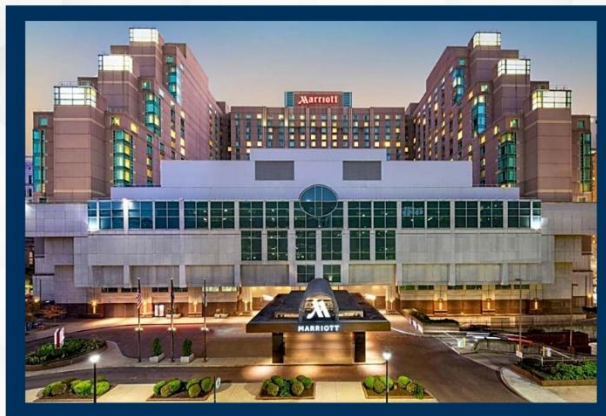




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October 7th, 2026

SPEAKER ABSTRACTS MORNING SESSION 1

Activation of the imprinted Prader-Willi Syndrome locus by CRISPR-based epigenome editing

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Abstract:

Epigenome editing with DNA-targeting technologies such as CRISPR-dCas9 can be used to dissect gene regulatory mechanisms and potentially treat associated disorders. Prader-Willi Syndrome (PWS) is caused by loss of paternally expressed imprinted genes on chromosome 15q11.2-q13.3, although the maternal allele is intact but epigenetically silenced. Using CRISPR repression and activation screens in human induced pluripotent stem cells (iPSCs), we identified genomic elements that control expression of the PWS gene *SNRPN* from the paternal and maternal chromosomes. We showed that either targeted transcriptional activation or DNA demethylation can activate the silenced maternal *SNRPN* and downstream PWS transcripts. However, these two approaches function at unique regions, preferentially activating different transcript variants and involving distinct epigenetic reprogramming mechanisms. Remarkably, transient expression of the targeted demethylase leads to stable, long-term maternal *SNRPN* expression in PWS iPSCs. Ongoing work includes delineating different methylation states catalyzed by various epigenome editing tools in proliferating iPSCs versus post-mitotic neurons, as well as identifying mechanisms to overcome resistance to epigenetic activation in neuronal cells. This work uncovers targeted epigenetic manipulations to reprogram a disease-associated imprinted locus and suggests possible therapeutic interventions.

Acknowledgements/Funding:

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Therapeutic epigenome editing for Prader-Willi Syndrome using a novel nonviral and non-nanoparticle CRISPR/dCas9 delivery platform

Presenting Author: Xiaona Lu

Additional Authors: Sung-Eun Wang, Ying Xie, Jiangbing Zhou, Yong-Hui Jiang

Institution(s): Yale University School of Medicine

Abstract:

Introduction: Prader-Willi syndrome (PWS) is a neurodevelopmental disorder caused by loss of paternal gene expression at 15q11.2-q13, primarily driven by the *SNORD116* cluster. While the paternal allele is absent or inactive, the corresponding genes on the maternal allele remain structurally intact but silenced by the PWS imprinting center (PWS-IC), a bipartite regulatory element that governs imprinted gene expression through allelic specific DNA methylation and repressive histone modifications. While small-molecule inhibitors of DNA methylation (5mC) or repressive histone marks such as H3K9me2 can partially reactive the PWS gene expression from the maternal chromosome, their genome-wide and nonspecific activity substantially limits translational applicability. Locus-specific epigenome editing using dCas9 and single-guide RNA (sgRNA) therefore provides a rational strategy to selectively reactivate genes silenced in PWS. In proof-of-concept studies, we demonstrated that targeting H3K9me2 at the PWS-IC using a fusion protein of dCas9 with the H3K9me2 demethylase JMJD2a (dCas9-JMJD2a) resulted in robust reactivation of *SNRPN* and the *SNORD116* from the maternal chromosome in patient cells. However, this approach relied on lentiviral delivery due to the large size of dCas9 protein, which poses substantial barriers to clinical translation due to genomic integration, limited dosage control, and safety concerns, underscoring the need for clinically viable, non-viral central nervous system (CNS) delivery platforms.

Methods: We introduce STEP (Stimuli-Responsive Traceless Engineering Platform), a non-viral, non-nanoparticle delivery system capable of penetrating the blood-brain barrier and brain parenchyma, thereby enabling CRISPR/dCas9-based epigenome editing to selectively reactivate disease-relevant genes in PWS. STEP-RNP is a chemically modified ribonucleoprotein (RNP) platform optimized for CNS applications, and enables highly efficient gene editing across fibroblasts, neural progenitor cells, iPSC-derived neurons, and cortical organoids. Importantly, cerebrospinal fluid (CSF) administration of STEP-RNP results in widespread biodistribution and robust gene-editing efficiency in both rodent models and non-human primates, including cynomolgus and rhesus macaques.

Results: We delivered STEP-dCas9-JMJD2a with sgRNAs targeting the PWS-IC to remove repressive H3K9me2 chromatin mark. Screening in patient-derived iPSC neurons carrying a maternal *Snrpn*-EGFP reporter identified sgRNAs achieving >90% editing efficiency.

Complementary screening in maternal *Snrpn*-EGFP reporter mouse embryonic fibroblasts (p^+/m^{S-E}) similarly identified high-efficiency sgRNAs capable of robust *Snrpn*-EGFP reactivation. Both single and repeated administrations of STEP-dCas9-JMJD2a via intravenous (IV) or intrathecal (IT) delivery resulted in robust *Snrpn*-EGFP reactivation across brain, muscle, and liver tissues of p^+/m^{S-E} reporter mice. Remarkably, a single 24-hour exposure to STEP-dCas9-JMJD2a in human PWS fibroblasts led to stable *SNRPN* reactivation for at least 8 passages, indicating durable epigenetic remodeling without repeat dosing. Consistently, *Snrpn*-EGFP reactivation remained detectable in p^+/m^{S-E} mice following two administrations at postnatal days 7 and 14 in mice, persisting up to 8 months, the endpoint of observation.

Therapeutic efficacy was further evaluated in patient-derived iPSC neurons and brain organoids, as well as in two PWS mouse models: one carrying a paternal deletion spanning *Snrpn*-*Ube3a* ($PWS^{m+/pS-U}$), and a newly generated model harboring an approximately 6-Mb paternal deletion of the human 15q11.2-q13 homologous region ($PWS^{m+/p-LD}$). Efficient reactivation of maternal *SNORD116* was observed in patient-derived iPSC neurons. In vivo, STEP-dCas9-JMJD2a mediated epigenome editing, delivered via intrathecal IT or IV)

administration, produced profound phenotypic rescue for perinatal lethality associated both PWS mouse models. Untreated cohorts exhibited >80% perinatal lethality in the *PWS^{m+/pS-U}* model by postnatal day 21 and 100% lethality in the *PWS^{m+/p-LD}* model by postnatal day 3. In contrast, STEP-treated animals showed robust rescue of perinatal survival and significant improvements in postnatal growth (Fig.2). Behavioral analyses further revealed marked improvements across multiple domains, including locomotor activity, learning, and memory in the *PWS^{m+/pS-U}* model.

Conclusions: These findings establish STEP as a highly effective, non-viral CNS delivery platform capable of achieving durable, brain-wide epigenome editing with therapeutic rescue in a severe neurogenetic disease. This work provides a clinically actionable framework for treating PWS and broadly redefines the translational potential of CRISPR/dCas9-based epigenetic therapeutics for rare genetic and epigenetic disorders.

Acknowledgements/Funding:

An innovative non-viral delivery of CRISPR/dCas9 epigenome editing-based therapy for Prader-Willi Syndrome, Foundation for Prader-Willi Research (FPWR) Pilot Grant (09/2024-02/2027)

SPEAKER ABSTRACTS MORNING SESSION 2

PWS-Smart Start – Replication in a Randomized Control Trial

Presenting Author: Kasey Bedard¹

Additional Authors: Annette Griffith¹, Kelly Krukowski¹, Delyla Ulm¹

Institution(s): ¹ Department of Behavior Analysis, The Chicago School, Chicago, IL, USA

Abstract:

Introduction. Behavioral challenges associated with Prader-Willi syndrome (PWS), including emotional outbursts, rigidity, food-related behavior, repetitive behavior, and skin picking, can significantly affect child functioning and caregiver well-being. Despite these needs, few behavioral interventions have been developed specifically for children with PWS. PWS Smart Start is a telehealth-delivered, behavior-analytic caregiver training program designed to teach caregivers evidence-based strategies to reduce challenging behavior and support adaptive skills.

Methods. Fifty-eight caregiver-child dyads participated in a two-phase randomized waitlist-controlled trial. Children with PWS were between 3 and 12 years of age. Families were assigned using stratified randomization to balance groups on relevant participant characteristics before being allocated to either immediate treatment or waitlist control/treatment-as-usual. The intervention included 16 weekly individualized telehealth coaching sessions. In addition to pre/post caregiver-report measures, an embedded single-subject ecological momentary assessment component was used with a randomly selected subset of participants. Caregivers received brief text-based surveys twice daily to report recent occurrences of targeted child behaviors, allowing repeated measurement of behavior across baseline, intervention, and maintenance phases.

Results. Participation in PWS Smart Start was associated with significant improvements across multiple domains. Caregivers demonstrated reductions in parenting stress and parental burnout, increases in positive parenting practices and behavioral approaches to parenting, and improvements in family quality of life. Caregiver reports also indicated significant reductions in child behavior challenges, including food-related behavior, repetitive behavior, skin picking, cognitive rigidity, disruptive behavior, and the overall impact of behaviors of concern. The embedded ecological momentary assessment (EMA) data provided additional individualized evidence of behavior change, documenting reductions in emotionally dysregulated behavior, aggression, rigidity, task refusal, repetitive verbal behavior, and elopement for several participants. Although treatment response varied across participants, the EMA component successfully identified both responders and non-responders, providing proof of concept that intensive real-time behavioral measurement can be feasibly embedded within caregiver-training research and can detect individualized patterns of behavior change that may not be apparent through group-level analyses alone.

Conclusions. Findings provide further evidence that behavior-analytic caregiver training can be feasibly and effectively delivered via telehealth to families of children with PWS. The randomized waitlist-controlled design, stratified allocation procedures, and embedded single-subject ecological momentary assessment component strengthen the evaluation of PWS Smart Start by combining group-level outcome measurement with repeated individualized behavior data. Results support the use of accessible, syndrome-specific caregiver training to address unmet behavioral support needs among families affected by PWS.

Acknowledgements/Funding: This project was made possible through the generous support of the Foundation for Prader-Willi Research (FPWR). We are grateful for their commitment to supporting behavior analytic research as an avenue for improving the lives of people with PWS and their families. We also extend our sincere thanks to the families who participated in this study. Your time, dedication, and willingness to share your experiences made this research possible.

