virus administered by intracranial injection resulted in a much longer lifespan with some animals living to almost 300 days of age, indicating a synergistic effect of BMT+GT. Immunomodulation may be important as a therapeutic mechanism since there is some inflammatory component to the demyelination. BMT reduces inflammatory cells in the brain, and decreases microglial activation and astrocytosis, resulting in an almost normal histological appearance. Nevertheless, there was some limitations of GT+BMT, because the treated Twitcher animals had decreased weight gain and had abnormal behavior. Dr. Hawkins therefore used a combination of 3 therapeutic modalities (GT, BMT and SRT with L-cycloserine) and found that the mice survived for up to 450 days (average 300 days) and behaved normally. These studies highlight the probable need for combination therapy of Krabbe disease and other leukodystrophies.

4-Aminopyridine is a drug that has shown some efficacy in patients with multiple sclerosis. The drug is a reversible potassium channel blocker, which improves the impaired nerve conduction velocity caused by myelin damage. Wolfgang Koehler, M.D. (Fachkrankenhaus Hubertusburg, Wermsdorf, Germany) reported on the use of 4-aminopyridine in 18 patients with pure AMN. The patients were administered 10 mg orally for 4 weeks. Approximately 30% of patients seemed to respond with a 20-30% increase in walking velocity. Some patients reported improved balance, muscle strength, spasticity and bladder function, but there was a great deal of variability. The benefit seemed to be independent of the stage in the disease or severity of impairment. The response in AMN was similar to that seen previously in multiple sclerosis. This initial pilot study is encouraging for AMN patients and points to the need for further investigation.

Aurora Pujol, M.D., Ph.D. (Institut d’Investigació Biomèdica de Bellvitge, Barcelona, Spain) reported on a pilot clinical trial for treatment of AMN using antioxidants. This trial is based on prior studies in cultured fibroblasts and the X-ALD mouse model that showed evidence of increased oxidative stress. Oxidative damage is an early occurrence in X-ALD mice. Treatment of Abcd-/- mice with antioxidants lowered markers for oxidative stress, increased ATP levels and prevented oxidative damage in the spinal cord of the mice. Antioxidant treated mice showed increased balance and ran on a treadmill much longer than untreated mice. Based on these studies, an open label clinical trial of antioxidants has been started in 13 AMN patients with monitoring of oxidative biomarkers, biochemical efficacy and neurologic function. Patients will be treated for 12 months. Interim biochemical results after several months showed a reduction in most oxidative biomarkers. No adverse effects have been seen so far. The trial is still ongoing and will be completed in 2013. We have hopeful anticipation that this therapy will improve the clinical symptoms of AMN.

DON’T FORGET TO SAVE THE DATE:

OUR ULF 2013 SCIENTIFIC SYMPOSIUM AND FAMILY CONFERENCE DATES ARE:

THURSDAY, JULY 18, 2012 IS OUR ANNUAL MEDICAL & SCIENTIFIC MEETING
FRIDAY & SATURDAY, JULY 19 & 20, 2013 IS OUR ANNUAL FAMILY CONFERENCE
History and recent developments:

It was Hugo Moser’s dream to identify boys with ALD early, at a time before Addison’s disease and brain dysfunction occurred. In 2005 Hugo suggested to the national newborn screening committee that ALD be added to the list of disorders that would possibly benefit from newborn screening, however, at that time there was no test for ALD utilizing the sample collected on all newborns, the heel stick blood spot on filter paper.

