FOUNDATION FOR PRADER-WILLI RESEARCH

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2014 FPWR Funded Projects

Since its inception in 2003, FPWR has funded more than $4,500,000 in PWS-related research!

2014 Funding Year (~$1,200,000)

1. **EVALUATION OF AUTISM-LIKE BEHAVIORS IN MICE DEFICIENT FOR *Magel2*.** Christian Schaaf, M.D, Ph.D. Baylor College of Medicine ($65,921). Dr. Schaaf and co-workers recently identified mutations of the *MAGEL2* gene in individuals showing many features of PWS, including autism. Here he will study the *Magel2* deficient mice to see if they reflect the behavioral changes seen in humans. This study will provide the foundation for evaluating therapy to alleviate autism behaviors in those with PWS and/or *MAGEL2* mutations.

2. **ROLE OF THE LIPID-DERIVED SATIETY FACTOR, OLEOYLETHANOLAMIDE, IN PRADER-WILLI SYNDROME**. Daniele Piomelli, Ph.D. University of California, Irvine ($75,600). Oleoylethanolaminde (OEA) is a hunger-reducing signal generated by the body. This study will examine the presence and function of OEA in a PWS mouse model and in people with PWS.

3. **THE ROLE OF PREPL IN THE PATHOPHYSIOLOGY OF PWS: EVALUATION OF A NOVEL THERAPEUTIC APPROACH FOR THE TREATMENT OF HYPOTONIA.** John Creemers, Ph.D., University of Leuven, Belgium ($75,600). Dr. Creemers' group has identified deficiency in the enzyme PREPL as a possible contributing factor to hypotonia in PWS. This study will test whether treatment with the antibiotic sulfamethoxazole will improve neuromuscular transmission and muscle function in a mouse model of PWS and in infants with PWS.

4. **GENOME-WIDE SURVEY OF DNA METHYLATION IN PWS.** Soo-Jeong Kim, M.D., Seattle Children's Research Institute ($75,600). Methylation patterns of an individual's entire genome have a profound impact on overall gene expression and, in turn, the function of every body system. Dr. Kim's group will explore whether the genetic and epigenetic alterations in the PWS region also impact the overall global genomic DNA methylation patterns in other, non-PWS, areas of the genome.

5. ***HOW DOES OXYTOCIN CURE EARLY FEEDING AND ADULT SOCIAL BEHAVIOR ALTERATIONS IN MAGEL2 DEFICIENT MICE, A MODEL FOR THE PWS?** Francoise Muscatelli, Ph.D., Mediterranean Institute of Neurobiology, INMED ($75,000). Dr. Muscatelli's group has shown that administering a single dose of oxytocin to the Magel2 deficient mouse model of PWS at birth can restore suckling activity as pups and improve social behavior as adults. The group will now examine the mechanisms behind this effect to help define the relationship between Magel2 and the oxytocin system. Results from this work could impact the development of oxytocin therapeutic strategies for PWS.
   *Funded in collaboration with Prader-**Willi France.**

6. **UNRAVELING THE DEVELOPMENTAL NEUROBIOLOGY OF PWS: A CROSS-SECTIONAL BRAIN-IMAGING STUDY (Year 2).** Anita Hokken-Koelega, MD, Erasmus University ($73,007). These researchers will use advanced brain imaging techniques in combination with clinical data to better understand psychiatric problems in PWS. The goal is to identify markers for early detection of mental health problems to allow more timely and effective intervention.

7. **TRAINING TASK SWITCHING TO DECREASE TEMPER OUTBURSTS IN PEOPLE WITH PWS.** Kate Anne Woodcock, Ph.D., University of Birmingham, United Kingdom ($75,479). Individuals with PWS have a strong preference for routine and predictability, with changes or "task-switching" often being a major trigger for temper outbursts. This project aims to develop a software prototype directed at teaching and improving task switching in PWS. If successful, this could be the first step in developing a valuable tool that would improve the quality of life for those with PWS and their families/caregivers.

8. **INJECTABLE PROTEIN BASED GENE ACTIVATION THERAPY FOR PWS (Year 2).** David Segal, Ph.D., University of California, Davis ($75,360). Building on efforts to reactivate the maternal allele in PWS, Dr. Segal's group is designing injectable proteins targeted at turning on the maternal *SNORD116* cluster and *Magel2* gene. These funds will help test the effectiveness of the proteins in a mouse model of PWS. A rat model of PWS will also be developed.