Trajectory of Cognitive Abilities Over Time in a Clinical Sample of Youth with Prader-Willi Syndrome

Presenting Author: David Michalec, PhD

Additional Authors: Ahmed Mahmood, Kevin Stephenson, PhD, Kathryn Obrynba, MD

Institution(s): Nationwide Children's Hospital

Abstract:

Background: Prader-Willi syndrome (PWS) is a rare genetic disorder with subtypes defined by chromosome deletion, imprinting defects, or uniparental disomy. Individuals with PWS often have co-occurring intellectual and developmental disabilities. This study aimed to improve understanding of longitudinal cognitive development in individuals with PWS.

Method: A retrospective chart review was conducted on 45 individuals with PWS (N = 157 observations) who were evaluated longitudinally using the Stanford-Binet Intelligence Scales 5th Edition Abbreviated Battery. We examined the stability of Abbreviated Battery IQ (ABIQ) scores and deviation ABIQ, which extends scoring range and reduces floor effects. We also evaluated longitudinal change in change-sensitive scores (CSS).

Results: ABIQ remained moderately stable over time; however, there were significant age-related effects, with younger individuals showing slight decreases and older individuals showing slight longitudinal increases in deviation ABIQ. There was a significant group-level increase in CSS across time. Individuals with uniparental disomy showed significantly greater cognitive growth than those with deletions. Age and baseline ABIQ also moderated the rate of change in CSS. Use of deviation ABIQ improved within-individual consistency and yielded more precise estimates of cognitive ability.

Conclusions: This study reveals meaningful developmental trends in the cognitive abilities of children with PWS. Alternative scoring options, including deviation IQ scores and CSS improve precision and sensitivity compared to traditional SB-5 normative scores. Continued longitudinal research is needed to guide the development of future clinical interventions and care for individuals with PWS.

Acknowledgements/Funding:

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No external funding was used to support this project

Autism Features in Prader-Willi Syndrome are Distinct from Idiopathic Autism and Suggest a Generalised Rigidity and Compulsivity Profile.

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Institution(s): ¹Neuroscience and Mental Health Program, Peter Gilgan Centre for Research and Learning, Hospital for Sick Children, Toronto, Canada.

²Dept of Psychiatry, School of Medicine, Trinity College Dublin, Ireland

Abstract:

Background: Autism spectrum disorder occurs at elevated rates in Prader-Willi Syndrome (PWS), yet few studies have directly compared the autism phenotype in PWS with idiopathic autism using gold-standard diagnostic measures. This study characterised the autism phenotype in PWS compared to a matched autism sample derived from the Autism Genome Project.

Methods: Individuals with PWS (n=27; Trinity College Dublin) were compared to age-, sex-, and IQ-matched idiopathic autism sample from the Autism Genome Project (AGP; n=76) on autism severity (ADI-R, ADOS-2), adaptive behaviour (VABS-II), and repetitive and restricted behaviours (RBS-R) using MANOVA. Correlation structure of RBS-R domains was examined separately within each group. An expanded analysis incorporating an additional cohort recruited at the Hospital for Sick Children (Toronto) (total PWS n=38; AGP n=76) and examining associations between repetitive behaviours, maladaptive behaviours, and hyperphagia severity is ongoing and preliminary findings will be presented

Results: PWS demonstrated significantly lower autism severity than AGP across all ADI-R and ADOS-2 domains (all $p < 0.001$), with superior adaptive socialisation consistent with the socially motivated and approach-oriented phenotype described in PWS. Despite lower overall autism severity, compulsive behaviours were comparable across groups. Using gold-standard diagnostic instruments, autism diagnosis was confirmed in 18.5% of PWS participants, exclusively among individuals with mUPD. RBS-R correlation analyses revealed a generalised rigidity and compulsivity phenotype in PWS with moderate to strong intercorrelations spanning multiple RBS-R domains. This contrasted with the AGP sample, where repetitive behaviours clustered more narrowly.

Conclusions: PWS presents a phenotypically distinct autism profile from idiopathic autism, characterised by lower overall autism severity and a broad rigidity and compulsivity phenotype. These findings suggest that repetitive behaviours in PWS may reflect syndrome-specific mechanisms that differ from those underlying idiopathic autism and may have implications for understanding behavioural concerns including hyperphagia, and for developing more targeted interventions.

Acknowledgements/Funding: We would like to acknowledge funding from the Foundation for Prader Willi Research and the support of the Prader Willi Syndrome Association of Ireland.

Development of Repetitive Behavior/Restricted Interests Across PWS Genetic Subtypes

Presenting Author: David W. Evans, Ph.D.

Additional Authors: Jessica Bohonowych, Ph.D., Lauren Schwartz, Ph.D., Theresa V. Strong, Ph.D.

Institution(s): Bucknell University, Department of Psychology, Program in Neuroscience (Evans); Foundation for Prader-Willi Research (Bohonowych, Schwartz, & Strong)

Abstract:

Prader-Willi Syndrome (PWS) is associated with a broad behavioral phenotype, including repetitive behaviors and restricted interests (RBRI), such as hoarding, skin-picking, and repetitive questioning. We examined RBRI in PWS probands ($n=110$) and a typically-developing (TD) cohort ($n=1428$), across three age groups (0-5 years; 6-11 years; 12-18 years), on a multidimensional measure assessing three RBRI factors. We also compared PWS genetic subtypes (paternal deletions, maternal uniparental disomy), and Types I and II deletion cases to each other, and to the TD group. We explored the shared variance between RBRI factors and adaptive and maladaptive behaviors associated with PWS. For a subset of participants, we collected follow-up data, six months after the initial baseline testing, in order to examine longitudinal changes in RBRI. Caregivers from the Global PWS Registry completed several online questionnaires. The Childhood Routines Inventory (CRI-R), a 62-item, nationally-normed measure of Repetitive Behavior and Restricted Interests reflecting Total RBRI, Rigidity/Insistence on Sameness, and Repetitive Motor Behaviors/Compulsions. Caregivers also completed the PWS Anxiousness and Distress Behaviors Questionnaire (PADQ), and the Strengths and Difficulties Questionnaire (SDQ). Robust main effects were found for PWS status on Total CRI-R $F(1,1532)=38.67$, $p < .0001$ and for Rigidity/Insistence on Sameness $F(1,1532) = 20.40$, $p < .001$. The PWS group exhibited more overall RBRI than the TD group. These group differences varied by Age Group such that RBRI scores became increasingly divergent in the oldest age cohort – particularly for the PWS mUPD group. Finally, anxiousness predicted variance in RBRI, with Emotional Problems adding additional variance for the deletion, but not the mUPD group. We have begun to analyze the longitudinal trajectories of RBRI in this cohort, and early results show significant individual variation in terms of the trajectories of RBRI over a six-month period. These findings speak to the differences in the profiles of RBRI across PWS genetic subtypes, as well as developmental trajectories of RBRI important for establishing personalized clinical interventions.

Key words: Prader-Willi syndrome; repetitive behavior; restricted interests; genetic subtype; developmental trajectory; anxiety

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SPEAKER ABSTRACTS AFTERNOON SESSION 1

SNORD116 Modulates Cardiomyocyte Development and Metabolism Through Post-Transcriptional Regulation

Presenting Author: James G.W. Smith

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Institution(s): 1) University of East Anglia, UK; 2) Earlham Institute, UK; 3) University of Liverpool, UK; 4) University of Cambridge, UK; 5) Royal Papworth Hospital, UK; 6) Leiden University, The Netherlands; 7) Imperial College London, UK; 8) The Francis Crick Institute, UK; 9) University of Nottingham, UK (10) University of Oxford, UK

Abstract:

Obesity and impaired neurodevelopment are severe PWS phenotypes, yet SNORD116 expression extends to wider tissues, including the heart. Indeed, cardiac disease/failure is the second most common cause of death reported in PWS patients. Furthermore, cardiac anomalies are the most common congenital defects reported in PWS patients. Although suggested to influence cardiac function, the role of SNORD116 in cardiomyocytes, the dominant cell type of cardiac muscle, is poorly defined.

Here, using a 2D human induced pluripotent stem cell (hiPSC)-derived model, we demonstrate that SNORD116 expression decreased during hiPSC-cardiomyocyte (hiPSC-CM) differentiation, but was reactivated in response to hypoxic stress. Knockout (KO) of SNORD116 in hiPSCs led to delayed onset of cardiac marker expression and reduced proliferative capacity in early-stage cardiomyocytes. At later stages of hiPSC-CM differentiation, loss of SNORD116 was associated with impairment in hypertrophic growth, oxidative phosphorylation, viability and capacity to tolerate hypoxic stress. Transcriptomic and proteomic profiling indicated that these phenotypes appeared concomitantly with the dysregulation of cardiac development pathways, alongside significant alternative splicing and alternative polyadenylation. Alternatively spliced transcripts had longer 3'UTRs, a trend that reversed during cardiomyocyte differentiation. Coupled with shorter 3'UTRs, late stage SNORD116 KO hiPSC-CMs displayed aberrantly enhanced protein synthesis, which was ameliorated by beloranib, a pharmacological inhibitor of methionine aminopeptidase 2 (METAP2) developed clinically as a PWS therapeutic.

Together, our findings demonstrate for the first time that SNORD116 plays a critical role in cardiomyocyte development, primarily through mechanisms involving polyadenylation and post-transcriptional gene regulation.

***Magel2* deficiency drives microglial synaptic engulfment and alters neuron-microglia interactions in Prader-Willi syndrome**

Presenting Author: Dr. Ferdinand Althammer

Additional Authors: Jemima Helen, Moritz C. Wimmer and Berkan Kanmaz
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Abstract:

Prader–Willi syndrome (PWS) is a complex neurodevelopmental disorder characterized by hypothalamic dysfunction, hyperphagia, developmental delay, and cognitive impairment. Although neuronal dysfunction has long been implicated in PWS, the contribution of microglia - the resident immune cells of the brain - remains poorly understood. Here, we identify profound microglial remodeling and excessive synaptic pruning as previously unrecognized hallmarks of PWS.

Using high-resolution three-dimensional morphometric reconstruction, we found that hypothalamic microglia in *Mage/2* knockout (KO) mice exhibit marked deramification, reduced territorial domains, and altered surveillance morphology. Importantly, these changes emerged early during development and were largely independent of obesity, suggesting an intrinsic effect of *Mage/2* deficiency on microglial state. Single-nucleus RNA sequencing further revealed extensive transcriptional reprogramming in *Mage/2* KO microglia involving immune signaling, synaptic organization, ribosomal function, and translational pathways, with particularly pronounced alterations in females. Computational microglial state analysis demonstrated redistribution toward reactive, interferon-associated, cytokine-producing, and phagocytic states.