In order to develop a newborn test for ALD Hugo and I contacted Walter Hubbard, Ph.D. at the Dept. of Clinical Pharmacology at Johns Hopkins. Walter is an expert in liquid chromatography tandem mass spectroscopy (LC/MSMS) of lipids and he was interested in helping us devise a test for ALD utilizing the newborn dried whole blood spot (DBS). We first used LC/MSMS to measure the total lipid C26 fatty acid content of the DBS and also the C26 content of other lipids such as ceramides and sphingomyelins, but found that the naturally high red blood cell C26 content interfered and gave many false positives. Finally in January of 2006, we determined that the C26 content of the lyso phosphatidylcholines (lyso PC) was 5 to 10 fold higher in whole venous blood spots from ALD patients when compared with controls. This finding was published in the Molecular Genetics and Metabolism in 2006. There was still much more work to be done to validate the assay. We contacted Walter Shaw at Avanti Lipids and paid for the custom synthesis of an authentic C26:0 lyso PC standard and a 4 deuterium labeled C26:0 lyso PC as an internal standard. With IRB permission, we obtained the newborn blood spots from known ALD patients born in the states of CA and MI. At the same time we also tested anonymous leftover newborn DBS from the States of MD, CA, the CDC and Costa Rica and found no positives. The ALD newborn DBS had a 5 to 10 fold increased C26:0 lyso PC with no overlap when compared with the anonymous newborn DBS. These findings were published in Molecular Genetics and Metabolism 2009. Since that time we have developed a high throughput LC/MSMS screening procedure and have published a combined extraction of the C26:0 lyso PC with that of the acyl carnitines. Recently together with the MD State Newborn Screening Lab, we have completed the screening of 5000 consented newborns born in 3 local Baltimore hospitals and did not find one positive, thus we believe that using our procedure the false positive rate will be low.

From the beginning of our interest in developing ALD newborn screening, our colleagues Drs. Piero Rinaldo, Silvia Tortorelli and Dieter Matern at the Mayo Clinic were very supportive of our initial efforts and made significant contributions to the design of our study and to our method of analysis. In addition at the newborn screening lab at the Mayo Clinic, they developed their own rapid high throughput method of LC/MSMS analysis of the newborn DBS for ALD and obtained funds to do 100,000 anonymous newborn DBS from the state of California. To date they have analyzed 60,000 and have found 20 positive samples. The plan is to confirm these positives by DNA sequencing of the ALD gene in these positive newborn DBS samples. Steven Steinberg, PhD and colleagues at the DNA Diagnostic Lab at Johns Hopkins will provide the DNA analyses. We expect to find that most of the positives, males and females, will have a mutation in the ALD gene, but there may be a few positives from newborns with Zellweger spectrum disorders and these samples will be analyzed and confirmed by the Peroxisomal Lab at the Kennedy Krieger Institute.

In order to have ALD newborn screening confirmed for inclusion in the panel of disorders recommended for newborn screening nationally, Amber Salzman, PhD and Charlie Peters, MD prepared the nomination form for the inclusion of ALD. The nomination was reviewed and on September 13, 2012 Gerald Raymond, MD, Amber Salzman’s 12 year old son, Spencer Barsh, 14 year old Taylor Kane, daughter of Jack Kane who died with ALD, and I testified before the Secretary’s Advisory Committee on Heritable Disorders in Newborns and Children (HRSA) in Washington on behalf of many advocate organizations including: The Stop ALD Foundation, ALD/AMN Global Alliance, Be A Hero Become A Donor, Fight ALD, The Myelin Project, Run4ALD, ELA and the ULF. Unfortunately the HRSA Review Committee did not recommend inclusion of ALD in the Recommended Uniform Screening Panel at this time. The following quotes are from a letter from Joseph A. Bocchini Jr, MD, Chairperson of HRSA dated 10/1/12.

“The Committee recognizes ALD as a medically important disorder that deserves serious consideration, possessing a well-established case definition as well as screening, diagnostic, and treatment protocols. However, at this time the Committee has decided to not send the nomination forward to the external review group.

The Committee’s decision is based primarily on the determination that sufficient prospective data is not yet available from the large pilot study presently underway at the Mayo Biochemical Genetics Laboratory (MBGL).

After the additional data from the MBGL study is made available to the Committee for evaluation, we encourage you to contact us to facilitate an expedited review. The Committee will then determine whether the new data provides sufficient support for the Committee to request a formal review of the scientific evidence by the external condition review group.”

