

**SUMMARY: THE PRADER-WILLI SYNDROME RESEARCH STRATEGY WORKSHOP [1R13DK085332]
NOVEMBER 15-17, 2009
DOUBLETREE HOTEL EXECUTIVE MEETING CENTER, BETHESDA, MD**

Advances in the fields of genetics, appetite control, and neurobiology have established the foundation for understanding and more effectively treating the rare genetic disorder, Prader-Willi syndrome (PWS), but critical questions in basic and clinical science remain unresolved. The *Prader-Willi Syndrome Research Strategy Workshop* brought together a diverse group of clinical and basic scientists to discuss the strengths, opportunities, gaps in knowledge, and resources needed to advance the science of PWS. The Workshop was sponsored by the US National Institutes of Health [the Office of Rare Disease Research and the National Institute of Diabetes and Digestive and Kidney Diseases: 1R13DK085332], the Canadian Institutes of Health Research, and patient advocacy groups, including the Foundation for Prader-Willi Research (FPWR), the Prader-Willi Syndrome Association (USA) and FPWR-Canada. Approximately sixty-five scientists from eight countries provided expertise and insight towards the goal of developing a comprehensive research strategy to accelerate efforts to understand PWS at the molecular, cellular and systems level, leading to more effective therapeutic interventions.

Workshop participants focused on five areas of emphasis relevant to PWS: Emerging Clinical Issues, Obesity and Energy Balance, Mental Illness and Psychopathology, Molecular Genetics, and Animal Models. The opening evening of the meeting featured an address by the parent of a child with PWS [Keegan Johnson, President, FPWR-Canada] and a keynote address on the NIH's vision for advancing rare disease research from Francis Collins, NIH Director. For the general session on day 1, experts in each of the five areas of emphasis reviewed the current state of knowledge for their field. This was followed by breakout sessions in each area of interest, wherein participants prioritized basic and clinical research questions, discussed resource and training needs, and considered cross disciplinary opportunities. The final general session on day 2 included reports from each of the breakout sessions and a final wrap up discussion of priorities across research areas.

Several overarching needs were identified by participants. A more detailed analysis of the variability of phenotype across individuals and along the developmental spectrum is needed both to understand the spectrum of the disease and to more accurately ascertain genotype-phenotype correlations. Because the underlying genetic disruption remains incompletely understood in PWS, participants recommended the application of new genomic technologies to fully characterize transcripts in the Prader-Willi critical region (PWCR) and to delineate the function and targets of the PWCR snoRNAs. The use of mouse models of PWS and mouse and human *in vitro* models for molecular target definition was prioritized. Additional research focused on the neurobiology of appetite in PWS, including the changes associated with the shift from failure to thrive to hyperphagia was recommended. A strong need to develop standardized measures for evaluation of animal models of PWS with respect to metabolic and behavioral phenotypes was noted, as was the need to more accurately and consistently define behavioral problems and mental illness in PWS patients. Recommendations for resource development were also made. In this respect, the development of induced pluripotent stem cells from individuals with all genetic subtypes of PWS was deemed highest priority, as they should provide an excellent *in vitro* model system in which to explore research questions that currently cannot be adequately addressed. Finally, it was recommended that multidisciplinary working groups be convened to provide recommendations on advancing candidate anti-obesity and psychiatric interventions into clinical trials, with special attention to defining informative surrogate endpoints, designing trials with sufficient power to demonstrate efficacy, and with consideration of the unique ethical, medical, and logistical challenges that arise in performing clinical trials in this population. Enhanced multidisciplinary and international collaboration will be critical to effectively moving the field forward. Participants recognized that advancement of research for this rare disorder provides a unique and important opportunity to gain insight into a number of common public health concerns, including obesity, eating disorders, sleep disorders, and disorders of behavior and mental health.