Functionally, *Mage/2* deficiency increased focal microglia-neuron interactions and enhanced synaptic engulfment, accompanied by reduced PSD95 density, indicating excessive synaptic pruning during hypothalamic circuit maturation. CellChat-based ligand-receptor inference uncovered major remodeling of microglia-centered communication networks, including altered trophic, adhesion, and immune signaling pathways linked to phagocytic activation and neuron-glia interaction dynamics.

Importantly, these findings translated to human disease. Analyses of post-mortem hypothalamic tissue from individuals with PWS revealed fragmented microglial morphology and markedly increased complement engagement, consistent with the enhanced phagocytic phenotype observed in mice.

Together, our findings position microglia as active contributors to hypothalamic circuit dysfunction in PWS and identify excessive complement-associated synaptic pruning as a novel pathogenic mechanism and potential therapeutic target in this disorder.

Acknowledgements/Funding:

- DFG (AL 2466/2 – 1) awarded to Ferdinand Althammer

Spatial transcriptomics of the minimal critical region of the PWS locus in the human hypothalamus

Presenting Author: Claudia A. Doege, MD

Additional Authors: Maria Caterina De Rosa, PhD; Betul Erol, MD; Rudolph L. Leibel, MD; Andrew F. Teich, MD, PhD

Institution(s): Columbia University Irving Medical Center

Abstract:

Goal: To determine the cell-type specific expression pattern of *SNORDs* of the minimal critical region in the human adult hypothalamus.

Rationale: Microdeletions in humans are strongly associated with hyperphagia and obesity, but *SNORD116* knockout mice do not become obese. Additional genetic or epigenetic factors, possibly including *SNORD109* (absent in mice) and/or the more primate specific *SNORD116* group III, may contribute to the metabolic dysregulation observed in human PWS patients. Understanding these species-specific differences is critical for interpreting results from animal models and their relevance to human disease. Via BaseScope, we previously detected abundant *SNORD109* expression in the human ARC. Nearly all AGRP and POMC neurons expressed *SNORD109*. However, more than 40% of *SNORD109*-positive cells were neither AGRP nor POMC neurons, warranting the investigation of their cellular identity. *SNORD109*-positive cells showed a partial overlap with *SNORD116-8* and *SNORD116-25*. There were also *SNORD109*-negative cells expressing *SNORD116-8*. The expression pattern of group II or the outgroup *SNORD116s* has not been investigated yet in the human hypothalamus.

Hypothesis: Group I, II, III and outgroup *SNORD116s* and *SNORD109* expression will be partially overlapping, suggesting a cell-type specific combinatorial expression pattern with distinct functional roles.

Experimental Approach: We are running spatial transcriptomics (Xenium In Situ, 10x Genomics) on fresh-frozen hypothalamic sections of neurotypical donors. The custom panel design of 480 genes includes probes for the *SNORDs* of the minimal critical PWS region, cell-type specific marker, neuropeptides, receptors involved in the regulation of appetite and satiety, transcription factors and genes of interest to the PWS research community.

Expected Outcomes: We anticipate identifying the distinct expression pattern of the genetic elements of the minimal critical PWS region for specific cell types across feeding-related brain regions in the hypothalamus. We will define the expression patterns for adult neurotypical donors and thus provide a framework for future studies in subjects with PWS and extension of this study to prenatal and ages 0-40 years human postmortem brains. Our studies are expected to inform future functional studies in human stem cell-derived cell types that will define the distinct roles of the specific genetic elements in the minimal critical region of the PWS locus in humans.

Acknowledgements/Funding: FPWR

Defining the Mechanism of Action of Beloranib to Inform Potential Next-Generation Fumagillin Derivatives

Presenting Author: Michael R. MacArthur

Additional Authors: Sarah J. Mitchell

Institution(s): Princeton University

Abstract: Beloranib is the most efficacious therapeutic tested in PWS to date. Unfortunately, clinical development of beloranib was halted due to embolic events in a late-stage phase 3 trial. Subsequent development efforts were hampered due to a fundamental lack of understanding of beloranib's mechanism of action. Beloranib, and other structurally-related compounds, bind and inhibit Methionine Aminopeptidase 2 (MetAP2) and It has been widely hypothesized that beloranib works via MetAP2 inhibition. In this presentation we present evidence that beloranib-class compounds may work in a MetAP2-independent manner. First, we find that the predominant cellular effect of belornib, cytostasis, is intact in MetAP2-knockout cells and that genetic dependencies are comparable between wild-type and MetAP2 knockout cells as determined by genome-wide CRISPR knockout screen. Second, we find that beloranib's weight loss phenotype is intact in neuronal MetAP2-knockout mice. Finally, we find that compounds which are structurally-related to beloranib, but do not inhibit MetAP2, still induce weight loss. Our data support the hypothesis that the efficacy of beloranib-class compounds in PWS may not relate to MetAP2 inhibition, which could open the door to new drug development focused on an alternative target.

Acknowledgements/Funding: This work was funded by the Foundation for Prader-Willi Research and formerly by Zafgen

Neural circuits of impaired satiation in Magel2-null mice

Neural circuits of impaired satiation in Magel2-null mice

Presenting Author: Haijiang Cai

Additional Authors: Matthew Schmit, Masa Miscevic, Marco Contreras

Institution(s): Department of Neuroscience, University of Arizona

Abstract:

Prader–Willi syndrome (PWS) is a genetic disorder characterized by insatiable appetite and the development of severe obesity after infancy. However, the neural mechanisms underlying impaired satiation in PWS remain poorly understood. Under normal conditions, food intake is suppressed after a meal by satiation signals such as cholecystokinin (CCK), a gut-derived hormone released during eating. Interestingly, circulating CCK levels in individuals with PWS are comparable to, or even slightly elevated relative to, those in healthy controls. These findings suggest that the central processing of satiation signals, rather than their peripheral production, may be disrupted in PWS. Because MAGEL2 deficiency contributes to many of the eating and metabolic abnormalities associated with PWS, Magel2-null mice have been widely used as a model of the disorder. Here, we show that CCK fails to suppress food intake in Magel2-null mice. Consistent with this behavioral deficit, CCK-evoked activity is significantly reduced in protein kinase C-delta-expressing neurons of the central amygdala (CeA^{PKC-δ}), a key component of the neural circuitry that mediates satiation. Furthermore, we identified two distinct dynamics of CeA^{PKC-δ} neuronal activity during eating behavior: persistent activation associated with satiation and transient activation associated with food approach. We found that both activity dynamics are disrupted in Magel2-null mice. Together, these findings demonstrate that neural processing within the satiation circuit is impaired in a mouse model of PWS. Our results suggest that restoring the function of satiation-related neural circuits may represent a promising therapeutic strategy for reducing hyperphagia and controlling body weight in individuals with PWS.

Acknowledgements/Funding: This research was supported by the NIDDK (R01 DK124501), NICHD (R21HD116113), and a grant from the Foundation for Prader-Willi Research.

SPEAKER ABSTRACTS AFTERNOON SESSION 2

The Epidemiology of Prader Willi Syndrome in the US: Descriptive findings from a cohort of 14,000 people with PWS

Presenting Author: Eric Rubenstein

Additional Authors: Rafeya Raqib, Zoe Li-Khan, Andrew Stokes

Institution(s): Boston University School of Public Health, Harvard College

Abstract:

Background: Prader Willi Syndrome (PWS) is a rare genetic condition with an estimated between 1 in 10,000 and 1 in 30,000 live births. Because of this rarity, it can be difficult to study the PWS *population* since only a small and non-representative proportion of the PWS population are represented in registries and specialty clinic studies. Further, administrative data has been hampered by a period without a specific International Classification of Disease (ICD) code and reliance on cross sectional studies.

Objective: Therefore, our objective was to describe the demographic distribution of PWS, characterize healthcare use, and document incidence and prevalence of co-occurring conditions using the Komodo Healthcare Map Data, and claims database of 330,000,000 people in the US.

Methods: Komodo Healthcare Map is the largest and most complete U.S. database of de-identified, real-world patient data. The Healthcare Map uses artificial intelligence and advanced analytics to track individual encounters with the healthcare system for over 330 million patients from 2015 to present. We will identify PWS using any one claim for the Q87.11 ICD code and as sensitivity analysis will require two claims. We will identify common chronic conditions using established claims algorithms and calculate prevalence and incidence of conditions.

Results: In preliminary analyses, we have identified 14,022 unique individuals with PWS. Among those identified, there are data on 371,865 health care visits. Slightly more than half the population are male, and more than half are under 24 years of age. The most common procedures identified are somatomedin testing and furosemide injection.

Discussion: Population statistics are critical for advocacy and understanding health outcomes across diverse populations. Our findings represent one of the largest epidemiologic assessments of PWS. We will discuss implications for health and health services.

Acknowledgements/Funding:

Funding is from the Foundation for Prader-Willi Research.

Non-invasive ^{31}P -MRS reveals skeletal muscle mitochondrial dysfunction in Prader-Willi syndrome

Presenting Author: Ching Leung¹

Additional Authors: Manoj Kumar Mahto², Louis Elfari², Gemma Andrews³, Mayen Briggs¹, Sherly Jose³, Michele Ferraro¹, Tracy Horn¹, Marion Hill¹, Mandour Mandour⁴, Darren Clements², Laura Watson^{3,4}, Anthony Holland⁵, Alison Sleight^{1,3,4}

Institution(s): ¹Clinical Neurosciences, ²Stem Cell Institute, ⁴Institute of Metabolic Science, ⁵Psychiatry, University of Cambridge, ³NIHR Cambridge Clinical Research Facility, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK.

Abstract:

Background: To date, there is limited evidence from small-sized studies in PWS of mitochondrial dysfunction in human fibroblasts¹, including aggregation of mitochondria in muscle², and altered transcription and expression of muscle mitochondrial genes^{3,4}. Although there has been speculation that mitochondrial function could relate to the PWS phenotype¹, this has not been fully investigated. This study, therefore, aimed to test if mitochondrial dysfunction is present in the muscle of people with PWS in vivo and if it relates to symptoms.

