2016 Spring Update - Research Grants
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Mission: To eliminate the challenges of PWS through the advancement of research

**General Grants Program: Investigator-Initiated Research**
Supports research that will significantly advance the understanding of PWS and/or develop and evaluate new therapeutic interventions for PWS

**Special Research Initiatives** – investments in targeted areas
- *Focused Scientific Meetings*
- *Development of Critical Research Resources*
- *PWS Preclinical Program*
- *PWS Clinical Development Initiative / Clinical Trials Consortium*
- *Molecular Resource Center*
- *Global PWS Registry*
Goals of the Investigator-Initiated Grant Program

- Support research that will significantly advance understanding of PWS and/or develop and evaluate new therapeutic interventions
- Support innovative, early stage and ‘high risk / high reward’ research
- Expand the base of PWS researchers, scope of research:
  - Draw scientists with expertise in relevant areas of study into the PWS field
  - Support promising young investigators who wish to become established in PWS research
    - Support established PWS researchers embarking on a new area of investigation
- Advocate Review:
  - Involve parents in the process of identifying relevant areas of research and selecting the most deserving research proposals

Objective: Establish a consistent source of funding, administered through a competitive grant program, to foster research relevant to PWS.
Key accomplishments of the Grant Program

- Supported >$7 million in PWS research, 123 projects, > 75 Investigators
- Published >80 papers in the peer-reviewed medical literature to date
- FPWR-funded investigators have received >$6 million in additional support from the National Institutes of Health and other government granting agencies to continue studies started with FPWR funds
- FPWR support has brought new scientists into the PWS field and helped young investigators get established
- FPWR has funded the development of key resources for use across the scientific community (new animal models, cellular models, bioinformatics) – these resources have been critical for advancing additional projects
- Multiple avenues to promote interaction and collaboration among scientists

http://www.fpwr.org/fpwr-funded-projects/
Investigator-Initiated Grants: Funded Investigator Profile

12 countries funded: US, Canada, UK, Israel, Australia, Germany, China, France, Belgium, Netherlands, Ireland, Slovenia

Grant submission received from 16 countries

<table>
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<tr>
<th>Year</th>
<th>Projects</th>
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PWS: Investigator published in the field of PWS prior to funding

Non-PWS: Investigator with expertise in a related field (neurobiology, obesity, behavior) but no PWS publications prior to being funding by FPWR (~40%)
FPWR Investigator-Initiated Grants 2004-2014: Funded Projects Profile

Research Category
In vitro: cells and/or molecular biology
Animal models: studies in PWS mice, for example
Clinical: involving human subjects and/or tissues

Research Area
Trends and Developments in the Grant Program

• Steady growth 2012: $412K; 2013: $1.08 million; 2014: $1.2 million; 2015: $1.9 million

• Now doing 2 cycles per year

• Success rate has stayed about the same (~25% - Exceptional-Excellent) (2015 >60 LOIs + bypass proposals; 1st cycle of 2016 – biggest yet)

• Formalized mid-project conference calls

• Continue to actively recruit new expertise and talent

• Shift from only helping projects to ‘get off the ground’ to providing some longer term funds for high priority, productive projects

• Broad portfolio of research: Fundamental Research, Therapeutic Development and Clinical Studies – hitting priority areas

• Metrics – articles published (~85, high impact journals), new grants generated; degrees grant; shared resources; intellectual property

http://www.fpwr.org/fpwr-research-outcomes/
http://www.fpwr.org/therapeutics-in-development-for-pws/
FPWR-supported publications in the medical literature late 2015/early 2016:


Fountain MD Jr, Schaaf CP. **MAGEL2 and Oxytocin-Implications in Prader-Willi Syndrome and Beyond.** Biol Psychiatry 78:28-38, 2015.
Long-term support necessary to bring fundamental concepts towards the clinic

Drug Repurposing – Dr. LaSalle

• 2011 Fundamental Research Project
R-Loop Formation and Chromatin Decondensation at the PWS Critical Locus

• 2 important publications:


• 2015 Drug Repurposing Project:
Rapamycin Treatment to Correct the Circadian mTOR imbalance in the Snord116 deletion mouse model of PWS.

