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Research Challenges in Central Nervous System Manifestations of Inborn Errors of Metabolism

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Abstract

The Research Challenges in CNS Manifestations of Inborn Errors of Metabolism workshop was designed to address challenges in translating potential therapies for these rare disorders, and to highlight novel therapeutic strategies and innovative approaches to CNS delivery, assessment of effects and directions for the future in the treatment of these diseases. Therapies for the brain in inborn errors represent some of the greatest challenges to translational research due to the special

properties of the brain, and of inborn errors themselves. This review covers the proceedings of this workshop as submitted by participants. Scientific, ethical and regulatory issues are discussed, along with ways to measure outcomes and the conduct of clinical trials. Participants included regulatory and funding agencies, clinicians, scientists, industry and advocacy groups.

Keywords

inborn errors of metabolism; central nervous system; rare disease; orphan drug designation; translational research

1.0 Introduction

On December 7 and 8, 2009, the National Institute of Health's Office of Rare Diseases Research, the National Institute of Neurological Disorders and Stroke, and the Food and Drug Administration's Center for Drug Evaluation and Research, Division of Gastroenterology Products hosted a workshop titled "Research Challenges in CNS Manifestations of Inborn Errors of Metabolism." Attendees included 147 participants from regulatory and funding agencies (57%), academia (15%), clinicians (10%), industry (5%) and patient advocacy groups (3%). The goals of the meeting were to identify impediments in the translation of potential drug and biological therapies for the treatment of central nervous system disease in inborn errors of metabolism(IEM) into clinical trials, and to develop a framework for addressing these challenges to help support and accelerate the development of potential treatments for these disorders.

The agenda was organized according to the major categories of challenges in clinical translation that had been identified by the workshop planners: 1) meeting regulatory requirements to move from the preclinical to clinical stage; 2) designing clinical trials for rare diseases of sufficient rigor to adequately describe the effectiveness and safety of the treatments; 3) selecting appropriate outcome measures for CNS disease; and 4) ethical issues in testing and evaluating therapies. In addition to state-of-the-art overviews, original research was presented to give specific examples of therapies that might realistically be considered for clinical application. Presentation slides for most of the presentations are available online at

http://rarediseases.info.nih.gov/files/Inborn_Errors_Metabolism_Agenda.pdf. What follows is a summary of the proceedings, contributed by the participants.¹

2.0 Background

Marc C. Patterson, M.D

Rare diseases are defined by the Orphan Drug Act (ODA) [1] as those with a prevalence of 200,000 or fewer in the US. All inborn errors of metabolism (IEM) are rare diseases, but collectively they pose a substantial burden to affected individuals, their families and the health care system, because of the severity of their manifestations, and the large numbers of such disorders(estimated at 7,000, affecting a total of 30 million people in the US [2]). This burden includes the dollar and human cost of diagnosis, which is frequently delayed, and often requires specialized testing to which access is limited, the direct costs of care for children and adults with complex multisystem disease, the loss of income for family members caring for affected individuals, and the loss of the potential contributions of IEM

¹The opinions expressed in each summary are the opinions of the individual presenters and do not necessarily reflect the position of all participants nor the institutions they represent.

patients to society. Within this group, those disorders that affect the nervous system represent the most dramatic challenges to researchers and clinicians. Patients have severe and often life-shortening disabilities, and there are few, if any, tools to measure the progression of their neurologic disease or its response to therapeutic interventions. Biologically, the brain poses specific problems related to the difficulty of delivering therapeutic agents across the blood brain barrier, and targeting them to very specific neuronal populations and networks. Although the brain contains stem cells, its potential for self-regeneration is limited, in contrast to most other tissues. As potential disease-modifying therapies have emerged in recent years, the need for reliable and valid instruments to measure neurologic function, and for validated biomarkers, has become more pressing.

Clinical trials in rare diseases are difficult to power adequately owing to the limited pool of potential participants and marked individual variation within these small cohorts. In addition, there are relatively few disorders for which prospective studies of natural history have been performed or for which validated clinical rating scales are available. Federal legislation (the Orphan Drug Act) has provided incentives for pharmaceutical manufacturers to develop drugs to treat rare diseases, but existing regulations do not make concessions for the special challenges investigators face in designing and executing clinical trials in rare diseases. The conventional pathway to approval of drugs in common diseases, where large, relatively homogenous cohorts can be recruited, permits demonstration of small, but clinically significant effects and has withstood the test of time. Unfortunately, the heterogeneity and small size of study cohorts in rare IEM are such that even substantial therapeutic effects may be difficult to demonstrate using such approaches, leading to type II errors and the risk of discarding much needed treatments because of methodological challenges, rather than lack of biological effect.

The purpose of this workshop is to bring together investigators, federal officials (from regulatory and funding agencies), industry representatives and, most important, patients and their advocates, to define the challenges and identify paths towards the development and approval of desperately needed therapies for people suffering from CNS manifestations of inborn errors of metabolism.

3.0 Translational Medicine and Rare Disease Research: Overview

Translation of therapies for the IEM with CNS manifestations presents many challenges scientifically, ethically, and practically, approaches to which are illustrated using the example of Menkes disease. Additionally, in order to support the approval and commercial availability of potential treatments, the regulatory considerations for conducting adequate and well-controlled clinical trials and for the clinical investigation of treatments intended for rare disorders are discussed.

3.1 Menkes Disease: An Example of Translational Research into CNS Therapies for IEM. Stephen G. Kaler, M.D

Recent investigation of Menkes disease and related disorders provides a potential paradigm for translational research into CNS therapies for IEM. Careful delineation of the natural history of this copper transport disorder caused by mutations in the *ATP7A* gene [3], an open label clinical trial of systemic treatment which showed success for some, though not all, affected subjects [4], and preclinical studies of aggressive brain-directed treatment including gene therapy in a mouse model [5] forms a body of work useful in considering common issues in IEM translational research efforts.

Menkes disease involves infantile -onset cerebral and cerebellar neurodegeneration, failure to thrive, peculiar hair, and connective tissue abnormalities. These features are coupled with

a biochemical phenotype (low copper levels in the blood, and a copper deficiency in the brain) that denotes abnormal copper metabolism. The entry of copper across the blood-cerebrospinal fluid barrier and blood-brain barrier (BBB) is mediated by ATP7A, and the response to early treatment in cases of Menkes disease seems to rely on the residual copper transport activity mediated by mutant ATP7A molecules, predictable by a yeast complementation assay [4]. The defects in *ATP7A* that cause Menkes disease encompass the usual spectrum of genetic mutations, and a considerable proportion of such mutations lead to complete loss of function of the transporter, a circumstance in which even early copper treatment bestows limited benefit. Naturally occurring mouse models of Menkes disease exist and have been studied to evaluate potential therapies for this disorder, including brain-directed gene therapy.

Issues relevant to research on *ATP7A* copper transport disorders seem appropriate to many other inherited neurometabolic disorders. Questions raised reflect many of the general difficulties involved in devising treatments to the CNS, measuring outcomes there, and overcoming barriers to translation to clinical trials and beyond. For example, should treatment of neurometabolic diseases be tailored for specific subpopulations of affected patients, e.g., based on mutation type and severity? Are more aggressive than usual treatment approaches acceptable in certain circumstances? Is greater risk acceptable in patients with forms of a disease involving severe prospective outcomes? Some *ATP7A* mutations involve complete loss of copper transport function and connote a more dismal prognosis than other *ATP7A* alterations. The natural history and genotype-phenotype data that we have accrued over a 15-year period are invaluable in understanding long-term expectations in patients. This information could be rationally applied whereby high-risk brain-directed treatment approaches are reserved for asymptomatic patients with known severe mutations. Applying aggressive approaches early, before symptoms develop, would enhance the likelihood of meaningful benefit. In contrast, aggressive treatment of advanced neurometabolic disease offers minimal benefit but the same level of risk.