Methods: This cross-sectional study included 11 people with PWS and 12 age, BMI, and sex-matched control participants. Mitochondrial function was assessed non-invasively using ^{31}P magnetic resonance spectroscopy⁵, by measuring the rate of phosphocreatine recovery post-exercise and fitting to a mono-exponential model, to yield a rate constant which reflects oxidative capacity⁶. In addition, participants had the option of a muscle biopsy to enable the study of mitochondria by electron microscopy. Body composition was assessed by Bioelectrical Impedance Analysis. Cardiac magnetic resonance imaging, lower-limb and hand grip strength, six-minute walk test, and body composition were also undertaken. Physical activity was quantified using the standard International Physical Activity Questionnaire Short Form. Behavioural features and hyperphagia in PWS were assessed using the Aberrant Behaviour Checklist Irritability subscale and the hyperphagia questionnaire⁷. Between-group comparisons were performed using two-tailed independent-samples t-tests, with non-normally distributed variables logarithmically transformed before analysis; statistical significance was set at $p < 0.05$.

Results: Age, BMI, sex, and physical activity did not differ significantly between groups (all $p > 0.4$) (PWS vs controls age: 27 ± 8 vs 29 ± 5 years; BMI: 31.8 ± 9.8 vs 30.7 ± 8.5 kg/m²; total MET-min/week: 4222 ± 3026 vs 3335 ± 1661).

The PWS group showed a significantly lower kPCr than the control group, indicating reduced mitochondrial oxidative capacity (Figure 1). kPCr did not differ significantly between the DEL and UPD subtypes (DEL: $n = 7$, 1.92 ± 0.47 ; UPD: $n = 3$, 1.95 ± 0.31 ; $p = 0.940$). Genetic subtype was unknown in one participant. The relationship of this metric with clinical measures will be reported.

Conclusions: To our knowledge, this is the first study to assess mitochondrial function non-invasively in vivo in individuals with PWS. The results support initial reports¹⁻⁴ that PWS is associated with mitochondrial dysfunction.

Acknowledgements: We thank all the participants. We also acknowledge Addenbrooke's Charitable Trust and the National Institute for Health and Care Research (NIHR) Cambridge Clinical Research Facility.

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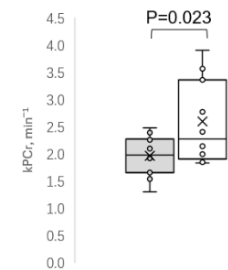


Figure 1. kPCr of the PWS (grey) is significantly lower than that of the control (white).

Precision Medicine in Prader-Willi Syndrome: Clinical Utility Beyond Molecular Diagnosis in a Fully Remote Cohort

Presenting Author: Elizabeth A. Worthey¹

Additional Authors: Brandon M. Wilk^{1*}, Manavalan Gajapathy^{1*}, Donna M. Brown¹, Caroline Vrana-Diaz², Gurpreet Kaur¹, Tarun Karthik Kumar Mamidi¹, Deeptha Srirangam¹, Jessica Bohonowych², Jaimie L. Richards^{1,3}, Shaurita D. Hutchins¹, Bitota Lukusa-Sawalena¹, Theresa V. Strong^{2,4}

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Abstract: Prader-Willi syndrome (PWS) is a complex neurodevelopmental disorder caused by loss of paternally expressed genes on chromosome 15 and characterized by hypotonia, hyperphagia, endocrine dysfunction, behavioral disturbance, and substantial medical complexity. Standard molecular testing reliably establishes the diagnosis and broad molecular class, but often lacks breakpoint resolution and does not evaluate genome-wide variation that may influence comorbidities, medication response, or individualized risk. To assess whether genome sequencing can extend clinical utility beyond molecular diagnosis, we performed genome sequencing in 50 individuals with molecularly confirmed PWS using a fully remote recruitment, consent, sampling, and return-of-results framework. We integrated chromosome 15 copy-number and regions-of-homozygosity analysis, genome-wide small-variant and structural-variant review, pharmacogenomic profiling, and caregiver-reported phenotyping within an n-of-1 precision medicine framework. Genome sequencing refined or resolved PWS molecular subtype assignments in 16% of participants, including reclassification of deletion subtype, resolution of a previously unknown subtype, and identification of structural complexity not captured by prior testing. Actionable pharmacogenomic findings were identified in 40% of participants with pharmacogenomic data, including recommendations relevant to medications commonly used in PWS for psychiatric, behavioral, gastrointestinal, and neurologic indications. ACMG secondary findings were returned in 4.3% of opt-in participants, and additional non-ACMG findings with plausible management relevance to PWS were identified in 24%. Overall, clinically relevant findings were generated for 68% of the cohort. These findings demonstrate that genome sequencing in PWS can provide clinically meaningful information beyond diagnostic confirmation, including improved molecular stratification, medication guidance, individualized risk assessment, and surveillance-relevant findings. This fully remote, registry-enabled model reduced participant burden, supported responsible return of results, and provides a scalable framework for applying genome-informed precision medicine in PWS and other rare, medically complex disorders.

Acknowledgements/Funding: We thank the participants. Funded by the Foundation for Prader-Willi Research

Prader-Willi Syndrome Clinical Investigation Collaborative (PWS-CLIC) Clinical Database

Presenting Author: Amy Fleischman, MD

Additional Authors: Lynne M. Bird, MD; Kelsee Halpin, MD; Rachel Massa, MD; Shawn McCandless, MD; Isabella Niu, MD; Kathryn Obrynba, MD; Elizabeth Roeder, MD; Sani Roy, MD; Ann Scheimann, MD; Diane Stafford, MD; David Viskochil, MD, PhD; Caroline Vrana-Diaz, PhD; Theresa V. Strong, PhD

Institution(s): Boston Children's Hospital, Rady Children's Hospital San Diego, Vanderbilt University, Children's Hospital Colorado, Seattle Children's Hospital, Nationwide Children's Hospital, CHRISTUS Health, Cook Children's Medical Center, Johns Hopkins University, Stanford University, University of Utah, Foundation for Prader-Willi Research

Abstract

Background: The Prader-Willi Syndrome Clinical Investigation Collaborative (PWS-CLIC) was established in 2021 as a North American network of expert clinicians dedicated to improving the quality of clinical research and medical care for people with Prader-Willi syndrome (PWS) across the lifespan. To establish a resource that supports evidence-based care, a centralized clinical database has been created for a consistent collection of data from participants who receive medical care at PWS-CLIC member sites.

Methods: The PWS-CLIC clinical database was developed in 2023 on the Studytrax (www.studytrax.com) platform, an electronic data capture system for academic research and disease organizations. Standardized data elements chosen to represent common clinical features and co-morbidities associated with PWS are included in the database, including demographics, developmental milestones, anthropometrics, mental health, GH use, endocrine, orthopedics, sleep, and other medical issues, and data are captured longitudinally at regular clinic visits. Laboratory findings and medication and supplement use can also be recorded.

Results: As of June 1st, 2026, there are 263 participants with PWS enrolled in the PWS-CLIC clinical database from 12 different PWS-CLIC sites across the United States. The participants range in age from 0 – 35 years old and 55% are female. Most participants have PWS by deletion (53.7%) or UPD (29.1%), followed by unknown or not found (11%), other (4.9%), or imprinting defect (1.3%). Most participants are White (70.5%), followed by Asian (8.1%), Black or African American (5.2%), Other (6.45%), American Indian/Alaska Native (2%), and Multiracial (2%), while 25% of the population database are Hispanic or Latino. The average BMI (SD) of the participants included currently in the database is 15.9 (2.3) for 0–2-year-olds, 16.8 (2.9) for 3–4-year-olds, 20.4 (7.3) for 5–7-year-olds, 22.8 (9.6) for 8-12-year-olds, 27.7 (10.2) for 13-17-year-olds, and 30.2 (11.4) for those 18 and older. Most participants (89.6%) have been on growth hormone, and the mean age of growth hormone initiation was 21.4 months (SD of 33.5 months). Ten participants (3.8%) have been prescribed Vykat XR since the FDA approval in March 2025.

Conclusions: The newly created PWS-CLIC database has been actively growing since its inception, both in the number of active clinical sites and the number of participants. The demographic breakdown is currently more representative of the US population than the Global PWS Registry and previous PWS clinical trials. We expect this database will prove a valuable resource for answering important clinical questions and supporting evidence-based care in PWS.

Acknowledgements/Funding: This database is funded by FPWR. We thank all the individuals with PWS and their families who are participating.

Unravelling the Genetic Architecture of Phenotypic Complexity in Prader-Willi Syndrome: Insights from Genome-Wide Association and Whole Genome Sequencing Analyses

Presenting Author: Elena G Bochukova

Additional Authors: Sadaf Ambreen¹, Cecilia San Vicente Huizar¹, Xiaoyang Dai¹, Caroline J. Vrana-Diaz², Jessica Bohonowych², Brandon M. Wilk³, Donna Brown³, Neil Cowen⁴, Julia Ramirez⁵, Elizabeth A. Worthey³, Theresa V Strong^{2,6}

Institution(s):

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Abstract:

Prader-Willi Syndrome (PWS) is a complex neurodevelopmental disorder arising from the loss of expression of multiple imprinted genes within the Prader-Willi critical region on chromosome 15q11-13. Considerable phenotypic heterogeneity has been observed across affected individuals, a variability that has long been hypothesised to reflect underlying genotype-phenotype relationships. In particular, the two principal genetic subtypes — deletion and non-deletion — have consistently demonstrated statistically significant differences in the frequency and severity of a broad range of clinical features, underscoring the importance of genotype in shaping clinical presentation.

To systematically characterise the genetic determinants of this phenotypic complexity, we assembled a large, deeply phenotyped PWS cohort (n=155), integrating comprehensive clinical assessments with genotyping data. Across this cohort, we examined thirty-nine clinical features and measurements, reporting detailed descriptive statistics, phenotypic correlations, and cross-subtype comparisons. Multiple clinical phenotypes demonstrated convincing genotype-phenotype associations, providing a robust foundation for further genomic investigation.

Building on this foundation, we subsequently incorporated Whole Genome Sequencing (WGS) data from an additional 50 participants recruited through the Global PWS Registry. Following rigorous genetic data harmonisation and imputation, we conducted a Genome-Wide Association Study (GWAS) across the combined cohort for all phenotypes with available data. This analysis identified novel genetic signals associated with BMI, body weight, and Hyperphagia Questionnaire for Clinical Trials (HQCT) score in PWS, including previously unreported variation within the extended chromosome 15 PWS region itself. Crucially, these findings may harbour significant translational potential, offering a pathway toward the identification of genetically-informed, targeted therapeutic strategies. Ultimately, this work advances our understanding of the molecular basis of PWS heterogeneity and lays important groundwork for precision medicine approaches in this population.