(2004 Francke)
Newly Funded in 2016 – 9 grants >$850,000

THE MAGEL2 PHENOTYPE IN COMPARISON TO CLASSIC PRADER-WILLI SYNDROME. Christian Schaaf, MD, PhD, Baylor College Medicine ($106,941)

LOSS OF MAGEL2 AND HYPOTONIA IN PRADER-WILLI SYNDROME. Rachel Wevrick, PhD, University of Alberta ($84,387)

A POST-MORTEM STUDY OF VON ECONOMO NEURONS IN THE FRONTAL CORTEX OF BRAINS OF PERSONS WITH PWS. Patrick Hof, MD. Mount Sinai ($75,600)

MITOCHONDRIAL COMPLEX I DYSFUNCTION IN PRADER WILLI SYNDROME: A NEW THERAPEUTIC TARGET. Ingrid Tein, MD. Hospital for Sick Children, Toronto (108,000)

PREDICTORS OF PSYCHOSIS IN PRADER WILLI SYNDROME. Carrie Bearden, PhD, UCLA. ($107,991)

PLASTIC TASTER: A SWITCHING TRAINING GAME FOR PEOPLE WITH PWS THAT ADAPTS TO INDIVIDUAL NEEDS. Kate Woodcock, Ph.D. Queens University, Belfast ($86,400) (Year 2)

OXYTOCIN TREATMENT IN MAGEL2 DEFICIENT MICE Francois Muscatelli, PhD INSERM ($86,450) (Year 2)

PRECLINICAL STUDIES OF A NOVEL EPIGENETIC THERAPY FOR PRADER-WILLI SYNDROME. Yong-hui Jiang, MD, PhD, Duke University ($108,000)

REACTIVATION OF THE PWS LOCUS VIA DISRUPTION OF THE ZNF274 SILENCING COMPLEX. (Year 2) Marc Lalande, PhD University of Connecticut ($86,400)
It takes a village:

FPWR- Canada        FPWR UK
Prader-Willi France  PWSA – UK
OSS Hosts
All of our amazing fundraisers and donors!
Advocate reviewers
What is the role of PWS region genes, and how do they contribute to the PWS phenotype (characteristics)?

THE MAGEL2 PHENOTYPE IN COMPARISON TO CLASSIC PRADER-WILLI SYNDROME
Christian Schaaf, MD, PhD, Baylor College Medicine ($106,941)

LOSS OF MAGEL2 AND HYPOTONIA IN PRADER-WILLI SYNDROME
Rachel Wevrick, PhD, University of Alberta ($84,387)
THE MAGEL2 PHENOTYPE IN COMPARISON TO CLASSIC PRADER-WILLI SYNDROME

Christian Schaaf, MD, PhD, Baylor College Medicine ($106,941)

Dr. Schaaf has found that loss of Magel2 function results in autism, intellectual disability, and other PWS features in humans (“PWS-like” – renamed Schaaf-Yang syndrome)

Goals

• Detailed comparison of patients with classic PWS versus those with mutations to just the MAGEL2 gene

• Characterization of behavior, cognition, and endocrinology
Why we are excited about this grant!

• Strong background in genetic basis of neurodevelopment
• Clinical study that improves our understanding of how \textit{MAGEL2} specifically contributes to the PWS phenotype
• Provides a clinical picture/guidelines for those in our community with S-Y syndrome

Potential long-term contributions

• Better understanding of the role of Magel2 in cognitive deficits and autistic behaviors in PWS (with Ryan Potts’ ongoing study)
• Lays the groundwork to evaluate drugs/therapies that might decrease autistic behaviors and improve cognition in PWS
LOSS OF MAGEL2 AND HYPOTONIA IN PRADER-WILLI SYNDROME
Rachel Wevrick, PhD, University of Alberta ($84,387)

Dr. Wevrick group has found that mice missing the PWS gene Magel2 have reduced strength, activity levels and endurance

Goals
• Better characterize the muscle deficiencies in these mice
• Examine possible interventions including diet, supplements, drugs to improve muscle strength and endurance in PWS
• Identify therapies that are readily available and could be used in the clinic

* Funded in partnership with FPWR-Canada
Why we are excited about this grant!

• Expertise and career committed to PWS research

• Experimental methods are developed and well characterized, primed to study potential interventions

• Potential for quick clinical impact

Potential long-term contributions

• Identify already available drugs/therapies that improve muscle tone and endurance in PWS
A POST-MORTEM STUDY OF VON ECONOMO NEURONS IN THE FRONTAL CORTEX OF BRAINS OF PERSONS WITH PWS

Patrick Hof, MD. Mount Sinai ($75,600)

Dr. Hof is an expert in neuroanatomy, studying the structure and distribution of different types of neurons in the brain. Von Economo neurons are a certain subset critical for sensory awareness, social interaction and problem solving that have not been studied in PWS

Goals

• Characterize the structure and distribution of von Economo neurons in the PWS brain
• Differences would indicate that they play a role in the PWS phenotype and warrant further study

* Funded in partnership with Prader-Willi France
Why we are excited about this grant!