How should the unique risks of human gene therapy be weighed in the context of the devastating and irreversible CNS effects in some IEM? What are the relevant ethical issues in translation of CNS therapies for IEM (e.g., research involving subjects who are incompetent or mentally incapable of giving informed consent or minor children) and how is the informed consent of the parent (or legally authorized representative) ensured in difficult medical circumstances [6]? In Menkes disease, affected infants are usually not diagnosed until after symptoms have appeared at which point currently available treatments are unlikely to correct the neurodegeneration. Our stance has been that the decision concerning institution of treatment is best made by the patient's parents after reviewing with them the details of limited benefits and potential risks of treatment. After time to absorb this information, parents invariably seem able to act, and they welcome the autonomy.

The blood-brain and blood-CSF barriers complicate therapeutic approaches to the CNS. How can transport of therapeutic molecules across these barriers be accurately assessed [7,8]? For example, although differences in cerebrospinal fluid (CSF) copper levels in Menkes disease compared to normal controls are appreciable [9], trends in CSF copper levels for individual patients during treatment have proven somewhat elusive to track.

How does one determine the amount of preclinical data needed to transition from preclinical protocols to a clinical pilot study? For planning the application of pre-clinical treatment approaches in a mouse model of Menkes disease to eventual human trials, meetings with appropriate FDA experts to obtain their advice and guidance has been extremely useful.

How should investigators navigate the institutional review board (IRB), FDA, and data and safety monitoring board (DSMB) review processes, particularly when the therapeutic option involves aggressive treatment of pediatric patients? What advice and resources are available to guide investigators and sponsors in these endeavors? These illustrate just some of the issues and concerns that have emerged in research on Menkes disease [3,10,11], and other neurometabolic disorders.

3.2 Regulatory Requirements for the Clinical Investigation of Orphan Products. Anne R. Pariser, M.D

The ability to translate basic research findings first into investigational treatments, then into commercially-available therapies for IEM relies upon an understanding of the US regulatory requirements for clinical development of investigational agents for Orphan diseases. The ODA provides financial incentives to developers intended to make the clinical development of Orphan Drugs more financially viable, but the ODA does not alter the safety and effectiveness requirements for approval of drugs intended for use in rare diseases. To receive approval for commercial marketing in the US, drugs and biological products for Orphan (as well as for non-Orphan diseases) must demonstrate substantial evidence of effectiveness/clinical benefit, which has been defined as being able to distinguish the effects of the drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation, in adequate and well-controlled clinical trials [12]. Adequate and well-controlled trials must incorporate several major elements that should be prospectively defined in study protocols, including: 1) clear statement of purpose; 2) valid comparison with a control (concurrent or historical); 3) method of selection of subjects that provides adequate assurance that they have the disease being studied; 4) adequate measures to minimize bias; 5) methods of assessment of response that are well-defined and reliable (e.g., well-defined outcome measures and endpoints); 6) method of assigning patients to treatment and control groups that minimizes bias (e.g., randomization); and 7) analysis of the results is adequate to assess the effects of treatment.

Experience to date with rare disease drug development has identified some factors that may be more likely to result in successful clinical programs. Recommendations for designing IEM clinical development programs include: 1) planning out the program early and if possible, this should be done prior to initiating clinical trials; 2) involving FDA in the planning process and discussing study designs early, preferably in the pre-IND phase. Continuing to interact and reach agreement with FDA during clinical development is also recommended; 3) initiating natural history studies (e.g., longitudinal observational studies) as soon as possible, even prior to having a potential treatment available, in order to identify and develop targets for intervention and outcome measures to be used as endpoints in clinical trials; 4) exploring and defining biomarkers that may be used as surrogates or outcome measures; and 5) piloting small exploratory studies prior to performing pivotal trials whenever possible to inform the design of Phase 3 studies intended to establish effectiveness. Areas for future development include additional development of translational science, such as biomarkers, animal models and computational modeling to allow for the best use of sparse data and the limited opportunities for clinical study, and the use of adaptive study designs and statistical analyses where feasible.

4.0 Assessing Outcomes in the CNS: Signs and Symptoms

Assessment of the natural progression of IEM affecting the CNS and the effects of treatments targeted to the CNS can be difficult, and customized tools and outcome measures with sufficient sensitivity and specificity to adequately assess both progression and intervention need to be developed and qualified. This section provides an example of the development of a unique rating scale developed for the assessment of Batten disease, and

considerations for developing assessment tools for diseases encompassing small, phenotypically diverse patient populations.

4.1 Batten Disease and the Unified Batten Disease Rating Scale. Jonathan W. Mink, M.D., Ph.D

Translation of therapies to clinical trials requires carefully designed endpoints. One challenge is the lack of sensitivity of available outcome measures for CNS disease, which when coupled with the small study size in rare disease trials, makes measurement of efficacy exceedingly difficult. Development of clinical outcome measures in neuronal ceroid lipofuscinosis (NCL) is a tremendous challenge, owing to the rareness of the disease, the severity of its effects, and the difficulty in diagnosis. The NCLs are a group of neurodegenerative diseases of variable age of onset that are associated with lysosomal accumulation of ceroid lipofuscin, causing intellectual and visual impairment, seizures, movement disorders, and early death [13]. The term “Batten disease” has been used to refer to all forms of NCL, but the disease originally described by Batten refers to juvenile-onset neuronal ceroid lipofuscinosis (JNCL) (symptom onset between age 4 and 10 years). In partnership with the Batten Disease Support and Research Association, the principal lay organization for Batten disease in the US, a cohort of patients was identified for a natural history study. The *Unified Batten Disease Rating Scale* (UBDRS) was developed to measure physical, behavioral, seizure, and functional capability domains in patients with JNCL [14]. The UBDRS has been administered to 99 subjects with Batten disease over 8 years. Of the 99 subjects, 82 had JNCL with known CLN3 mutations, and 42 subjects were evaluated more than once on an annual basis. The UBDRS physical subscale shows decline over time that proceeds at a quantifiable linear rate in the years following initial onset of clinical symptoms. This decline correlates with functional capability and is not influenced by gender or CLN3 genotype. The UBDRS is a reliable and valid instrument that measures clinical progression in JNCL, and demonstrates that carefully designed natural history studies can lead to new tools for clinical trials.

4.2 Longitudinal Studies of Progressive Neurodegenerative Diseases. Elsa G. Shapiro, Ph.D

Longitudinal studies of progressive neurodegenerative diseases can be designed to answer questions of disease progression and treatment response, with different study designs having been selected based upon the characteristics of the disease and the treatment under study. Natural history designs may provide comparison data, and in some circumstances, historical controls. For example, in the mucopolysaccharidoses (MPS), yearly focused quantitative MRI, neuropsychological tests, and biomarker analysis are hypothesized to reveal specific localized findings for each MPS disorder, and to be affected by both treatment benefits and disease/treatment risk factors [15]. In Sanfilippo (MPS III) Type A, an MRI and neurobehavioral study is underway (NCT01047306), with the goal of informing future clinical trials. Controlled trials are obviously preferable in the assessment of new therapies, but may not be possible for some study populations. For example, a randomized crossover design with treatment and placebo and the subject serving as their own control minimizes error variance, but the washout period is not feasible with long-acting treatments including enzyme replacement therapy, gene therapy or bone marrow transplantation, and randomization to placebo can severely hinder subject recruitment or may not be ethical in certain circumstances (e.g., rapidly progressive lethal diseases) [16]. A randomized partial crossover design can be useful in these cases. In this study design, one group receives investigational treatment and the other placebo or no treatment, then the control group crosses over to investigational treatment. This averts the problem of washout, and all patients eventually receive the investigational treatment, but if the N is small there is danger

of non-comparability of the two groups. An example is the intrathecal trial of enzyme replacement therapy for cognitive impairment due to MPS I(NCT00852358) [17].