Based on the letter from HRSA we are proceeding with our plan to confirm the positive newborn DBS from the pilot study at Mayo. It is our hope that sufficient data will be available for the May 16th 2013 meeting of HRSA and that the Review Committee will accept the nomination that ALD newborn screening be forwarded to the external review group where it will take up to a year before the final recommendation of ALD to the Uniform Screening Panel.
Yesterday I forwarded 120 anonymous venous DBS from ALD, ALD heterozygotes, and Zellweger spectrum disorders from our collection of consented research samples to Silvia Tortorelli, MD at the Mayo Clinic so that the positive sample data collected by the Mayo Clinic can be augmented. We thank all the patients and their families for their willingness to provide samples for the ALD DBS screening data.

Ann Moser, January 9, 2013

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Maximilian Bokemeier: November 29, 2010, loving son of Uwe and Heike Bokemeier, loving brother of Theresa Bokemeier, Kirchlenegern, Germany
Paula K. Brea: 63 yrs old, September 22, 2012, loving mother of Anthony (Rosie) Brea and Anne (Brea) Walker, Sycamore, IL
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Tyler Clarke-Uhman: 21 yrs old, May 19, 2012, loving son of Andy and Carol Clarke, Ontario, Canada
Philip C. Collins: 90 yrs old, September 26, 2012, loving father of Clark (Donna) Collins, Tom (Cindy) Collins, Barbara (Rod) MacDonald and Carolyn (Mike) O’Brien, Wilmington, DE
Dorothy Enright: 88 yrs old, January 23, 2011, loving mother of Roger Chapman, Dr. Debbie DeBiasse, Marsha Hargreaves, Patty Prochazka and Michele Montgomery, Solomon, KS
Giavanna Hope Fabrazzo: 3 mos old, November 3, 2010, loving daughter of Joseph and Rachelle Fabrazzo, Jr., loving sister of Gabriella Fabrazzo, Belleville, NJ
Wilma Jean Forsyth: April 21, 2011, British Columbia, Canada
Tadan Charles Foss: 5 yrs old, April 26, 2012, loving son of Carisa Rockers and Todd Foss, Belton, MO
Nickolaus Alan Frisch: May 7, 2011, loving son of Shawnee and Jeffrey Frisch, Troy, NY
James Garbern, M.D., Ph.D.: 58 yrs old, November 10, 2011, loving husband of Angela Garbern, loving father of Jessica Garbern and Stephanie Garbern, Rochester, NY
Joseph E. Glenn: February 3, 2012, loving husband of Toni Glenn, loving father of Thomas (Anne) Glenn, Villanova, PA
Shaun Graham: January 29, 2011, Westland, MI
