1. Meeting Summary

Judith Fradkin (Director, Division of Diabetes, Endocrinology and Metabolic Diseases NIDDK) introduced the meeting, noting that the primary objective was to stimulate research that will translate basic cell biology, biochemistry and biophysics findings about protein structure and assembly into potential therapies for monogenic and other misfolding and misprocessing disorders.

The meeting was well-attended with 208 participants. The audience included clinicians, clinical researchers and basic scientists at all career levels from academic institutions, the NIH, and the private sector.

On the first morning, speakers focused on the basic biology of protein folding and processing, beginning with two keynote presentations; one by Linda Hendershot (Saint Jude’s Children’s Research Hospital) focusing on the basic cellular machinery involved in protein folding and quality control in the endoplasmic reticulum (ER) and another by David Ron (NYU School of Medicine) focusing on potential therapeutic opportunities related to the unfolded protein response. The afternoon session entitled “ER Stress and Mis-folding in Disease, Novel Outcomes” began with the presentation of an exciting new concept called proteostasis by Jeff Kelly (Scripps). He gave several examples of how in amyloidoses there are often multiple pathways, some of which or now well described, that can be modulated together each in small ways, resulting in improved outcomes in disease models. Subsequent speakers continued discussing the insights that have been gained about the biology of specific conformational diseases in model organisms, such as alpha1 anti-trypsin deficiency, Wolfram syndrome, cystic fibrosis and congenital hyperinsulinism.

The second day was devoted to talks about human disease and how researchers are focusing on translating their basic finding into novel therapeutic strategies. Several speakers described exciting pre-clinical or clinical results. Some of the highlights included a talk by Bill Balch (Scripps) describing work on the modulation of several proteostatic pathways that provide promising avenues for treatment of certain subtypes of cystic fibrosis. Alan Verkman (UCSF) summarized his work on using small molecules screens to identify two types of potential therapeutics (correctors and potentiators) for cystic fibrosis, polycystic kidney disease and diseases resulting from mutant water channels. These more detailed presentations were followed by seven short talks on how a number of laboratories have been using a variety of moderate and high throughput screening methods to develop novel probes to interrogate the pathways and signaling complexes involved in protein and mis-folding, mis-processing and mis-trafficking, with the ultimate goal of developing therapeutics for a wide variety of rare diseases with processing and trafficking defects.

Mark Scheidler (NINDS), a program officer heavily involved in NIH’s Molecular Libraries Initiative, also gave an update on the active NIH supported screening centers and he described for the audience what the screening centers do, and how academic researchers can interact with the centers to gain access to high throughput small molecule screening facilities and the unique chemistry expertise some of them provide. The workshop also had a discussion lead by the meeting organizers which solicited input on opportunities and road blocks encountered in
developing and using small molecule screens for developing tools and therapeutics for treating a wide variety of mis-folding and mis-trafficking diseases.

In all, there were 27 scientific talks, 4 of which were selected from abstracts submitted by junior investigators. A total of 55 posters were presented at two active and crowded poster sessions, and 9 travel awards were provided to junior investigators.

Rare diseases specifically covered in presentations are as follows:

- Cystic Fibrosis
- Nephrogenic Diabetes Insipidus
- Alpha 1 anti-trypsin Deficiency
- Congenital Hyperinsulinism
- Wolfram Syndrome
- Polycystic Kidney Disease
- Familial Amyloidosis
- Familial Amyloid Polyneuropathy
- GM1 Gangliosidosis
- Congenital Hyperinsulinism
- Pseudohypoaldosteronism (PHA)
- Huntington’s Disease
- Prion Disease
- Autosomal dominant familial isolated hypoparathyroidism (AD-FIH)
- Aspartylglucosaminuria (AGU)
- Primary Hyperoxaluria
- Niemann-Pick C1 (NPC1) Disease
- Amyotrophic Lateral Sclerosis (ALS)
- Congenital Lipoid Adrenal Hyperplasia (lipoid CAH)
- Dementia with Lewy Bodies (DLB)
- Spondyloarthropathies
- Autosomal Dominant form of Retinitis Pigmentosa
- Fabry Disease
- Neonatal Diabetes
- Pompe Disease
- Hermansky-Pudlak Syndrome (HPS)
2. Plans to publicize meeting results

The attached meeting summary will be posted on the NIDDK Website at http://www.niddk.nih.gov/fund/other/protein_misfolding/index.htm.

3. Proposed or initiated research activities for rare diseases related to the meeting

PA-04-068 (http://grants2.nih.gov/grants/guide/pa-files/PA-04-068.html) - DEVELOPMENT OF ASSAYS FOR HIGH THROUGHPUT DRUG SCREENING.

The purpose of this PA is to encourage the use of high throughput small molecule screening for use in both research and drug discovery programs by funding the development of innovative assays that may be adapted for automated screening. The assays would aim to identify new tools for basic research and promising new avenues for therapeutics development, especially in areas related to the missions of NIDDK, NCI and NIAID…

Relevant topics include, but are not limited to:

- Assays for molecular chaperones or molecules that improve the post-translational targeting, folding, or assembly of proteins, especially involving mutant proteins responsible for inborn errors of metabolism, cancers, or other rare diseases…”

A follow-on PA (FY ’06) is currently under discussion at NIDDK to assist researchers in optimizing the results of high-throughput screens.