- Determine if a particular subset of neurons important for social awareness and problem solving is disrupted in patients with PWS
- These neurons are only in primates and humans, so this study can’t be done in mice
- Bringing an expert in neuroanatomy into PWS research

Potential long-term contributions

- Connect the dots from brain structure to some of the PWS phenotype
- Identify a new therapeutic target
- If differences are found, there are therapies currently targeted at these neurons
MITOCHONDRIAL COMPLEX I DYSFUNCTION IN PRADER WILLI SYNDROME: A NEW THERAPEUTIC TARGET

Ingrid Tein, MD. Hospital for Sick Children, Toronto ($108,000)

Dr. Tein is an expert in energy metabolism and muscle fitness. They have identified a potential mitochondrial dysfunction in PWS that may benefit from CoQ10 supplementation

Goals

• Characterize the effects of CoQ10 on motor function, strength, endurance, and muscle function in PWS
• Determine if CoQ10 improves mitochondrial function at the cellular level
• Develop guidance for the clinical use of CoQ10 in PWS

* Funded in partnership with FPWR Canada
**Why we are excited about this grant!**
- Brings an expert in muscle bioenergetics into PWS – to examine mitochondrial activity and muscle function
- Clinical study characterizing the potential benefit of a supplement already in common use
- Improving muscle function and endurance will help increase metabolism

**Potential long-term contributions**
- Fundamental understanding of the basis for poor muscle function and endurance in PWS
- Develop clinical guidelines for optimal use of CoQ10 in PWS
Can behavior, cognition, and mental health in PWS be improved?

PREDICTORS OF PSYCHOSIS IN PRADER WILLI SYNDROME
Carrie Bearden, PhD, UCLA. ($107,991)

PLASTIC TASTER: A SWITCHING TRAINING GAME FOR PEOPLE WITH PWS THAT ADAPTS TO INDIVIDUAL NEEDS
Kate Woodcock, Ph.D. Queens University, Belfast ($86,400) (Year 2)

OXYTOCIN TREATMENT IN MAGEL2 DEFICIENT MICE
Francois Muscatelli, PhD INSERM ($86,450) (Year 2)
Mental Wellness in PWS is a High Priority
2015 Mental Health Workshop

**PWS Mental Health Research Priorities**

✧ Obtain longitudinal and natural history data on mental health in PWS

✧ Develop effective outcome measures for PWS mental health intervention studies

✧ Determine the influence of weight management, hormones, and environment on mental well being over the life course

✧ Advance mechanistic research on the neurobiology underlying mental health and behavioral issues in PWS

✧ Identify markers of impending mental illness and characterize the prodromal phase to allow mitigation of psychotic symptoms
PREDICTORS OF PSYCHOSIS IN PRADER WILLI SYNDROME

Carrie Bearden, PhD, UCLA. ($107,991)

PWS is associated with a high rate of mental illness. Dr. Bearden’s research focuses on identifying the earliest warning phase in the onset of mental illness, the “prodromal” phase

Goals

• Applying lessons from other populations, can we characterize the prodromal phase in PWS?
• Define predictors of impending mental illness in PWS
**Potential long-term contributions**
- Early identification of those at highest risk and those showing early warning signs to allow for early intervention
- Goal of preventing or mitigating psychotic illness in PWS – clinical intervention

**Why we are excited about this grant!**
- Bringing a leading expert in prodromal research, mental illness in ID, into PWS research
- Understudied area of PWS research as identified at the PWS Mental Health Workshop
- Use of data from the Global PWS Registry
- Provide a resource for families to be aware of “warning signs”
PLASTIC TASTER: A SWITCHING TRAINING GAME FOR PEOPLE WITH PWS THAT ADAPTS TO INDIVIDUAL NEEDS
Kate Woodcock, Ph.D. Queens University, Belfast ($86,400) (Year 2)

Dr. Woodcock has characterized the difficulty in “task-switching” in PWS using brain imaging and behavior studies. Her studies further suggest that routines become harder and harder to break for those with PWS.

Goals
• Build upon the software prototype
• Adapt/tailor to individual needs
• Improve ability to handle changes in routines and decrease temper outbursts
**Why we are excited about this grant!**

- Temper outbursts can significantly impact QOL for the individual with PWS and the family
- Development of a new behavior intervention tool
- An understudied area that impacts greatly on quality of life
- Young investigator building a career in PWS research
- [https://www.fpwr.org/studies-on-task-switching-in-pws/](https://www.fpwr.org/studies-on-task-switching-in-pws/)

**Potential long-term contributions**

- Development of an at-home software system to help improve their task switching skills
OXYTOCIN TREATMENT IN MAGEL2 DEFICIENT MICE
Francois Muscatelli, PhD INSERM ($86,450) (Year 2)

In mice, loss of Magel2 leads to abnormal development and function of oxytocin neurons in the brain, affecting feeding and behavior. This can be corrected in part with a single dose of oxytocin at birth.