These designs require repeated sensitive measurements to detect change in the CNS over a relatively short period of time with a baseline assessment to control for stage of disease. They must be feasible, clinically useful, and theoretically sound. Neuroimaging is a surrogate marker of brain structure and function, and neuropsychological testing is a semi-direct marker of function. Clinical MRIs and clinical neuropsychological testing are designed to reach a diagnosis, not to understand the disease process, are not quantitative and often do not correlate with change as they focus on highly stable aspects of disease. Quantitative MRI methods (volumetric changes, diffusion tensor imaging, and magnetic resonance spectroscopy) are more sensitive and correlate with function. One obstacle is comparability across centers, which can be solved by within-patient designs. Clinical neuropsychological testing also may measure multiple functions and be confounded. A reductionist approach, measuring single functions with minimal “noise” yields more accurate data. Short standard fixed batteries will minimize the effects of practice, fatigue, and age. The influence of physical factors (sensory and motor limitations) as well as emotional/behavioral factors need to be minimized. In younger and very impaired populations, use of within-patient developmental growth curves using slope of development/change of raw scores is essential to understand disease progression. Correlations of the results of these two methods to measure change in the CNS will strengthen the evidence for brain-based changes and validates their usefulness in measuring change as a result of disease and treatment.

4.3 Neuropsychological Evaluation of Children with IEM. Kendra J. Bjoraker, Ph.D

Neuropsychological assessment of children with IEM is an ongoing process of systematic observation and analysis, the purpose of which is to understand the child’s CNS competencies and the resources most likely to assist the child in making the best use of his or her developmental potential. With various treatment options, it is important to monitor development longitudinally from infancy to adulthood in order to understand efficacy of the treatment, and the course and prognosis for clinical and research utility as well as quality-of-life.

Challenges assessing children with IEM include the understanding that these disorders are generally complex, and have variable expression and a long course of illness with long-term and often systemic complications. Not only is neuropsychological standardized terminology and vocabulary not well defined, but the development of valid and reliable tools to collect and manage geographically distributed clinical research data using standardized data elements is complicated. Given these challenges, a neuropsychologist requires specialized training and experience working with medical compromised children and families. This training should include: 1) using multiple sources and multiple components in assessment along with providing a meaningful sequence for assessment based on a decision tree approach; 2) respecting and evaluating child-caregiver relationships and other psychosocial factors; 3) basing assessments on a framework and knowledge of typical development; 4) emphasizing the functional capabilities of the child; 5) focusing on the child’s current strengths and needs in the context of rare diseases; and 6) understanding the sensory/physical factors that may influence the outcomes.

Future research directions in neuropsychological and quality of life outcomes in rare genetic diseases include developing sensitive monitoring instruments to track outcomes of treatments, gathering natural history of brain structure and function, correlating neuropsychological measures with medical, neurological, and neuroradiologic findings,

identifying risks and protective factors for neurocognitive decline, and identifying possible treatments and interventions for these diseases.

4.4 The Assessment of Short-and Long -term Neurocognitive Development in Urea Cycle Disorders. Lauren Krivitzky, Ph.D

Consortia can be beneficial in the study of IEM, as they allow a wider net to be cast for subject recruitment, as well as collaboration with sharing of expertise and data. In urea cycle disorders (UCDs), a large consortium was developed to study short- and long-term neurocognitive development through neuropsychological assessment at set time points (enrollment, 6 months, 18 months, 4 years, 8 years, 15 years, and 18 years) [18]. UCDs are a group of rare IEM that commonly present in childhood with episodes of vomiting lethargy and coma. Symptoms result from accumulation of ammonia, a toxic product of protein degradation, which is not properly metabolized in the liver due to an enzyme deficiency. Ammonia crosses the blood brain barrier and can result in significant neurologic sequelae. UCDs are inherited as recessive traits, with the exception of the most common disorder (Ornithine Transcarbamylase Deficiency-OTC) which is inherited as an X-linked trait. UCDs are generally managed with a low -protein diet and management of hyperammonemia; however, even with early diagnosis and the best current management, most individuals show cognitive deficits [19]. One challenge in UCDs, as with many IEM, is that several distinct diseases are represented within the family of UCDs (8 in total; 6 enzyme deficiencies and 2 transporter deficiencies), and considerable variability is observed in their outcomes over time. In order to overcome the variability issue, three separate neuropsychological testing batteries were developed so that all individuals can be appropriately assessed [20]. These include a battery for: 1) very low functioning individuals--those falling into the severe to profound range of intellectual disability; 2) low functioning individuals--those with full scale IQ score below 70, but able to complete test measures including IQ and motor testing; and 3) those with IQ scores of 70 or greater--complete a full range of neuropsychological measures. In addition to the issue of variability, there is also the challenge of broad age range. Given the rarity of these disorders and the potential for change over time, the study is longitudinal and includes individuals of all ages. Although there are many benefits to a longitudinal study, it poses challenges in selecting test measures for each age group that are developmentally appropriate and allow for intra-individual comparison over time.

Another way to increase sample size in studies of IEM is to include multiple sites, both nationally and internationally. Although there are benefits to this approach, it also provides unique challenges when developing appropriate neuropsychological outcomes. Although some measures can be used more broadly (e.g., motor testing, non-verbal reasoning tests), other measures cannot be used across different countries due to language and other cultural/norming issues. This has also proven to be problematic within a US sample when there are non-English speaking subjects and caregivers. One solution, employed by the UCD consortium, is to create a “Non -English Speaking” battery for each age group.

5.0 Assessing outcomes in CNS: Neuroimaging

Advances in CNS neuroimaging present an opportunity for rapid and non-invasive assessment of disease state, and longitudinal assessment of progression and treatment effects by assessing structural and/or biochemical changes to the brain. Correlating the imaging results to clinical outcomes and biochemical and laboratory assessments, and the sensitivity, specificity and reproducibility of different techniques are discussed in this section.

5.1 Use of Conventional and Advanced Magnetic Resonance Imaging Techniques for Assessment of IEM. James Provenzale, M.D., and Andrea Gropman, M.D

Drug-induced improvement, stabilization or reversal of neurological symptoms of many IEM is a goal for many diseases. Research is now focusing on the earliest stages of disease where a therapeutic intervention is likely to have the greatest impact. To accomplish this, one needs brain biomarkers. Neuroimaging can provide brain biomarkers that are non-invasive repeatable measures. Imaging of the brain before and after administration of therapy provides one form of biomarker for assessment of therapeutic response. The data provided by imaging studies, on occasion, provides information that is not available by other means. To be useful they should have correlation with pathology/disease state and/or correlation with clinical, laboratory, functional or cognitive measures.

CNS outcomes for some IEM can be successfully monitored using standard imaging. Neuroimaging can provide information about timing, extent, reversibility and possible mechanism of neural injury and can be used to measure changes over time in an individual patient, or to perform a group analysis as an adjunctive measure to predict clinical and neurocognitive outcome and response to therapy.