9. ***SMALL MOLECULES AND THERAPEUTIC POTENTIAL FOR PWS (Year 2).** Yong-Hui Jiang, M.D., Ph.D., Duke University ($75,600). All individuals with PWS have a set of normal genes on their maternally-derived chromosome, but the

genes in the PWS regions are 'silent'. Dr. Jiang will screen a library of 10,000 small molecules to identify candidate drugs that can reactivate the PWS region genes on the maternal chromosome 15, specifically SNRPN and snoRNAs. Promising candidate molecules will be tested for efficacy in PWS models, with the goal of ultimately evaluating their effects in patients. *Puzzle project

10. **INHIBITORY CIRCUITS AND TRANSMISSION IN THE HYPOTHALAMUS IN A MOUSE MODEL OF PWS.** Garret Stuber, Ph.D., University of North Carolina, Chapel Hill ($75,600). Using advanced neurobiology techniques and the Magel2 knockout mouse model of PWS, Dr. Stuber's group will be characterizing the distribution of Magel2 throughout regions of the brain and the role of Magel2 in neurotransmissions related to hyperphagia. These studies will help map the neurocircuitry in the PWS brain, a critical foundation for the development of future targeted therapies.

11. **DEVELOPMENT OF APPETITE-RELATED NEURAL CIRCUITS IN A MOUSE MODEL FOR PWS** (Year 2). Sebastien Bouret, PhD, Children's Hospital Los Angeles ($75,600). Dr. Bouret's group has previously shown that abnormally elevated levels of the gut-hormone ghrelin and loss of Magel2 can both impact normal development of hypothalamic neurons. This impacts key physiological processes including appetite regulation. In year 2, his group will explore the mechanism behind this impaired development. They hypothesize that stress to a specific part of the cell (endoplasmic reticulum, ER) may be a main contributing factor and could be targeted with inhibitors of ER stress.

12. **GUT MICROBIOME IN INDIVIDUALS WITH PWS**. Robert Shulman, MD, Baylor College of Medicine ($75,600). We each carry a large and diverse population of bacteria in our gut, collectively called the "gut microbiome". These bacteria vary among individuals, are critical to normal gastrointestinal function, and can be manipulated by diet and supplements. There is an emerging field of research exploring how changes in the composition and activity of the gut microbiome may contribute to a variety of health issues, diseases, and disorders. This is the first study to compare the gut microbiome between PWS and non-PWS individuals to explore its potential contribution to hyperphagia and weight in PWS.

13. **COMPREHENSIVE BEHAVIORAL INFORMATICS APPROACH TO CNS FUNCTION IN PWS MOUSE MODELS**. Laurence Tecott, MD, University of California, San Francisco ($75,600). In recent years, there has been an exciting and rapid development of new animal models for PWS research. These models are valuable tools in testing the effects of potential therapeutics on PWS related behaviors. However, the most effective use of these models requires developing accepted standardized approaches to assess changes in behavior that can be used universally by different laboratories. Dr. Tecott's group has expertise in automated home cage monitoring systems and plans to use these to define detailed behavioral phenotypes of the Magel2 and SNORD116 deletion mouse models of PWS.

14. **NUTRITIONAL ASPECTS OF PWS AND CHILDHOOD OBESITY: A METABOLOMICS APPROACH**. Daniel Driscoll, MD, PhD, University of Florida ($75,600). Hyperphagia and food related behaviors in PWS have been defined into six distinct nutritional phases. However, the mechanism(s) underlying the various nutritional phases and specifically that transition from one phase to another remain poorly understood. Dr. Driscoll's group plans to use a metabolomics approach to analyze differences in specific metabolites among individuals in the six different nutritional phases. This study will provide insight in to the biochemistry underlying each phase and how that biochemistry shift from one phase to another providing potential targets for therapeutic development.

15. **THE ROLE OF SNORD116 IN PRADER-WILLI SYNDROME** (Year 2). Rudolph Leibel, MD, Columbia University ($75,600). Genetic mapping data from PWS patients with "microdeletions" of SNORD116 implicate the gene as a major contributor to PWS. This group we will generate and compare iPSC neurons from PWS microdeletion patients and unaffected individuals to study the specific effects of loss of SNORD116. Understanding how PWS effects the brain at the cellular and molecular level can inform novel therapeutic targets for PWS patients.

CLINICAL TRIALS INITIATIVE

16. **DOSE TRITRATION STUDY OF DIAZOXIDE FOR PWS.** Neil Cowen, Essentialis Inc., ($75,600) Diazoxide is an FDA-approved drug, currently in use in infants through adults for a rare form of insulin overproduction. The drug works by activating K-ATP channels in certain neuron in the brain, and studies in animals and humans suggest it might be able to improve metabolism and decrease hunger in PWS. We are working with a biotech company to partially fund a trial to evaluate this drug in children with PWS.

17. **TRANSCRANIAL DIRECT CURRENT STIMULATION (TDCS), STARTLE MODULATION AND EVENT-RELATED POTENTIAL OF THE BRAIN TO EVALUATE HYPERPHAGIA IN PWS.** Merlin Butler, MD, PhD University of Kansas Medical Center ($75,600). tDCS is a noninvasive method to stimulate targeted regions of the brain. This study will evaluate the effectiveness of tDCS in decreasing food craving in individuals with PWS. Weight, calorie intake and degree of hyperphagia will be measured.