Goals
• How does Magel2 impact brain development?
• How does loss of Magel2 impact the oxytocin system in the brain?
• What is the best way to recover function of that system? Is there a critical period?

* Funded in partnership with Prader-Willi France
Why we are excited about this grant!
• Trying to connect the dots from genetic level to clinical presentation:
  • Magel2-brain development-oxytocin neurons-feeding and behavior
• Developing new animals models – resource for future work
• Innovative approach looking at temporal impact of gene expression
• May provide valuable data to help interpret results from the multiple ongoing clinical trials of oxytocin

Potential long-term contributions
• Better understanding of role of Magel2 in brain development
• Guide the development human clinical studies with oxytocin
Can the PWS genes on the maternal chromosome be activated? (and will it help?!)

### Normal
- PWS genes active

### Deletion
- PWS genes inactive

### UPD, imprinting
- PWS genes inactive

#### Ongoing:
- **Injectable protein based gene activation therapy for PWS.** Segal (engineered zinc-finger protein for activation)
- **Activation of silenced genes in Prader-Willi syndrome.** Nicholls (genetically engineered CRISPR-based activator)

#### New in 2016

**PRECLINICAL STUDIES OF A NOVEL EPIGENETIC THERAPY FOR PRADER-WILLI SYNDROME**
Yong-hui Jiang, MD, PhD, Duke University ($108,000)

**REACTIVATION OF THE PWS LOCUS VIA DISRUPTION OF THE ZNF274 SILENCING COMPLEX** (Year 2)
Marc Lalande, PhD University of Connecticut ($86,400)
Dr. Jiang has identified small molecule drugs that can activate the maternal PWS genes in cell culture (Puzzle Project). In preliminary studies, these drugs activate maternal PWS genes in a PWS mouse model.

**Goals**

- Determine feasibility of using these gene activating drugs to turn on the maternal PWS genes in a mouse model of PWS
- Optimize/determine parameters (including timing, dosing, side effects)
Why we are excited about this grant!

- Small molecules to reactivate maternal allele…first steps towards a drug to treat the underlying genetics of PWS
- Lead compounds identified from a screening project previously funded by FPWR
- Previously funded FPWR researcher committed to work in neurodevelopmental disorders
- These drugs will us explore the feasibility of gene activation strategies overall

Potential long-term contributions
- Laying ground work for potential new drugs to treat PWS at the genetic level
REACTIVATION OF THE PWS LOCUS VIA DISRUPTION OF THE ZNF274 SILENCING COMPLEX (Year 2)
Marc Lalande, PhD University of Connecticut ($86,400)

This group is working to reactivate the PWS region on the maternal chromosome by identifying and disrupting the “OFF” switch. Identified a part of this switch in year 1 of funding

Goals
- Use advanced genome editing technologies to optimize disruption of ZNF274 and improve efficiency of reactivating PWS genes
- Studies will be performed in 3-D brain “organoids” in a dish

* Funded in partnership with PWSA-UK
Why we are excited about this grant!

• PWS gene reactivation - will advance our knowledge of the PWS region
• Established expert in PWS iPSCs and neuron differentiation
• Active member of FPWR research community
• Building upon previously funded FPWR work and resources

Potential long-term contributions

• Component of the “OFF” switch are new targets for potential drug development
• This study will lay some of the groundwork for potential genetic treatment of PWS
2016 - Plans

Continue to fund cutting edge PWS research through our investigator-initiated grant program (45 LOIs in review – advocate reviewers needed in May)

Continue to facilitate collaboration and interaction among scientists and clinicians in PWS and families:

• IPWSO Conference July 20-24 (Workshop, PWS Clinical Trials Consortium, Scientific Meeting)

• FPWR family research conference October 28-30

Capitalization on advances coming out of the grant program – translational research

New initiatives to advance therapeutics in the most efficient way possible

Accelerate PWS Clinical Trials
INTERNATIONAL CONSORTIUM TO ADVANCE CLINICAL TRIALS FOR PRADER-WILLI SYNDROME (CT-PWS)

WORK PLAN & BUDGET 2016

Nathalie Kayadjanian Ph.D
FOUNDATION FOR PRADER-WILLI RESEARCH

Consortium of Pharmaceutical Companies, Academic Scientists & Clinicians, Patient Advocacy Groups: A multidisciplinary expert network dedicated to identifying key challenges and advancing solutions for current and future clinical trials in PWS
• >800 enrolled
• Using with ongoing research projects
• Planning for expanded uses in PWS research

Looking ahead in 2016 – big plans!
• Working with GRDR – NIH
• FDA Natural History Studies are a priority – critical for drug development (see https://www.youtube.com/watch?v=2GDU7f75MVI)
• Integrating with clinical records, electronic health records
• Translation to other languages
• Working with International Partners

Please complete your surveys!
Thank you!