Routine anatomic MRI can characterize gray matter and white matter microstructural and macrostructural changes by taking advantage of signal abnormalities on T1, T2W images. Routine sequences can detect damage at the macroscopic level, but the MRI findings may lag behind clinical changes (see Table 1). For instance, in many cases, clinical changes following institution of therapy may be subtle for many months or even a few years; however, imaging studies may indicate definite improvements in terms of the imaging metrics employed. Furthermore, many imaging features are quantifiable and highly reproducible, which may not be the case for some forms of clinical assessment. However, one must always keep in mind that improvement on imaging studies means little in the absence of clinical improvement. Thus, imaging findings always need to be carefully correlated with clinical parameters. This comparison serves a dual purpose. First, the comparison validates the use of the imaging findings. Second, if the imaging studies are then validated, the comparison allows testing to be performed at remote sites, which can be important when dealing with rare diseases in which patients and families may need to travel great distances to reach the medical center at which treatment is administered and assessment is coordinated. In drug studies, the goal is to be able to invoke earlier indices of disease such as microstructure analysis of white matter by using diffusion tensor imaging, neural circuitry (fMRI), or metabolism (spectroscopy).

Since many IEM are first diagnosed very early in life and many patients are first evaluated by magnetic resonance (MR) imaging in infancy, it is worth mentioning some issues in MR imaging of infants. The first issue is that little inherent tissue contrast is present on brain images, and especially on T2-weighted images. This fact can make it very difficult to identify abnormalities on MR imaging. The second issue (in part related to the first issue) is that, at birth, few milestones indicative of brain development are present, which can provide difficulty for individuals who are not highly skilled in imaging of the infant brain to fully assess abnormalities.

Since MR imaging abnormalities are known to occur in specific locations in various diseases, an MR scoring system can be used to assess disease severity, disease progression and treatment response. One such scoring system, termed the Loes scale, was originally developed for evaluation of patients with adrenoleukodystrophy [21]; this scoring scale has subsequently been applied to Krabbe disease [22]. Krabbe disease (globoid cell leukodystrophy) is a neurodegenerative lysosomal storage disease, and is rapidly fatal in the infantile form, with death expected before age 2 years [23]. Brain MR imaging shows

diffuse white matter changes due to demyelination in the cerebrum, cerebellum and brain stem, and cerebral atrophy. In an attempt to further determine the clinical utility of the Loes scale, MR scores were recently compared using the Loes scoring system and neurobehavioral developmental scores in children who had undergone unrelated donor umbilical cord blood stem cell transplantation for treatment of Krabbe disease [24]. The study group consisted of 9 children, who underwent a total of 16 MR scans, with neurodevelopmental testing of mental development, gross motor skills and fine motor skills within one month of MR imaging. Comparisons included: (1) each neurodevelopmental test vs. total brain MR score, (2) fine motor and gross motor tests vs. MR score for a general part of the brain relevant to these functions (i.e., the pyramidal tract, and (3) fine motor and gross motor tests vs. MR score for a portion of the brain highly specific for these functions (i.e., the internal capsule). The correlation of the whole brain MR score with each neurodevelopmental test was relatively high, as was that of the MR score of the pyramidal system and the fine motor function score. Correlation of the MR score of the pyramidal system and the gross motor function score was only moderate, while the correlation for the other comparisons was low.

Although scoring systems based on conventional MR imaging studies can be informative, the fact that brain abnormalities can fail to be depicted on conventional studies is a limitation. An MR technique that is sensitive to abnormalities that were not conspicuous on conventional MR images, such as diffusion tensor imaging (DTI), MR spectroscopy or functional MR imaging, would be expected to provide distinct advantages. The experience gained in use of DTI for assessment of stem cell transplantation for Krabbe disease may provide a model for the use of advanced imaging to assess outcomes in CNS. In order to place this work in perspective, a brief review of the principles behind DTI, and the information that DTI can provide, is now presented. DTI is based on the principle that microscopic water motion occurs in all living tissues. To various degrees, such water motion may be random (which is termed isotropic) or highly directional (or, anisotropic). Within highly organized and compact white matter pathways, such as the corpus callosum, microscopic water motion is relatively anisotropic because water molecules tend to diffuse along the long axis of parallel axons and other microstructural elements aligned in the same direction. In less compact white matter regions, which may be characterized by many crossing fibers (as opposed to a parallel alignment of fibers), water motion is less anisotropic than in compact, parallel white matter regions. Finally, in gray matter, structures, water motion is even less anisotropic than in relatively noncompact white matter regions. Using DTI, one is able to determine degrees of anisotropy (fractional anisotropy, FA); these features can be depicted on a map of the organ being studied and measured in a reproducible manner. Degrees of anisotropy are calculated and expressed in a number of types of numerical values, of which fractional anisotropy (FA) is one of the most commonly used. At any single age during life, a relatively narrow range of degrees of anisotropy are seen in any specific white matter region. This fact allows one to compare anisotropy values in specific regions of normal brains with those in the same regions in disease-bearing age-matched patients. Our group (J.P.) has extensively studied FA values in normal infants during the first year of life [25]. Infants at the end of the first year of life had higher FA values in all brain white matter regions studied compared to those at the beginning of the first year of life, with increased numbers of axons and degree of myelination. These changes also continue well beyond the first year of life [26]. Thus, DTI is uniquely suited for evaluation of white matter and can be used to study normal white matter development as well as to assess white matter diseases, such as pediatric leukodystrophies.

Based on these principles, white matter regions in untreated patients with Krabbe disease were compared to normal age-matched infants and to Krabbe patients who had been treated with umbilical cord blood stem cell transplantation [27]. FA values in untreated Krabbe

patients were markedly decreased in all white matter regions studied compared to normal infants. On the other hand, values in treated Krabbe patients were always intermediate between normal values and untreated infants. Concordantly, treated infants, while also experiencing neurological disability, were substantially less affected than untreated infants. In later studies, we compared serial DTI results in two groups of treated Krabbe patients who underwent transplantation during the first month of life [28]. The first group consisted of infants who underwent transplantation after a clinical diagnosis was made in the first few months of life; as a result of the time needed for clinical symptoms to become manifest, these infants were treated after 4 months of age. The second group of infants was considered, at the time of birth, as being at-risk on the basis of a sibling previously affected by Krabbe disease. The study showed that, at the time of transplantation, FA values in the infants transplanted at 5–8 months of age were already markedly lower than age-matched normal controls, while those transplanted in the first month of life were near normal in all white matter regions studied. Furthermore, in the first two years after transplantation, FA values in the children transplanted at 5–8 months of age continued to markedly decrease compared to normal children; FA values in the children transplanted during the first month of life also decreased compared to normal infants but to a substantially lesser degree. These imaging changes generally mirrored clinical findings in both groups.

One the basis of these studies, it appears that advanced MR imaging procedures that are quantifiable and highly reproducible, such as DTI, hold promise for evaluation of disease severity and response to therapy in a number of inborn errors of metabolism. Larger studies that correlate the findings of such imaging studies with clinical features are needed, and the applicability of these imaging procedures to individual diseases will need close examination before they can be adapted for a specific disease process.

6.0 Executing Clinical Trials in Rare Diseases: Novel Approaches

Assessing the effects of treatment/intervention in ongoing and completed clinical trials for CNS manifestations of IEM can be difficult. CNS disease may not be reversible, making early intervention essential, phenotypes can be variable and difficult to define (e.g., mitochondrial disease), and in rapidly progressive disease, it may not be possible to perform controlled studies. This section provides examples of clinical studies of CNS therapies of IEM, and the challenges they faced.