Kenneth Griffiths: 73 yrs old, November 8, 2012, loving husband of Sallie Hodge Griffiths, loving father of Kenna (Shawn) Coates, Gen Griffiths and Joelle Griffiths, Powel, TN
George Haines: 69 yrs old, loving husband of Cheryl Haines, loving father of Danielle (Jon) McGovern, Dawn (David) Postlewait, David (Lisa) Haines and stepson Jerry Hall, Olathe, KS
Russ Allen Hargrove: 22 yrs old, December 24, 2010, loving son of Steven Lee and Lori Allen Hargrove, loving brother of Hannah (Jacob) Bishop, Sheffield, AL
Ava Harms: 1 yr old, May 24, 2012, loving daughter of Matthew and Sara Harms, St. Louis, MO
Elaina Faith Hayslett: 9 yrs old, June 24, 2011, loving daughter of Gabie and Dave Hayslett, Covington, VA
John R. Hennessey: September 24, 2010, Crossville, TN
Catherine S. Higgins: 17 yrs old, February 12, 2012, loving daughter of Karen and Jason Higgins, loving sister of Anna Higgins and Mathew Higgins, North Wales, United Kingdom
Wade Hinson: 89 yrs old, September 18, 2012, loving father of Phill (Debbie) Hinson, Anne Hinson and Janice (Ron) Wilson, Lancaster, SC
Weldon Hunter: 84 yrs old, June 22, 2012, loving husband of Jo Ann Hunter and loving father of Pam (Mike) Berg, Mike Hunter, and Susan Hunter-Miller. Albuquerque, NM
Barbara Jacobs: April 26, 2012, Manalapan, NJ
Lloyd Johnson, Jr.: 86 yrs old, December 14, 2011, loving husband of Patricia Johnson, loving father of Glenn Johnson, Peter Johnson and Lynn (Robert) Austin, Eatontown, NJ
Joshua Kaltman: 5 mos old, December 30, 2010, loving son of Scott and Jen Kaltman, Ponte Vedra Beach, FL
Sharon Marie Bernadette Kelly: 42 yrs old, June 28, 2012, beloved daughter of James and Patricia Kelly and sister of Teresa and Philip (Lynne), Falmouth, KY
Matthew Kelly: March 29, 2012, loving son of Jim and Mary Kelly, loving brother of Tyler Kelly, El Cajon, CA
Donald F. Kiesling: 67 yrs old, January 13, 2012, loving husband of Penny Kiesling, loving father of Donald (Jean) Kiesling, Timothy (Jennifer) Kiesling, Thomas (Anita) Kiesling and Kurt Kiesling, Menomonee Falls, WI
Kelli Elaine Kovacs: April 13, 2012, loving daughter of Bill and Kathy Kovacs, loving sister of Lori Kovacs and Lori’s fiancé, Mark Johnson, Oceanside, CA
Rosella Della Lee: 87 yrs old, December 11, 2009, loving mother of Ann (Robert) Knutson, Jean (Jerry) Hartzog and Deborah (Dale) Bregerg, Dawson, MN
Lilli Ann Lingenfelter: June 21, 2011, loving mother of Russ (Deb) Lingenfelter, Deborah (John) Mallow, John Lingenfelter, Linda (Michael) Haigh and Scott (Paula) Lingenfelter, Altoona, PA
Sympathies