Acknowledgements/Funding: Foundation for Prader-Willi Research

POSTER SESSION

Single Center Clinical Experience with GLP-1 and GLP-1/GIP Receptor Agonists in Patients with Prader-Willi Syndrome: A Case Series

Presenting Author: Katherynne Greve, DO

Additional Authors: Amy Fleischman, MD, MMSc

Institution(s): Boston Children's Hospital

Abstract:

Introduction: Prader-Willi syndrome (PWS) is characterized by marked hyperphagia resulting in obesity without significant intervention. Conventional management targets caloric restriction with exercise, though many develop obesity despite these measures, spurring exploration of pharmacologic strategies in obesity treatment. In recent years, GLP-1 receptor agonist (RA) therapy has been explored with some studies suggesting potential reduction in hyperphagia, although the data are limited. We present our clinical experience of 9 patients with PWS on GLP-1 RA and combined GLP-1/GIP RA therapy.

Case: In this case series, we describe 9 patients with PWS (13-24 years of age) prescribed GLP-1 RA and GLP-1/GIP RA therapy.

Results: Within our cohort, patients were prescribed either semaglutide, liraglutide, dulaglutide, and/or tirzepatide. Six patients had concurrent type 2 diabetes diagnoses for which 3 required insulin treatment. One patient had >10% weight loss with semaglutide with <5% continued weight loss with transition to low dose tirzepatide. None of the other patients had >5% weight loss with GLP-1 RA therapy. Six patients (both with and without Type 2 diabetes) gained weight on GLP-1 RA therapy.

Subjectively, three patients reported reduced hyperphagia on semaglutide, and one patient perceived weight loss with reduced food seeking behavior on tirzepatide but measurements did not support the weight loss. Side effects were reported most commonly with semaglutide, including abdominal pain, belching, asymptomatic hypoglycemia (independent of insulin therapy), and diarrhea, leading to discontinuation of semaglutide in one patient. No other related side effects were reported.

Conclusion: Pharmacologic hyperphagia and weight management strategies in patients with PWS are limited. Use of GLP-1 RA and combined GLP-1/GIP RA therapy in PWS is expanding, though our clinical experience suggests variable impact on hyperphagia with most patients continuing to gain weight despite therapy. Further research is needed to determine optimal strategies for obesity and hyperphagia management in this population.

Acknowledgements/Funding: N/A

Interoceptive Mechanisms and Hyperphagia in Prader–Willi Syndrome: The Role of Emotion Regulation

Presenting Author: Sentisenla Imsong

Additional Authors: Dr Surekha Chukkali

Institution(s): CHRIST University, Bangalore, India

Abstract:

Hyperphagia and emotion dysregulation are core symptoms of Prader-Willi Syndrome (PWS) that cause immense clinical burden and psychological stress, yet they are predominantly studied and managed as parallel, independent phenomena. Current neurobiological perspectives of hyperphagia attribute this symptom to hypothalamic dysfunction which disrupts satiety signaling, while emotion regulation is categorized largely as a behavior comorbidity. Despite their co-occurrence and reciprocal reinforcement, the relationship between these two phenomena remains insufficiently understood, and interoception may provide a useful framework to bridge that gap. This paper proposes a framework wherein the disrupted interoceptive processes contributes to emotional dysregulation, and, in turn, to food-seeking behavior in PWS. This framework offers a three-level testable mechanism, spanning molecular, interoceptive, and behavioral levels, and may inform future development of assessment, behavioral intervention, and mechanistic treatment. Drawing on the predictive coding framework, constructed emotion theory and existing neurobiological evidence in PWS, we posit that altered interoception may weaken body-state awareness and impair the identification of internal cues such as hunger, satiety, and affective tension. This may impair emotional regulation and contribute to poor modulation of distress, which in turn, may promote food-seeking as a maladaptive coping mechanism. Over time, this process may create a reinforcing loop in which emotional distress and hyperphagic behavior mutually maintain one another. This framework repositions hyperphagia in PWS as partly an interoceptive-regulatory phenomenon and provides a conceptual pathway for future empirical research targeting emotional and feeding behaviors in clinical care and trial design.

Keywords: Prader-Willi Syndrome, hyperphagia, interoception, emotion regulation, framework development

Acknowledgements/Funding: None

Design of a Phase 2A Clinical Trial Evaluating CSTI-500 Using PK-Guided Individualized Dosing in Individuals with Prader-Willi Syndrome

Presenting Author: Shuang Liu¹

Additional Authors: Elizabeth Roof², Beth Mack³, Sarah Sheldrick¹, Lois Rosenberger³, Jill Rasmussen¹

Institution(s): ¹ConSynance Therapeutics, Inc. Rensselaer, New York, USA; ²Vanderbilt University, Nashville, TN, USA; ³LBRIA Regulatory and Clinical Consulting Services, Inc. Florence, KY, USA

Abstract:

Background: Prader-Willi syndrome (PWS) is a rare genetic neurodevelopmental disorder characterized by hyperphagia and behavioral dysregulation, including anxiety, rigidity, and compulsive behaviors. Currently available treatment targets hyperphagia. However, the behavioral symptoms provide the greater challenge to families and carers. CSTI-500 is a novel centrally acting small molecule designed to simultaneously increase levels of serotonin, dopamine, and norepinephrine in the brain—neurotransmitters that are dysregulated in PWS. CSTI-500 has been evaluated in three Phase 1 clinical trials involving nearly 100 participants, including individuals with PWS. The program has demonstrated brain target engagement in healthy volunteers using positron emission tomography (PET), along with a favorable safety profile. Pharmacokinetic (PK) and brain target engagement (PD) data supports a personalized dosing strategy designed to optimize safety and efficacy as the program advances into Phase 2.

Objectives: This Phase 2A clinical trial is designed to evaluate the safety, tolerability, and pharmacokinetics of CSTI-500 in individuals with PWS. Exploratory objectives include assessing potential signals of clinical improvement in behavioral and hyperphagia symptoms.

Methods: This is an open-label, dose-escalation study enrolling 12 participants aged 13–50 years with genetically confirmed PWS. The study will be conducted at Vanderbilt University Medical Center (VUMC). Participants will receive individualized CSTI-500 dosing guided by PK measurements to achieve target steady-state plasma concentrations predicted to correspond to three ascending levels of target engagement based on human PK/PD data. Safety and tolerability assessments include monitoring of adverse events, laboratory evaluations, vital signs, and electrocardiograms (ECGs). Exploratory clinical endpoints include changes from baseline in caregiver-reported and clinician-rated measures relevant to PWS symptom domains, including the Hyperphagia Questionnaire for Clinical Trials (HQ-CT), Aberrant Behavior Checklist (ABC), PWS Anxiousness and Distress Questionnaire (PADQ), and Clinical Global Impression scales (CGI-S and CGI-I). These measures will inform the selection of outcome measures for future placebo-controlled studies. **Conclusions:** This study introduces a PK-guided individualized, escalating dosing approach for optimizing safety, tolerability, PK, and early signs of clinical efficacy of CSTI-500 in individuals with PWS. Findings will inform dose selection, endpoint selection, and design considerations for subsequent controlled trials evaluating CSTI-500 as a potential treatment for behavioral and hyperphagia symptoms associated with PWS.

Acknowledgements/Funding: This study is sponsored by ConSynance Therapeutics, Inc. We thank the Foundation for Prader-Willi Research (FPWR) for its venture philanthropy investment to support the advancement of CSTI-500 into this Phase 2a clinical study in PWS.

Development of Type 1 Diabetes Mellitus in Patient with PWS After Starting VYKAT XR

Presenting Author: Isabella Niu, MD

Additional Authors: Melinda Pierce, MD

Institution(s): Seattle Children's Hospital, University of Washington

Abstract:

Introduction: Most cases of dysglycemia in Prader-Willi syndrome (PWS) are secondary to insulin resistance and type 2 diabetes (T2D), however there are case reports of type 1 diabetes (T1D) and even Monogenic Diabetes of the Young (MODY) in people with PWS, though these are more rare. The newly approved medication for hyperphagia in PWS, dioxide-choline controlled release (Vykat XR), has hyperglycemia as a known adverse effect, which can impact the interpretation of dysglycemia in the clinical setting. We report the case of a 6-year-old with PWS who developed T1D within months of starting Vykat XR for hyperphagia.

Case Description: The patient is a 6 yo female with PWS secondary to type 2 deletion, on stable treatment with growth hormone and levothyroxine, and BMI at 31st percentile for age, who was started on Vykat XR for hyperphagia in August 2025. She was titrated up to the full target dose per manufacturer's recommendations by early October 2025. Family denied any side effects other than mild hirsutism. Baseline A1c was 5.4%. Fasting morning blood sugars were 70-90 mg/dl on the first two doses of the titration schedule, but after starting the target dose of 100 mg daily, fasting blood sugars increased to 100-130 mg/dl. In late January 2026, after a sudden increase in fasting blood sugars and new-onset bed wetting, Vykat XR was stopped. Family reported post-prandial blood sugars over 300 mg/dl with weight loss, polyuria and nocturia and were recommended to visit their local emergency room for evaluation for diabetic ketoacidosis. Labs showed A1c 9.4%, bicarbonate was normal, with UA positive for ketones. T1D autoantibodies eventually resulted with positive islet-cell autoantibody and Zinc Transporter 8 antibody. She was started on a small dose of long-acting insulin and followed up with our outpatient diabetes clinic to start basal-bolus insulin. She continues to also follow with our endocrine providers for her PWS care, and she has not restarted back on Vykat XR.

Discussion: To our knowledge, this is the first case of type 1 diabetes mellitus diagnosis after starting Vykat XR. While increase in blood sugars is a known side effect of Vykat XR, many cases of hyperglycemia are transient and related to underlying insulin resistance. Similarly, most cases of diabetes that develop in patients with PWS are T2D, with a prevalence as high as 24% by adulthood. There have been some case reports of those with PWS developing T1D and/or latent autoimmune diabetes in adults (LADA), however, this is fairly rare. There are also cases of those with presumed T2D who also have T1D autoantibody positivity, and may be better classified as having LADA or T1D with some preserved beta cell function. While it is likely our patient had the predisposition to develop T1D prior to the start of Vykat XR, and her age and non-obese body composition were not typical of severe insulin resistance, the mechanism of action of Vykat XR with decreasing insulin secretion likely precipitated the progression to Stage 3 T1D while also contributing to some early diagnostic confusion. Her case highlights the importance of not forgetting the possibility of other types of diabetes in our patients with PWS, especially in the setting of novel medications.

Diazoxide Choline Controlled-Release (DCCR)–Associated Stabilization of Severe Obesity and Hyperphagia in a Pediatric Patient with Prader–Willi Syndrome and Early-Onset Type 2 Diabetes

Presenting Author: Sayali Ranadive, MD

Institution(s): Rady Children's Specialists of San Diego, San Diego, California

Abstract

Background: Prader-Willi syndrome (PWS) is a complex neurodevelopmental genetic disorder characterized by severe hyperphagia and behavioral challenges, with limited effective treatment options. Diazoxide choline extended-release tablets (DCCR) have recently been approved for the treatment of hyperphagia in individuals with PWS ≥ 4 years of age. This case describes a child diagnosed with PWS in infancy and treated with DCCR starting at age 7 years and 10 months.