6.1 Irreversibility of Disease: Allogeneic Transplantation in Selected IEM Disorders. Paul J. Orchard, M.D

For several of the inherited disorders affecting the CNS, including Hurler syndrome (MPSIH) and early cerebral adrenoleukodystrophy (ALD), allogeneic transplantation has proven effective and is the standard of care. From 50% to 80% of transplanted Hurler syndrome patients currently achieve survival and engraftment [29,30,31,32]. Transplantation for Hurler syndrome treats or prevents many systemic complications of the disorder, and is the only available therapy to achieve stabilization of the CNS manifestations of disease. Outcomes are improved when transplantation is performed early in the disease course [33]. For cerebral X-linked ALD, transplantation in early stages of the disease has the capability of preventing progressive central demyelination, with 5-year survival over 80% in this population [34]. For both Hurler syndrome and early cerebral ALD transplantation is considered the standard of care. However, for other diseases, including Hunter syndrome (MPSII) and Sanfilippo syndrome (MPSIII) transplantation has proven less effective and is not considered standard therapy [35]. For many lysosomal disorders, including metachromatic leukodystrophy and globoid cell leukodystrophy (Krabbe disease), disease phenotype and neurologic function at the time of transplantation are important factors in determining neurologic outcome. Patients with severe phenotypes, or with advanced disease

at the time of hematopoietic stem cell transplantation have not shown substantial neurologic benefit [34,36,37]. Historically, for MPSIH, transplantation in children older than 3 years has not typically been performed, as these patients continue to deteriorate intellectually despite engraftment [38,39]. The reasons why transplantation proves more effective in specific disorders and not in others remains unclear, and will require additional information regarding the biology of these disorders and factors affecting the capacity to deliver enzyme to the CNS by hematopoietically derived cells, specifically the microglia. In order to achieve optimal outcomes for neurologic disease, transplantation should be performed before significant cognitive impairment has occurred. The experience with cognitive outcomes following transplantation suggests that most clinical CNS disease in IEM patients is not reversible.

Another issue relates to modification of existing interventions in an attempt to optimize outcomes within the disorders currently being treated by transplantation. For instance, while a successful transplant can slow or arrest the neurologic progression of Hurler syndrome, significant deterioration is often observed prior to stabilization [40]. Much of this progression may be due to the amount of time that is required to achieve the engraftment of donor microglia into the brain of the recipient, which may prove 6 months or longer. With the availability of recombinant enzyme there is the opportunity to utilize enzyme intravenously prior to transplantation to decrease the burden of glycosaminoglycans, potentially improving outcomes of transplant [30,31]. Additionally, studies testing the delivery of enzyme into the spinal fluid in the peri-transplant period are underway to establish the safety of the procedure (NCT00638547), and to determine if this approach has the potential for decreasing neurologic progression until stabilization is achieved. The use of combined therapy for these disorders has the potential to achieve improved outcomes in those diseases currently treated with transplantation. There is also the possibility that combination therapy may prove effective in situations where transplantation alone is inadequate. Finally, the potential for neonatal screening to identify these disorders very early in the course of disease may provide opportunities to significantly improve outcomes.

6.2 Measuring Success: Lorenzo's Oil in Adrenoleukodystrophy. Gerald Raymond, M.D

Another novel approach to treat CNS disease in IEM is the use of small molecules that act competitively to reduce the accumulating substrate. Lorenzo's oil was developed in the 1980s for X-linked adrenoleukodystrophy. While not completely understood, its mechanism of action appears to be the competitive inhibition of production of saturated very long chain fatty acids, which are hypothesized to be involved in the pathogenesis of adrenoleukodystrophy. Using this compound, there is a rapid normalization of plasma very long chain fatty acids within 4–8 weeks of treatment onset. However demonstration of long-term efficacy of this agent in adrenoleukodystrophy has been difficult.

Adrenoleukodystrophy is characterized by progressive CNS impairment, seizures, ataxia, and lower extremity spasticity with abnormalities in vibration sensation, strength, walking and balance. Issues that are peculiar to adrenoleukodystrophy are variable manifestations of disease that range from a severe childhood cerebral form to a serious, but slower progressive adult form. These variable phenotypes may present in the same family and therefore, it is not presently possible to predict which manifestation an affected male will develop. This variation potentially prolongs the necessary treatment windows through decades making standard study designs unrealistic, and despite many years of clinical use of Lorenzo's oil, to date, no placebo-controlled study of Lorenzo's oil has been completed. Open studies have shown some promise of a preventative effect, but have their limits.

In order to assist in the further evaluation of the treatment effects of Lorenzo's oil, we have recently developed and validated functional measures which appear to be more sensitive and

reliable than previously used clinical rating scales such as the Kurtzke Expanded Disability Status Scale (EDSS) [41], which identified subgroups that may reflect stages of disease progression, and has the potential to assist in the evaluation of therapeutic interventions. In addition, we continue to develop the use of magnetic resonance imaging as an outcome measure and demonstrate that this should be considered as bioequivalent as clinical and pathologic determinations in drug development especially in rare diseases such as adrenoleukodystrophy.

6.3 Defining the Phenotype: Challenges of Translational Research in Mitochondrial Diseases. Bruce H. Cohen, M.D

Mitochondrial diseases (principally disorders of oxidative phosphorylation) are a heterogeneous group of disorders that are difficult to diagnose and resistant to current therapeutic interventions. The clinical symptoms of mitochondrial diseases are due to dysfunction of organs that are post-mitotic at birth, and although the signs and symptoms are well-established, they are not specific to mitochondrial dysfunction. Testing for these disorders includes evaluation of blood, urine and CSF analytes, enzymatic and functional biochemical testing on tissues, microscopy and immunohistochemical techniques, protein studies and genetic testing. Many test result findings are not specific for mitochondrial dysfunction. The recent expansion of clinically available genetic testing resulted in proper diagnosis of many patients, but has led to many more questions than answers because of issues that include the true effect of low-level mitochondrial DNA (mtDNA) heteroplasmy, lack of understanding of the true nature of mtDNA polymorphism, the interaction between mtDNA haplotype and disease susceptibility, nuclear DNA copy number variant disorders, insufficient information about pathogenicity of novel mutations found in mitochondrial-targeted nuclear genes, understanding the true nature of compound heterozygosity and haploinsufficiency whether due to monoallelic expression or the heterozygote state. Further complicating the issue is that many medical disorders and non-mitochondrial genetic diseases do affect the mitochondria to the extent of causing measurable mitochondrial dysfunction in the laboratory, which can lead the clinician away from the real underlying disorder.

The clinical variability of even the well-established mtDNA disorders with a tight genotype-phenotype correlation is huge, suggesting that haplogroup typing or additional genetic mutations may play a role in the illness, but extreme clinical variability can occur even among first-degree relatives, which suggests an additional environmental component to clinical variability. A good example of interaction between disease and environment is the acute encephalopathy that can occur at the tail end of a mild and non-specific viral infection (such as a rhinoviral illness) that occurs in Leigh syndrome patients. The variability seems to hold true for those diseases caused by mtDNA mutations as well as many (but not all) of the nuclear DNA mitochondrial disorders. Therefore the natural history of these well-established disorders, although well-defined, cannot be applied to an individual. Encephalopathy is one of the most common manifestations of mitochondrial disease in children, and is an example of the type of broad clinical variability that can be seen in these disorders. What is interesting is why encephalopathy is a large component of some well-defined mitochondrial disorders, but not others. It is not clear if the long-term prognosis for children with mitochondrial disorders is worse in those that have acute encephalopathy as opposed to those with a slow chronic-progressive encephalopathy. There seem to be some correlation between specific diagnosis and specific developmental time periods during which metabolic stress is more likely to have adverse consequences. Disorders affecting the tricarboxylic acid cycle, organic acid metabolism, urea acid cycle and some, but not all, disorders in fatty acid oxidation, tend to have onset of presentation with encephalopathy during infancy. The mtDNA disorders have a wide age range of presentation, although for a