Linda Mae Mackie: 64 yrs old, February 20, 2012, loving mother of Martin (Vivian) Schultz and Craig (Debbie) Schultz, Bartlesville, OK
Alice Anne Marton: April 15, 2012, loving mother of Raymond Davis, Charles Davis and Linn Marton, Magnolia, TX
Beryl May Meade: May 18, 2011, loving mother of David Meade, Debbie Meade and Paulette Studybaker Sacramento, CA
Kathy Milburn Goldstein: September 8, 2012, loving mother of Darrin (Jane) Milburn and Michelle (Patric) Gent, Marion, IL
Alex Gregory Montilla: 21 yrs old, December 31, 2010, loving son of Melania Felix, Lynn, MA
Rosemary C. Morgan: 81 yrs old, June 26, 2011, loving mother of Darlene Morgan, Mary Jane Tyler, Joanne Rychlik, Colleen Rothhaar and Michael Morgan, Arlington Heights, IL
Michael Joseph Morrissey: January 10, 2008, loving son of Larry and Stacy Morrissey, Rockford, IL
Ann Murray: 66 yrs old, June 23, 2010, loving mother of Wade (Kim) Murray and James Murray, Brunswick, GA
Billy Papagiannis: 53 yrs old, January 27, 2011, loving husband of Patricia Papagiannis and loving father of Mark Papagiannis, Eric Papagiannis and Monica Papagiannis, Ontario, Canada
Gerry Louis Patrick: March 6, 2011, loving mother of Kathleen (Lewis) Vaughn and Phillip Andrew Patrick, Dayton, OH
Luka Pelka: 10 yrs old, June 29, 2012, loving son of John and Terry Pelka, San Francisco, CA
Louis S. Perri: 94 yrs old, November 9, 2011, loving father of Mary Lou (Tom) Rioux, Cicero, IL
Mary Jane Putzler: July 9, 2012, loving mother of Dennis (Meredith) Putzler and Roger (Linda) Putzler, Albany, OR
Grace Ragon: 10 yrs old, November 22, 2012, loving daughter of JP Ragon and Angie (Brad) Abner and loving sister of Ella Ragon and Avery Abner, Germantown, OH
Linda Janice Ray: December 24, 2011, loving wife of Rex Ray, loving mother of Robin Ray Carlton and Randee Ray, Longview, TX
Janet Eileen Read: August 3, 2011, loving wife of James Read, loving mother of Therese Read and James R. Read, Cortland, IL
Farooq Rehman: April 16, 2011, loving husband of Annila Rehman, loving father of Shiraz (Beth) Rehman, Montreal, Canada
Mohammed Riaz: 34 yrs old, January 5, 2003, loving husband of Karen Gerrard-Riaz, Birmingham, England
Mary K. Roberts: 60 yrs old, January 16, 2011, loving wife of Steven Roberts, loving mother of Brad Roberts, Kevin Roberts and Kristina Kay Harris, Findlay, OH
Brittany Lea Ruport: 12 yrs old, December 23, 2010, loving daughter of Tonia and Mark Ruport, loving sister of Brendan Ruport, Mantorville, MN
Genevieve Scott: 79 yrs old, May 6, 2012, loving wife of Joseph Scott and loving mother of Pam Scott, Joe (Jane) Scott, Janet (Bruce) Jupena and Suzanne (Scott) Kaina, Trafford, PA
William Slanina: May 7, 2011, loving father of Rita (Steve) Takahashi and James (Linda) Slanina, Davidson, NC
Benson Smith: 61 yrs old, March 15, 2012, loving husband of Teresa Smith, loving father of Deana (Thomas) Burson and April O’Bryant, Buford, GA
George Spanos: September 29, 2012, loving father of Peter (Charlene) Spanos and Thomas (Melissa) Spanos, Tinley Park, IL
Gabriel Montgomery Stephens: February 4, 2012, loving son of Glen & Emily Stephens, Charlotte, NC
JoAnn Todd: February 20, 2011, loving wife of Guy Todd, Concord, NC
Zita Turkowitch: May 11, 2011, loving mother of Christine Turkowitch, Karen (Wesley) Fredericks, Colleen Turkowitch, Konrad Turkowitch, Joseph Turkowitch and Gerard (Sandra) Turkowitch, Menomonee Falls, WI
Gabriel Wyse: April 18, 2011, loving son of Madeline Wyse, United Kingdom
Suzanne Rene Yamnitz: 23 yrs old, May 19, 2011, loving daughter of Larry and Delores Yamnitz, loving sister of Allison (Alan) Hughes, Jefferson City, MO
Etheleen Brooks Woodard: 89 yrs old, November 9, 2011, loving mother of Ruth Wood (Larry Young), Alandra Three Feathers and Bobby (Carol) Woodard, Charlotte, NC
Sammy Zeltser: August 16, 2011, loving son of Gelena & Aleksandr Zeltser, loving brother of Marana Zeltser and Eva Zeltser, Deerfield, IL
2012 Benefit Drawing Winners

T. Henderson, Mississippi won the Orange Lake Resorts week in Kissimmee, FL

E. & M. Monroe, Wisconsin won the Getaway Package at Christmas Mountain Village in Wisconsin Dells, WI

M. & D. Massey, New Jersey won the Floral Tone Quilt, hand made by Anita Lewis.

J. Roth, Louisiana sold the most tickets and won the “2013 Conference Registration for Two!”

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SAVE THESE DATES!

Thursday, July 18th
Annual International Scientific Symposium

Friday & Saturday, July 19th & 20th
Annual International Family Conference

Schedules and more information will be posted soon on our website at www.ulf.org