Case Report: The child was born at approximately 41 weeks gestation, weighing 2.56 kg. At birth, the child was noted to have intrauterine growth restriction/small for gestational age, as well as hypotonia, poor feeding, micrognathia and mild hypoglycemia. Whole genome sequencing at 2 weeks of life showed a 2.3 MB deletion of chromosome 15q11q13 and confirmed PWS by methylation. Growth hormone was initiated at 3 weeks of age and discontinued in December 2023 when she developed diabetes mellitus. The child has expressive language disorder and scoliosis (both characteristic of PWS), is on the autism spectrum, and has experienced premature adrenarche. Management of PWS has been complicated by early onset rapid weight gain since 25 months of age, severe hyperphagia starting at age 3.5 years, and development of diabetes mellitus at 6.5 years. Her weight and body mass index (BMI) crossed the 97th percentile for age at 3 years, and increased continuously, despite treatment with a glucagon-like peptide 1 receptor agonist since 5.5 years of age. In December 2023, the patient was diagnosed with type 2 diabetes (fasting glucose 204 mg/dL; hemoglobin [HbA_{1c}] 9.2%) requiring treatment with metformin 1000 mg twice daily and basal-bolus insulin >100 units/day. DCCR was initiated in April 2025 (age 7 years, 10 months) at a starting dose of 150 mg and titrated to the patient's current dose of 375 mg. Within weeks of DCCR initiation, the child's parents reported reduced food-seeking behavior and decreased interest in food. Anthropometric trends have shifted from rapid BMI escalation to stabilization at approximately 42.0 kg/m² (March 2026) despite ongoing linear growth. In addition, modest improvements in glycemic control have been observed, with HbA_{1c} decreasing from 11.8% (July 2025) to 10.1% (February 2026). No edema or other major adverse effects have been reported since initiating DCCR treatment.

Conclusion: This case highlights the complexity of managing PWS and the significant comorbidities associated with hyperphagia. DCCR provided a meaningful decrease in hyperphagia with associated stabilization of weight gain and improved blood glucose control without adverse side effects.

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Real-World Demographics and Clinical Characteristics of Patients with Prader–Willi Syndrome Initiating VYKAT XR (Diazoxide Choline Extended-Release Tablets): Baseline Results from the PWS-VISTA Observational Study

Presenting Author: Julie S. Perry, MD

Additional Authors: Jennifer L. Miller, MD¹, Diane E. Stafford, MD²; Deepan Singh, MD^{3,4}; Daniel Shumer, MD⁵; Gayan Makumbarage⁶; Jina Lee, PharmD⁶; Julie S. Perry, MD⁶

Institution(s): ¹University of Florida; ²Stanford Medical Pediatrics; ³DNAi Systems Co; ⁴Maimonides Medical Center; ⁵University of Michigan; ⁶ Soleno Therapeutics – A Neurocrine Biosciences® Company

Abstract:

Background: Prader–Willi syndrome (PWS) is a rare genetic neuroendocrine disorder characterized by hypotonia, hyperphagia, excess body fat, and behavioral challenges. Diazoxide choline extended-release (DCCR; VYKAT XR) is an FDA-approved treatment for hyperphagia in individuals aged ≥4 years with PWS. Real-world evidence is needed to further characterize treatment outcomes in routine clinical practice. **Methods:** PWS-VISTA is a prospective, multicenter, observational study evaluating the safety profile, clinical characteristics, and real-world outcomes of patients with PWS treated with VYKAT XR in the United States. Approximately 200 patients are expected to be followed for up to 2 years under routine clinical care, without protocol-mandated interventions. The study uses a hybrid data collection approach that combines prospective longitudinal data with retrospective clinical and trial-derived data where available. Assessments in PWS-VISTA reflect routine clinical practice and include demographics, disease characteristics, VYKAT XR exposure, treatment adherence and persistence, and safety outcomes, as well as patient- and caregiver-reported outcomes where available. The study evaluates outcomes of clinical interest including hyperglycemia, edema-related events, hospitalizations, and other adverse events, along with treatment patterns, including dose modifications, discontinuations, and swallowability of VYKAT XR tablets. **Results:** At the time of analysis, 17 patients were enrolled. The mean (SD) age at enrollment was 13.2 (6.05) years, and 8 (47.1%) were female. The mean (SD) weight was 65.6 (34.04) kg and mean (SD) body mass index (BMI) was 30.5 (11.26) kg/m². The study population reflects early diagnosis of PWS, with a mean (SD) age at diagnosis of 0.8 (2.23) years. Genetic subtype included 10 (58.8%) patients with PWS deletion and 6 (35.3%) with non-deletion forms of PWS, and most patients (16 [94.1%]) had been treated with growth hormone. Hyperphagia onset occurred at a mean (SD) age of 7.4 (4.79) years, with a mean (SD) duration of hyperphagia at current severity of 27.1 (49.68) months at study enrollment. Behavioral characteristics commonly associated with PWS were frequently reported. A history of anxiety was present in 10 patients (58.8%), aggression in 7 (41.2%), and irritability in 6 (35.3%). Prior to first VYKAT XR dose, hyperglycemia was reported in 3 patients (17.6%). Steps taken to optimize glucose were reported in 3 patients (17.6%), including dietary adjustments (3 [17.6%]), VYKAT XR/DCCR dose adjustments (1 [5.9%]), physical activity (1 [5.9%]), lifestyle modifications (1 [5.9%]), and medications (1 [5.9%]).

Conclusion: By capturing longitudinal real-world data across a heterogeneous PWS population, PWS-VISTA is expected to provide important insights into treatment durability, variability in clinical response, and factors influencing outcomes in patients receiving VYKAT XR. These findings will complement data from clinical trials and help inform clinicians, patients, and caregivers on the long-term safety and effectiveness of VYKAT XR for the management of hyperphagia in PWS.

Acknowledgements/Funding: This study is sponsored by Soleno Therapeutics – A Neurocrine Biosciences® Company.

Development and Initial Psychometric Evaluation of the Comprehensive Prader-Willi Syndrome Behavior Checklist (CPWS-BC) in an Indian Clinical Sample

Presenting Author: Deepan Singh, MD¹

Additional Authors: Sushma Gopalan²; Sentisenla Imsong³

Institution(s): 1: Maimonides Medical Center; DNAi Systems Co.; 2: Child Life Services, Manipal Hospitals; 3: School of Psychological Sciences, Christ University

Abstract:

Background: Prader-Willi syndrome (PWS) has a complex behavioral phenotype that drives morbidity and caregiver burden. Current assessment relies on general psychopathology scales, narrow domain-specific tools, or brief syndrome-specific questionnaires, none of which captures the full breadth of clinically relevant PWS behaviors within a single instrument. No PWS behavioral instrument has been validated in an Indian clinical cohort. **Objective:** To develop and conduct an initial psychometric evaluation of the Comprehensive PWS Behavior Checklist (CPWS-BC), a multidimensional, caregiver-reported instrument designed to capture the full PWS behavioral phenotype across developmental stages. **Methods:** A multi-phase development and validation design was used. Item generation drew on behavioral-phenotype models, empirical literature, multidisciplinary clinical observation, and caregiver experience, producing 168 candidate items across 18 dimensions. A seven-member multidisciplinary expert panel conducted content validation. Internal consistency (Cronbach's alpha, McDonald's omega) and item-total correlations were examined in caregivers of individuals with genetically confirmed PWS ($n = 25$). Concurrent validity was assessed using Bayesian Kendall's tau against standardized measures.

Results: Content validation removed 46 and revised 15 items, yielding a consolidated scale across 14 domains. Overall internal consistency was excellent ($\alpha = .949$, 95% CI [.923, .973]); subscale reliability ranged from adequate to excellent ($\alpha = .700$ to $.903$). The Impulsivity subscale was excluded from the final reliability model for insufficient internal consistency. Concurrent validity was supported for hyperphagia ($\tau = [[0.55]]$, $BF+0 = [[601.4]]$), caregiver burden ($\tau = .573$, $BF+0 = 1081$), sleep disturbance ($\tau = .385$, $BF+0 = 16.36$), and self-injury ($\tau = .391$, $BF+0 = 18.24$). The total checklist correlated strongly with an established PWS behavioral measure ($\tau = .456$, $BF+0 = 66.22$).

Conclusions: The CPWS-BC shows promising initial reliability and concurrent validity. Its distinctive contributions are the breadth of behavioral domains assessed, uniquely integrating caregiver burden, developmental constructs, and school functioning within a single instrument, and the first validation of a PWS-specific behavioral instrument in an Indian clinical sample. It complements existing instruments such as the PWS Profile (Dyken et al., 2024). The modest pilot sample precludes factor analysis and test-retest evaluation; validation in larger international samples is warranted.

Acknowledgements/Funding: PWS Association, USA, PWS Indian Families, Pediatric Endocrinology Team Manipal Hospitals, IPWSA (Indian PWS Association)

BRAVE-PWS: Burden and Real-World Assessment of Caregiver Voice and Experiences in Prader-Willi Syndrome—Study Design of an Observational, App-Based Health-Tracking Cohort Study

Presenting Author: Christopher Joshi, MD, MPH

Additional Authors: Christopher Joshi, MD, MPH¹, Robert Dufour, PhD², Samantha McStocker, BS¹, Sarah Leuzzi, DPT¹, Mae Kwong, PharmD²

Institution(s): ¹ Folia Health, ²Soleno Therapeutics – A Neurocrine Biosciences® Company

Abstract:

Objectives: Prader-Willi syndrome (PWS) is a rare genetic disorder marked by cognitive and behavioral challenges, developmental delays, endocrine issues, and chronic hyperphagia requiring continuous supervision. Caregivers face substantial mental, social, and financial burden, largely driven by hyperphagia and behavioral symptoms. The recent approval of a pharmacologic treatment for hyperphagia in PWS provides a timely opportunity to quantify how specific aspects of burden change as the therapeutic landscape evolves.

The Folia Health (FH) app enables caregivers to capture structured, longitudinal home-reported outcomes (HROs) reflecting lived experience. Here, we describe the design of an observational study using the FH app to systematically track and quantify PWS caregiver burden over time in an untreated population (Part 1).

Methods: Semi-structured interviews were conducted with caregivers of individuals with PWS and clinician experts to inform study design. This study will enroll 50 caregivers of individuals with

PWS (age ≥ 4), who will track HROs at least weekly over a six-month period via the FH app. Participants will also complete monthly caregiver-reported outcome (CRO) measures (PROMIS-10, ZBI-12, and Food Safe Zone) and survey questions assessing aspects of caregiver burden.