given mutation, the window tends to be narrower. The nuclear DNA disorders causing mitochondrial disease have a variable age of disease presentation. For disorders not characterized by known mutations, when regression occurs, young age seems to be a factor. Although some metabolic stresses have been defined, such as infection, fever or exposure to high ambient temperatures, dehydration, starvation, sleep disturbance and some medications, they have not been well-characterized. Although there are cases in children with evidence of mitochondrial dysfunction where vaccination against common childhood disease is temporally associated with encephalopathy, these cases are quite uncommon. Encephalopathy after routine vaccination in children having well-characterized (and ultimately more devastating) mtDNA and mitochondrial-targeted nDNA mutations has not been reported after vaccination, suggesting the metabolic stress of vaccines is less than that which would occur with common illnesses such as rhinoviral infections, where encephalopathic regression is well-documented. The practice patterns of most doctors caring for children with mitochondrial diseases is to recommend the routine schedule of immunizations, including seasonal influenza vaccination, although there are occasional cases where because of prior temporal relationships with deterioration or social concerns, immunizations are deferred. The nDNA disorders causing mitochondrial disease have a variable age of disease presentation. The phenotypic variability in both mtDNA and nDNA disorders has contributed to the current uncertainty over the long-term effectiveness of therapeutic intervention, despite several clinical trials.

In order to advance the understanding of encephalopathic deterioration with metabolic stress, including that stress caused by vaccination, more study is needed. For those with identified mutations, mitochondrial haplogroup, detailed examination of what are thought to be non-pathogenic mtDNA polymorphisms, mtDNA content, biomarkers of oxidative stress and cytokine levels over time and during the month following exposure to metabolic stress will need to be studied. Performing such study using healthy siblings (same mitochondrial haplogroup) and other age- and gender-matched controls from that child's neighborhood (potentially other mitochondrial haplogroup and probably different mitochondrial SNP pattern) may provide the necessary control groups.

6.4 Human Central Nervous System Stem Cell Therapy in Neuronal Ceroid Lipofuscinosis.

Robert D. Steiner, M.D

Brain-directed stem cell therapy has been investigated in a recent clinical trial for CNS disease in infantile and late-infantile neuronal ceroid lipofuscinosis. Infantile and late-infantile neuronal ceroid lipofuscinosis (INCL and LINCL) are universally fatal neurodegenerative disorders caused by lysosomal enzyme deficiencies. An open-label dose-escalation Phase I trial of human CNS stem cells (HuCNS-SC®) was conducted in subjects with INCL and LINCL [42]. This study represents the first investigational use of purified human neural stem cells in clinical testing. The primary goal of the trial was to evaluate the safety of the surgical technique, the immunosuppression regimen, and the cells. Six moderately to severely affected children underwent HuCNS-SC transplantation. HuCNS-SC cells were delivered surgically directly to the cerebral hemispheres and lateral ventricles. Immunosuppression was administered for twelve months following transplantation.

The preliminary results of the trial show that the surgery, immunosuppression and HuCNS-SC transplantation were well tolerated. There was no evidence of undue reaction to HuCNS-SC delivery demonstrated by imaging or clinical examinations. There were no unexpected Adverse Events and no Adverse Events were definitely attributed to HuCNS-SC. One subject expired from disease progression 11 months after transplantation. The results of the brain-only autopsy in this patient revealed no signs of HuCNS-SC transplantation toxicity, but evidence of engraftment in the CNS was present. Preliminary efficacy measures included a broad range of neuropsychological and developmental tests, and in general, the

results were consistent with the natural history of the disease. The open-label design of the study, cohort size, and the advanced stage of disease at transplantation limits interpretation of efficacy data collected (manuscript in submission).

Study design and choice of endpoints are challenging for trials in rare neurodegenerative disorders, particularly for later stage and pivotal investigations. Ethical guidelines pertaining to research in pediatric subjects are also a special consideration, made even more complex by the first-in-human nature of the Phase I trial. These factors contributed to a study design that ultimately included only patients in the advanced stage of a known fatal disease. Despite the fact that NCL has no effective approved therapy, the sponsor and investigators were also well aware of the potential for therapeutic misconception and care was taken to address this concern with each patient enrolled.

7.0 Ethical Issues in CNS Therapies for IEM

Many of the IEM with CNS manifestations affect children, and the enrollment and treatment of children in clinical research present ethical challenges as well as medical and scientific concerns. Investigators frequently confront the need to balance the protection of the health and welfare of children with serious diseases while allowing access to investigational therapies for patients with severe and often life-threatening disorders. This section discusses ethical principles in clinical research in vulnerable populations, and the regulatory provisions intended to provide structure and context to these situations.

Sara F. Goldkind, M.D., M.A. Robert (Skip) M. Nelson, M.D., M. Div., Ph.D.

7.1 Ethical Considerations for IEM Trials in Children

The IEM with severe CNS manifestations are almost always incurable and life-threatening, with few if any available proven interventions. While it is well-recognized that scientific data on dosing, safety, and efficacy should guide use of medicinal products, the aggressive deterioration often seen in these life-threatening diseases may drive demand for early access to little-studied yet potentially promising therapies. Parents are often willing to sacrifice much in hope of improving a child's chances for either an extension or improvement in quality of life. Given the lack of alternate treatments, there is a willingness on the part of parents and often investigators to accept higher risks and potential toxicity early on in product development in hopes of a potential therapeutic breakthrough. The likelihood that new treatments are only available in the research setting potentially exacerbates the therapeutic misconception, that is the conflation of research with medical care. In addition, for much of the affected population there is limited ability to enroll in existing clinical trials as they tend to be small and involve rare and geographically dispersed diseases. Finally, there are often limited data by which to anticipate potential safety and efficacy issues due to the lack of an appropriate animal model and/or limited applicability of adult data, if any exist at all.

The primary obligation is to ensure that children are only enrolled in clinical trials when necessary to answer an important question about the health and welfare of children. In the case of IEM, it is frequently not possible to conduct useful clinical trials in adults (other than perhaps phase 1 trials in healthy adult volunteers to determine a maximum tolerated dose). Given this limitation, it is especially challenging to design clinical trials that will yield credible scientific results. What dosing strategy should be selected so that we strike the appropriate balance of risk and potential benefit? How should we establish this dosing strategy in the absence of appropriate animal models? What population of children should be selected for enrollment in an early phase trial? If children are selected with a more severe manifestation of the disease, one may obscure potential safety signals (i.e., adverse events

might be interpreted as disease progression) and undermine the possibility of demonstrating a therapeutic effect. However, if children are selected with a less severe manifestation of the disease, they may be placed at risk of unacceptable toxicity in the absence of any demonstrable therapeutic benefit. Is the natural history of the disease understood at these different levels of severity so that one can draw meaningful conclusions from an open-label, non-concurrent historical (or concurrent untreated) controlled clinical trial? The scientific and ethical challenge is to design a clinical trial that will yield credible scientific results while striking an appropriate balance between risk and potential direct benefit for the children enrolled in the clinical trial.

The ethical guidelines for the design of clinical trials involving children require that experimental interventions presenting greater than minimal risk must offer the enrolled children a sufficient prospect of direct benefit to justify those risks.² Given this guideline, is it ever ethical to perform early phase clinical trials in children even when they are suffering from a life threatening disease with no other available treatment? Answering this question requires scientific and clinical judgment as it involves selecting a dosing strategy that justifies the risks of the experimental intervention with the possibility that the child may experience a direct therapeutic benefit, and is comparable to the risks and potential benefits of alternate treatment strategies. What standard of evidence from either preclinical animal or adult human studies is required or desirable before initiating clinical trials in children with rare and often life-threatening diseases? The proposed clinical trial should also be placed into the context of overall product development, given that the goal is to establish sufficient safety and efficacy to make that product generally available to the affected population. Many if not all of these products would be considered orphan products, a designation which guarantees seven years of market exclusivity for a specific indication following FDA approval. Nevertheless, approval still requires sufficient evidence of safety and efficacy from adequate and well controlled studies.

7.2 Regulatory Provisions for Investigational Access to Potential Treatments for Serious Diseases

In addition to incentivizing the development of drugs for rare diseases, FDA has long recognized the compelling need for programs allowing access to investigational therapeutic products under certain conditions. Several FDA regulatory provisions include a degree of flexibility in applying the statutory standards for safety and efficacy in the setting of life-threatening illnesses and severely-debilitating illnesses where satisfactory alternatives are not available [43]. The new expanded access regulations try to appropriately balance providing access to investigational drugs for treatment use, minimizing risk to patients, and ensuring the integrity of the drug approval process. Moreover, they attempt to reconcile an individual's desire to make healthcare decisions with society's need to ensure that drugs are labeled and marketed based upon rigorous scientific evidence about safety and effectiveness.

Early access to investigational products often involves means to assure equitable distribution of scarce resources. This is not unique to this setting. Similar issues arise in the clinical arena of organ transplantation. Mechanisms which allow for the fair distribution of scarce resources include "first come, first served," and a lottery system. As a general matter, FDA

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²See 21 CFR 50.52. The guidelines allow for a limited exception to this approach for an intervention or procedure not offering a prospect of direct benefit, provided: the risk is no more than a minor increase over minimal risk; the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations; the intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition that is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians (21 CFR 50.53). As a general rule, all of the interventions being developed for treating inborn errors of metabolism present more than a minor increase over minimal risk, and thus fall under 21 CFR 50.52.

supports lotteries as an ethically acceptable and fair mechanism for distributing an investigational drug in an access program when the drug supply is limited. FDA does not believe that expanded access programs should be limited to only those situations in which there is an adequate drug supply for all potential subjects.³ One question is whether children who are sicker should be preferentially enrolled or should children who are less ill and potentially more likely to respond to research interventions be initially enrolled. Understanding how to proceed involves a complex interplay of considerations such as the scientific objectives of the protocol, the knowledge accrued to date on the therapeutic modality and the disease itself, as well as the likelihood that children with a given level of disease severity will respond to the investigational modality.

As for every research project, but particularly in this difficult context, it is incumbent upon investigators to educate families and prospective subjects (as applicable) about the differences between clinical research in which products are given with the prospect of direct benefit, and clinical care. Aiding in this effort are subject advocates and disease-based advocacy groups. Subject advocates serve important roles including being a resource about clinical trials more generally and a neutral buffer between desperate parents and overly enthusiastic scientists. Disease-based advocacy organizations help fundraise for research, control community resources and partner in setting research priorities.

8.0 Challenges and Future Directions in Rare Disease Research

The chronic, irreversible and slow progression of CNS manifestations of IEM is difficult to assess in relatively short-term studies, and there is a need to develop new tools to more rapidly assess the effects of potential therapies. Two overall strategies intended to aid translation of CNS therapies for IEM are presented in this section. The development of biomarkers and their possible use as surrogate markers is suggested, and the use of adaptive or novel statistical and clinical trials designs is proposed as areas of emerging research intended to support the development of potential therapies. The collaborative development of treatments using parallel multi-disciplinary approaches is also needed and is discussed here.

8.1 The Use of Biomarkers as Surrogate Endpoints. Emil Kakkis, M.D., Ph.D

CNS diseases tend to progress over long time frames, have long delays between disease injury and measurable impact, and very often have large irreversible components to the disease, making treatment efficacy harder to establish. Clinical studies using clinical endpoints may require the use of more difficult and lengthy study designs evaluating the prevention of decline rather than treatment. For example, for diseases like Sanfilippo or Niemann Pick C, the time course may extend over many years, but the time of injury, irreversibility and measurable change may not be readily apparent for each disease and for every patient. An example for this comes from adrenoleukodystrophy where patients may have apparent near normal function and onset of clinically unclear symptoms, while their brain is already substantially damaged when viewed on MRI, and their course of decline already set in motion [44]. The plasticity of the brain to compensate and temporize clinically then covers up the relationship between pathological disease state and measurable decline, whereas age and MRI score are good predictors of outcome.

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³Some examples of lotteries used in the past to fairly allocate limited drug supply are: Cephalon's myotrophin access program for ALS (See <http://www.nytimes.com/1996/06/25/science/early-access-for-new-drug.html>); Herceptin for HER2 positive Breast Cancer (See <http://www.charitywire.com/charity106/01800.html>); and Iressa for the treatment of terminal lung cancer (See http://www.timesonline.co.uk/tol/life_and_style/health/article6624061.ece).

The other source of complexity comes from the difficulty of measuring CNS disease. Measuring specific clinical outcomes might take years of progression to be evident and the treatment may have to begin before decline and diagnosis is usually perceived. In addition, the measures themselves, such as developmental quotients or IQ's, or developmental testing, have relatively low precision and accuracy and are subject to substantial interpatient differences in meaning and interobserver variation. Biochemical measures for genetic CNS diseases are considered even less certain with regard to predictive value, but if adequately studied in model systems and appropriate controls are used, many biochemical measures have the potential to give us a reasonable basis for believing that a therapy with a direct and clear mechanism of action is working. The challenge is that qualifying biochemical measures has been difficult and there is not sufficient science and formal exploration within animal models and humans to show how to decide what is reasonable and what is not. One example from my experience is the use of urinary glycosaminoglycan (GAG) data in MPS diseases, which has been considered to not accurately predict clinical outcomes such as the 6 minute walk test (6MWT); but I would argue that the error is less likely the interpretation of urinary GAG than the imprecision of the 6MWT and the impact of confounding clinical variables in multisystem diseases. In a study of laronidase (Aldurazyme) administration to patients with MPS I (n=45), a post hoc, unblinded analysis of a subset of teenage patients (n= 4) shows that these patients had a decrease in walk distance which was in part caused by patients with spinal cord compression secondary to improved neck joint mobility during treatment [45,46]. These same patients had increases in shoulder range of motion. The decision as to which clinical endpoint actually captures a complex disease makes interpretation of a measure like urinary GAG harder to interpret. However, in my opinion when looking at effects of antibody on efficacy, the negative effect of antibodies on drug efficacy is best detected and quantified with urinary GAG measures, which reflect tissue treatment effects more precisely than any of the clinical measures [47]. Therefore in some situations, the substrate measures may be better measures of drug action and effect than the relatively less precise and less accurate clinical measures. This may be important, if not critical in smaller studies with rare diseases, particularly when irreversible or complex neurologic disease is involved.