Results: Qualitative interviews were conducted with six caregivers of individuals with PWS aged 4–27 and three pediatric clinicians specializing in PWS. These interviews identified eight caregiver burden domains (e.g., time for self-care) and thirty-eight symptoms/observations for individuals with

PWS (e.g., hyperphagia behaviors, other psychiatric behaviors, sleep). A behavioral episode tracker captures details of outbursts common in PWS (including triggers and health-related quality of life effects). A life events tracker records important non-medical situations, such as going out to eat or missing school and the impact of PWS on these life events. This longitudinal HRO, CRO, and monthly survey data will be used to characterize the experience of caregiving for someone with PWS.

Conclusions: Qualitative interviews of PWS caregivers focused on key themes around PWS behaviors and management, quality of life effects on caregivers, and health tracking strategies, informing the design of an observational study to capture aspects of PWS that matter most to caregivers. The FH app is a caregiver tool to capture this data. A planned second phase will examine a population treated with VYKAT XR.

Acknowledgements/Funding:

The authors would like to thank the PWS caregivers and clinicians interviewed for their time and invaluable insights. This study is funded by Soleno Therapeutics – A Neurocrine Biosciences® Company.

The Impact of a Token Economy on Behavior in Patients with Pediatric Prader-Willi Syndrome

Presenting Author: Geethanjali Ravindranathan

Additional Authors: Blythe Stockton, BS, John W. Cassidy, MD

Institution(s): Nexus Health Systems

Abstract:

Objective:

Token economy systems are widely used in behavioral psychology but remain understudied in inpatient Prader-Willi Syndrome (PWS) populations. A token economy is a structured behavioral reinforcement system in which patients earn tokens for completing target behaviors, which can be exchanged for desired rewards. This study evaluates the impact of a structured token economy on behavioral outcomes in an inpatient pediatric PWS program, and examines whether length of stay moderates treatment response.

Methods:

Thirteen pediatric patients with PWS (7 male, 6 female; mean age 16.3 years, range 11 to 23) admitted to the Nexus Children's Hospital inpatient PWS program were included. Patients engaged in a daily token economy across six activities spanning five behavioral domains: Self-Care, Medical Adherence, Physical Activation, Structured Engagement, and Executive Functioning. Tokens were earned based on timeliness, pro-social behavior, participation, comprehension, and activity transitions, with a standardized daily incentive of up to 60 tokens redeemable weekly at the token store. Behavioral outcomes were assessed using the Agitated Behavior Scale (ABS), Developmental Behavior Checklist-2 (DBC-2), Modified Overt Aggression Scale (MOAS), and behavioral emergency frequency. Token economy performance was assessed from the third full week of admission (baseline) through discharge. Paired t-tests and Wilcoxon signed-rank tests were used; Pearson and Spearman correlations examined dose-response relationships with length of stay (LOS).

Results:

Mean LOS was 130 days (range 57 to 238). ABS scores improved significantly from admission to discharge (mean change of 1.23 points; Wilcoxon $p = 0.021$), with 10 of 13 patients improving, the most consistent finding across the cohort. Weeks achieving 80% or more of daily token economy earnings increased significantly from the first to second half of stay (mean 3.8 to 6.5 weeks; Wilcoxon $p = 0.025$), with 10 of 13 patients showing improvement, reflecting sustained gains in behavioral consistency over time. A significant dose-response relationship was observed between LOS and both token economy improvement (Spearman $r = 0.60$, $p = 0.029$) and weeks achieving 80% or more earnings (Spearman $r = 0.66$, $p = 0.014$), suggesting greater benefit with extended treatment exposure.

Ceiling effects were present in the overall token economy metric. Patients entering with 90% or more baseline earnings ($n = 5$) showed a mean decline of 4.8%, while those with greater behavioral impairment at baseline ($n = 8$) improved by a mean of 24.1% ($p = 0.050$), indicating that patients with the most behavioral room to improve responded most robustly. Medical Adherence and Physical Activation showed the largest domain-level gains (22.5% each), consistent with t-test significance ($p = 0.041$ and $p = 0.033$, respectively), though Wilcoxon tests did not reach significance in this small sample. Among the 5 patients with non-zero MOAS scores at baseline, 3 showed clinically meaningful reductions in aggression (mean decrease of

8.8 points). Behavioral emergencies decreased by 22% from the first to second half of stay, though this did not reach statistical significance.

Conclusions:

A structured token economy was associated with significant reductions in agitation and improved behavioral consistency in pediatric inpatient PWS, with a clear dose-response relationship between treatment duration and outcome. Patients with greater behavioral impairment at admission showed the most robust gains. These findings support extended inpatient programming as a clinically meaningful intervention for PWS and highlight the importance of adequate treatment duration. Prospective studies with larger samples and standardized LOS are needed to confirm these effects and clarify genotype-specific response patterns.

Acknowledgements/Funding:

The authors wish to thank the clinical staff at Nexus Children's Hospital for their dedication to patient care and their integral role in implementing the token economy program.

ECG Findings in Potential Participants for the VNS4PWS Clinical Trial

Presenting Author: Lisa Mateševac¹

Additional Authors: Caroline Vrana-Diaz¹, Lauren Schwartz¹, Allen Kidman², James Loker³, Theresa V. Strong¹

Institution(s): ¹Foundation for Prader-Willi Research, ²Propharma, ³Western Michigan University

Abstract

Background: Individuals with PWS are at a higher risk than the general population for cardiopulmonary medical complications, but there is limited information about cardiac function in the PWS population. As part of a clinical trial evaluating the safety and efficacy of transcutaneous vagus nerve (tVNS) stimulation for temper outburst behavior in PWS (theVNS4PWS trial), electrocardiograms (ECGs) were recorded on 110 potential trial participants.

Methods: Individuals with PWS who had a history of temper outburst behavior were recruited to participate in a clinical trial evaluating the use of tVNS. After meeting eligibility criteria, which excluded volunteers with a history of cardiac disease, and completing a screening period, participants had a baseline visit at one of 18 clinical trial sites in the US. As part of the baseline visit, participants received an ECG to confirm eligibility for the study. ECGs findings were reviewed by a board-certified cardiologist, subsequently confirmed by a pediatric cardiologist, and parameters including heart rate, RR interval, PR interval, QRS complex duration, QT interval, and QTcF were recorded.

Results: 110 individuals with PWS, age 10-37, completed the ECG recording. There were slightly more (53%) males than females and the PWS genetic subtype distribution was consistent with previously reported percentages. The average BMI for individuals age 10-17 years was 24.5(range: 14.7-64.7) and for 18+ years old was 33.2 (range: 18.5-61.2). Most ECG recordings were normal, with RR, PR, QRS and QT intervals within range for age. Thirty-two individuals had abnormal but not clinically significant findings on ECG. An additional 3 potential participants had abnormal, clinically significant findings including sinus bradycardia, long QTc with prominent U waves and right bundle branch block. Of those, one participant was allowed to proceed in the study after a normal echocardiogram. Overall, heart rate was slightly lower than expected based on population norms, with an average heart rate of 77.7 bpm in 10-17 year olds and 69.5 bpm in adults. Nine individuals (8.2%) showed QT intervals within normal range, but borderline high [425-450 msec, following correction for heart rate by Fridericia formula, without allowance for age or gender], which may be related to background medication use.

Conclusions: In this large cohort of individuals with PWS meeting inclusion criteria for theVNS4PWS trial, almost all ECGs were normal or abnormal but not clinically significant. The incidence of previously undetected, clinically significant ECG abnormalities was low.

Acknowledgements/Funding: We are grateful to the participants in the VNS4PWS clinical trial and their families, and the clinical trial sites. Funded by FPWR.

Real-World Experience with VYKAT XR Initiation in Individuals with Prader-Willi Syndrome: Findings from the Global PWS Registry

Presenting Author: Jessica E. Bohonowych^{1,2}

Additional Authors: Lisa Matesevac², Caroline Vrana-Diaz², Parisa Salehi³, Lauren Schwartz², and Theresa V. Strong^{1,2}

Institutions: ¹Global PWS Registry, ²Foundation for Prader-Willi Research, Covina, CA, USA; ³Division of Endocrinology and Diabetes, Seattle Children's Hospital, University of Washington, Seattle, Washington, USA

Abstract:

Background:

The Global Prader-Willi Syndrome (PWS) Registry is an international patient registry sponsored by the Foundation for Prader-Willi Research and hosted on the National Organization for Rare Disorders (NORD) IAMRARE platform. The Registry collects longitudinal, patient- and caregiver-reported information to characterize the natural history of PWS, advance research, improve clinical care, and inform the development and evaluation of treatments. VYKAT XR (diazoxide choline) was approved by the U.S. Food and Drug Administration (FDA) in March 2025 for the treatment of hyperphagia in adults and pediatric patients aged 4 years and older with PWS. With VYKAT XR entering clinical use, the Global PWS Registry provides an opportunity to capture real-world experiences with this treatment from individuals with PWS and their families.

Methods:

The VYKAT XR User Experience Survey was released through the Global PWS Registry in December 2025 and collects caregiver-reported information regarding the experience of initiating and using VYKAT XR. Data collected includes demographics; characteristics of the initial prescribing interaction; pre-treatment testing; insurance coverage and access; titration and monitoring practices, impact, and side effects.

Results and Discussion:

An analysis of the initiation and titration stage of VYKAT XR use is reported for 92 Registry participants who completed the survey. Among respondents, the majority of VYKAT XR prescriptions were provided by an endocrinologist, pediatric (72%) or adult (17%), respectively. Approximately half of initial prescriptions were covered by private insurance, and 66% of prescriptions were filled in <1 month. Early real-world data from the Global PWS Registry provides insight into how VYKAT XR is being introduced and monitored in clinical practice following FDA approval. These data highlight patterns in treatment awareness, prescribing, access, and monitoring during titration. Limitations include limited sample size, an English only survey, and a Global PWS Registry population that may not fully represent the entire PWS community. Despite these limitations, continued collection of longitudinal Registry data will be important for understanding the real-world experience with VYKAT XR, identifying potential barriers to treatment, impact, side effects, and informing best practices for clinical use.

Acknowledgements:

Thank you to the PWS families without whom this research would not be possible. Funding for this project is provided by the Foundation for Prader-Willi Research.