It is important then to consider ways to improve the accessibility of the Accelerated Approval pathway. An Accelerated Approval is an approval for commercial marketing in the US of a product for the treatment of a serious or life-threatening illness where the assessment of effectiveness rests on the results of a surrogate endpoint (a biomarker) that is reasonably likely to predict clinical benefit [48] (which contrasts with a standard approval under US law, where a clinical meaningful benefit must be demonstrated [12]). Novel surrogate markers may lack prior clinical experience and there may be uncertainty as to their ability to predict clinical benefit, but they may in fact be very good measures of treatment effect based on other scientific data. Therefore, I propose the development of qualification criteria for surrogate endpoints for efficacy determination in treatments for ultra-rare disorders, and these criteria should be based on the best available science but would not necessarily require prior clinical experience. I propose the following general criteria be considered:

- Disease basis and mechanism be well understood
- Drug mechanism of action is direct and understood, and is directly in line with disease process mechanism
- Surrogate marker has direct relationship to disease, is sensitive and specific with large dynamic range, and sampling compartment is relevant to disease compartment
- In preclinical/clinical qualification:

- Preclinical studies show dynamic dose-response
- Preclinical disease pathology predicted by surrogate response
- Clinical effect in an adequate animal model (optional)
- Clinical severity proportional to marker concentration in cross-sectional study (if available)

The development of qualification criteria would be particularly important for CNS diseases in which long timelines and imprecise methods make drug development intractable.

8.2 Directions for the Future. Stephen C. Graft, Pharm. D

There are insufficient resources available to address the research and development needs of all rare diseases. The Office of Rare Diseases Research and other institutes of the National Institutes of Health have created a number of initiatives to spur translational research in rare diseases. One NIH and ORDR program, the Rare Diseases Clinical Research Network with support from several Institutes and Centers, enables individual consortia of several rare disease investigators, working in collaboration with industry and patient advocacy groups, to develop a better clinical understanding of rare diseases and to share best care and treatment information. (RDCRN Website: <http://rarediseasesnetwork.epi.usf.edu/>) The Rare Diseases Clinical Research Network (RDCRN) consists of 19 distinctive consortia and 150 research sites collaborating to improve availability of rare disease information, treatment, clinical studies, and general awareness for both patients and the medical community. A major requirement of the research consortia is to provide training opportunities for the next generation of clinical research investigators with an interest in rare diseases. The direct involvement of over 55 patient advocacy groups in network operations, activities, and strategy is a major feature of the RDCRN. Each consortium in the network includes relevant patient advocacy groups in the consortium membership and activities. These patient advocacy group representatives serve as research partners within their own consortia. Collectively, the Coalition of Patient Advocacy Groups (CPAG) represents the perspective and interests of all patient advocacy organizations associated with the RDCRN. The RDCRN utilizes a Data Management Coordinating Center (DMCC) to develop uniform investigative clinical research protocols for data collection in collaboration with the RDCRN Steering Committee, monitor protocol adherence, data collection and data submission, and work with the each consortium's Data and Safety Monitoring Boards to establish protocols for adverse events notification and reporting.

Another program, the Therapeutics for Rare and Neglected Diseases (TRND) aims to create collaborations, encourage and speed the development of new drugs, and provide funding for specific research and development stages for potential products to conduct preclinical and clinical research studies of rare disease therapies. (TRND Website: <http://www.genome.gov/27531965>) Funds for this initiative have been made available for this activity at the National Human Genome Research Institute at the NIH. TRND will provide the bridge to cross the gap that frequently exists between basic research and initiation of clinical studies in patients. TRND will encourage investigators from both inside and outside of NIH, who have expertise in a broad and diverse range of scientific disciplines and disease areas, to submit projects for work within its intramural facility. This will create ongoing collaborations that will benefit researchers and, most importantly, patients with rare and neglected diseases. TRND will strive to develop candidate drugs for rare and neglected diseases that meet FDA requirements for an IND application prior to initiation of clinical studies in humans. TRND expects to license most of its IND-worthy candidate drugs to biopharmaceutical companies for clinical development.

As we enter a new era of product development, the aim of these and other programs is to develop and enhance multi-disciplinary approaches to the development of treatments for complex and difficult to treat diseases, especially for unmet medical needs in rare disease populations. This will require that activities from various disciplines be implemented in parallel throughout the entire research and development stages, and that potential therapies be actively shepherded through all phases of development. Specific goals must be set for actively working to get treatments to become available and into the hands of treating physicians to meet the needs of their patients. We should move towards this goal as expeditiously as possible. Development plans should include the best use of available preclinical and clinical research resources and special attention to necessary areas of drug development that are currently underserved, such as supportive toxicology and the development and qualification of appropriate animal models. In recent years research projects include obtaining advice from patients and their advocates throughout the research protocol development process and initiation of recruitment activities in addition to the monitoring of study results.

9.0 Conclusions

Developing treatments for IEM with CNS manifestations is one of the more challenging areas of drug and biological product development. In addition to the obvious limitations due to small numbers of patients available for study, additional considerations include inadequate descriptions of the natural histories of the diseases, highly diverse mechanisms and manifestations of diseases between the disorders and high phenotypic variability within the individual disorders, difficulties with diagnosis and patient identification, lack of specific and sensitive outcome measures for the assessment of patients, and delivery of treatments to the CNS, among others. Thus, to optimally develop products for these disorders, a multi-disciplinary approach will be necessary, and will require that elements from various disciplines be implemented, in parallel, throughout the entire development process.

The main goals of this conference were that there be communication and mutual exchange of ideas among stakeholders from academia, industry, governmental agencies and patient groups to determine where gaps in the existing knowledge remain, identify areas for further discussion and collaboration, and explore potential pathways forward for the development of drugs targeting the CNS. The eventual goal would be a sound scientific anchoring for the development programs for these drugs, and the identification of efficiencies that will help accelerate the drug development process. These discussions should be seen as first steps in what is hoped to be an iterative process intended to lay the ground work for future successes in IEM therapies.

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Abbreviations

CNS	central nervous system

IEM	inborn error of metabolism
FDA	Food and Drug Administration
ODA	Orphan Drug Act
CSF	cerebrospinal fluid
MRI	magnetic resonance imaging
DTI	diffusion tensor imaging
AAV	adeno-associated virus
IRB	institutional review board
DSMB	data and safety monitoring board
UBDRS	Unified Batten Disease Rating Scale
NCL	neuronal ceroid lipofuscinosis
MPS	mucopolysaccharidosis
UCD	urea cycle disorder
FA	fractional anisotropy
EDSS	Kurtzke expanded disability status scale
mtDNA	mitochondrial deoxyribonucleic acid
GAG	glycosaminoglycan
6MWT	six-minute walk test

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Table 1

Specific MRI findings of selected small molecule and large molecule IEM

Disorder	Anatomic MRI Feature	Location	Clinical Correlation
Maple syrup urine disease	Diffuse increase in T2 signal	Basal ganglia, brainstem, mesencephalon, thalamus and globus pallidus; cerebellum, periventricular white matter	Cytotoxic or intramyelinic edema
Phenylketonuria	T1: hyperintensity, T2: hypointensity increased T2	Globus pallidus White matter	Edema Edema
Lysosomal disorders	Thalamic hyperintensities, progressive atrophy, prominent Virchow Robin spaces	Thalamus, gray matter, white matter	Atrophy of gray matter, destruction or improper formation of myelin
Adrenoleukodystrophy	T1-weighted characteristic enhancement pattern in the intermediate zone T2-weighted MR image shows symmetric confluent demyelination	White matter Peritrigonal white matter and the corpus callosum	Active demyelination and inflammation Active demyelination and inflammation
Infantile neuronal ceroid lipofuscinosis	Atrophy	Cerebrum	Neuronal loss
Urea cycle: Proximal disorder	Increased T2 signal	Centrum semiovale white matter	Edema
Late onset	Increased T2 signal, atrophy	Basal ganglia, gray matter	Cell loss, diffuse ischemic injury and edema
Neonatal onset			