Long-Term Reductions of Hyperphagia with Diazoxide Choline Extended Release (DCCR) in Participants with Prader-Willi Syndrome

Presenting Author: Evelien Gevers

Additional Authors: Gevers EF^{1,2}, Bird LM^{3,4}, Salehi P⁵, Shoemaker AH⁶, Butler MG⁷, Obrynba K⁸, Stevenson DA⁹, Kimonis V¹⁰, Wilding J¹¹, Shaikh MG¹², Goldstone AP¹³, Lah M¹⁴, Littlejohn E¹⁵, Strong TV¹⁶, Matesevac L¹⁶, Bohonowych JE¹⁶, Cowen N¹⁷, Gong J¹⁷, Perry J¹⁷, Miller JL¹⁸

Institution(s): ¹Queen Mary University of London, Barts and The London Medical School, William Harvey Research Institute, Centre for Endocrinology, London, United Kingdom. ²Barts Health NHS Trust, Royal London Hospital, London, United Kingdom. ³Rady Children's Hospital of San Diego, San Diego, CA, USA. ⁵University of WA, Seattle, WA and Alaska Subspecialty Pediatrics Network, Anchorage, AK. ⁶Vanderbilt University Medical Center, Nashville, TN, USA. ⁷University of Kansas Medical Center, Kansas City KS, USA. ⁸Nationwide Children's Hospital, Columbus, OH, USA. ⁹Stanford University Pediatrics Medical Genetics, Palo Alto, CA, USA. ¹⁰University of California Irvine, Irvine, CA, USA. ¹¹University of Liverpool, Liverpool, UK. ¹²Royal Hospital for Children, Glasgow, Scotland, UK. ¹³Dept. of Brain Sciences, Imperial College London, Hammersmith Hospital, London, UK. ¹⁴Indiana University School of Medicine, Indianapolis, IN, USA. ¹⁵University of Michigan Health-Sparrow Clinical Research Institute, Lansing, MI, USA. ¹⁶Foundation for Prader-Willi Research, Covina, CA, USA. ¹⁷Soleno Therapeutics – A Neurocrine Biosciences® Company, Redwood City, CA, USA. ¹⁸University of Florida, Gainesville, FL, USA.

Abstract

Background: Prader-Willi syndrome (PWS) is a rare genetic neuroendocrine disorder characterized by hyperphagia, excess body fat, and behavioral challenges. Diazoxide choline extended-release (DCCR), a potent activator of the adenosine triphosphate (ATP)-sensitive potassium channel, is an FDA-approved treatment for hyperphagia in individuals aged 4 years and older with PWS. The DCCR development program included a 13-week randomized, placebo-controlled study (C601), an open-label extension study (C602OLE) up to 3 years, a 16-week randomized withdrawal study (C602RWP), and an ongoing open-label study C614. Hyperphagia Questionnaire for Clinical Trials (HQ-CT) is a validated questionnaire used to assess hyperphagia associated food related behaviors in clinical trials. We present results for the HQ-CT for up to 3 years from participants who received DCCR in C601/C602OLE compared to real-world natural history data from the PATH for PWS study (PATH). **Methods:** Participants who completed C601 could enroll in C602OLE and receive long-term open-label DCCR. HQ-CT total score was evaluated from DCCR Baseline and compared to non-DCCR exposed participants from PATH who met C601 age, weight and baseline hyperphagia inclusion criteria. Difference in change from Baseline (95% CI) of HQ-CT total score is presented; p-values were obtained from linear mixed effects model with unstructured covariance adjusting for key variables. Reduced scores reflect improvement. **Results:** Participants (N=352) were included (DCCR:123; PATH:229). Differences in demographics and baseline characteristics included: mean (SD) age in years (13 ± 6 , 18 ± 9), body mass index in kg/m² (27 ± 9 , 29 ± 10), and % of participants on growth-hormone (83, 57) for DCCR vs PATH. A majority were white (85% vs 81%) and deletion subtype (62% vs 58%) for DCCR and PATH, respectively. Baseline HQ-CT total scores were 21.6 ± 6.7 and 18.2 ± 5.0 for DCCR and PATH groups. Significant ($p < 0.0001$) reductions in hyperphagia occurred at all time points for DCCR compared to PATH cohort. Change in HQ-CT from Baseline between DCCR and PATH was -6.2 (95% CI: -7.8 , -4.5 ; $p < 0.0001$) at year 1, -6.5 (95% CI: -8.3 , -4.8 ; $p < 0.0001$) at year 2, and -6.2 (95% CI: -8.2 , -4.1 ; $p < 0.0001$) at year 3 demonstrating persistence of hyperphagia reduction in the DCCR treated cohort. **Conclusion:** DCCR administration resulted in significant, sustained improvements up to 3 years in hyperphagia as demonstrated by reduction in HQ-CT total score compared to natural history controls who did not spontaneously improve. DCCR represents an effective, long-term intervention for hyperphagia in patients with PWS. **Acknowledgements/Funding:** Study funded by Soleno Therapeutics – A Neurocrine Biosciences® Company. Originally presented at ENDO 2026 and first published in the Journal of the Endocrine Society (Endocrine Society); this content is reproduced without modification.

Impact of Long-Term Diazoxide Choline Extended Release (DCCR) Treatment and the Prader-Willi Syndrome Profile Questionnaire (PWSP)

Presenting Author: Evelien Gevers

Additional Authors: Gevers EF^{1,2}, Bird LM^{3, 4}, Salehi P⁵, Shoemaker AH⁶, Butler MG⁷, Obrynba K⁸, Stevenson DA⁹, Kimonis V¹⁰, Wilding J¹¹, Shaikh MG¹², Goldstone AP¹³, Lah M¹⁴, Littlejohn E¹⁵, Strong TV¹⁶, Matesevac L¹⁶, Bohonowych JE¹⁶, Cowen N¹⁷, Gong J¹⁷, Miller JL¹⁸

Institution(s): ¹ Queen Mary University of London, Barts and The London Medical School, William Harvey Research Institute, Centre for Endocrinology, London, United Kingdom. ² Barts Health NHS Trust, Royal London Hospital, London, United Kingdom. ³ Rady Children's Hospital of San Diego, San Diego, CA, USA. ⁵ University of WA, Seattle, WA and Alaska Subspecialty Pediatrics Network, Anchorage, AK. ⁶ Vanderbilt University Medical Center, Nashville, TN, USA. ⁷ University of Kansas Medical Center, Kansas City KS, USA. ⁸ Nationwide Children's Hospital, Columbus, OH, USA. ⁹ Stanford University Pediatrics Medical Genetics, Palo Alto, CA, USA. ¹⁰ University of California Irvine, Irvine, CA, USA. ¹¹ University of Liverpool, Liverpool, UK. ¹² Royal Hospital for Children, Glasgow, Scotland, UK. ¹³ Dept. of Brain Sciences, Imperial College London, Hammersmith Hospital, London, UK. ¹⁴ Indiana University School of Medicine, Indianapolis, IN, USA. ¹⁵ University of Michigan Health-Sparrow Clinical Research Institute, Lansing, MI, USA. ¹⁶ Foundation for Prader-Willi Research, Covina, CA, USA. ¹⁷ Soleno Therapeutics – A Neurocrine Biosciences® Company, Redwood City, CA, USA. ¹⁸ University of Florida, Gainesville, FL, USA.

Abstract

Background: Prader-Willi syndrome (PWS) is a rare genetic neuroendocrine disorder characterized by hyperphagia, excess body fat, and behavioral challenges. Diazoxide choline extended-release (DCCR), a potent activator of the adenosine triphosphate (ATP)-sensitive potassium channel, is an FDA-approved treatment for hyperphagia in individuals aged 4 years and older with PWS. The DCCR development program included a 13-week randomized, placebo-controlled study (C601), an open-label extension study (C602OLE) of up to 3 years, a 16-week randomized withdrawal study (C602RWP), and an ongoing open-label study C614. DCCR effect on behavior was assessed with the Prader-Willi Syndrome Profile (PWSP). We present 3-year PWSP results for DCCR-treated study participants vs natural history data from the PATH for PWS (PATH) natural history study. **Methods:** Participants who completed C601 could enroll in C602OLE and receive long-term open-label DCCR. The caregiver-administered PWSP includes 6 domains (aggressive behaviors [0-18], compulsivity [0-20], rigidity/irritability [0-20], anxiety [0-22], disordered thinking [0-12], and depression [0-10]). Least-square mean changes from baseline ($\pm$ SE) were compared between DCCR treatment and PATH and p-values were based on a mixed model with repeated measure adjusting for key variables. Reduced scores reflect improvement. **Results:** Participants (N=287) were included in this analysis (DCCR:105; PATH:182). Mean baseline PWSP domain scores for DCCR treatment and PATH were 7.6 ± 3.8 and 8.8 ± 4.2 for aggressive behaviors, 12.1 ± 4.9 and 12.4 ± 4.5 for compulsivity, 10.9 ± 5.3 and 12.0 ± 5.2 for rigidity/irritability, 12.9 ± 5.3 and 13.7 ± 5.1 for anxiety, 4.4 ± 3.3 and 4.5 ± 3.0 for disordered thinking, and 3.7 ± 2.3 and 3.8 ± 2.2 for depression, respectively. Significant improvements favoring DCCR compared to PATH in all 6 PWSP domains were observed at year 1 ($p < 0.001$), year 2 ($p < 0.01$), and year 3 ($p < 0.001$). LS mean (95% CI) differences between DCCR and PATH in change from baseline at 3 years were -2.1 ($-3.16, -1.07$) for aggressive behaviors, -2.3 ($-3.46, -1.24$) for compulsivity, -2.4 ($-3.64, -1.21$) for rigidity/irritability, -2.5 ($-3.67, -1.31$) for anxiety, -1.5 ($-2.15, -0.88$) for disordered thinking, and -1.1 ($-1.58, -0.54$) for depression, respectively. **Conclusion:** DCCR administration significantly improved PWS-related behaviors for up to 3 years as demonstrated by improved scores across all domains of the PWSP questionnaire as compared to natural history controls.

Acknowledgements/Funding:

Study funded by Soleno Therapeutics – A Neurocrine Biosciences® Company. Originally presented at ENDO 2026 and first published in the *Journal of the Endocrine Society* (Endocrine Society); this content is reproduced without modification.

Efficacy and Safety of Resuming Diazoxide Choline Extended-Release (DCCR) after 16-week Randomized Withdrawal in Prader-Willi Syndrome (PWS) (Study C614)

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Abstract

Background: Prader-Willi Syndrome (PWS) is a rare genetic neurobehavioral-metabolic disorder characterized by pediatric-onset hyperphagia, a chronic, life-threatening condition that leads to reduced life expectancy with a median age of death at 23 years. Diazoxide choline extended-release (DCCR) is approved in the United States as VYKAT™ XR an oral, once-daily treatment for adults and children 4 years and older with PWS who have hyperphagia. The objective of this study was to evaluate the efficacy and safety of resuming DCCR after randomized withdrawal in PWS. **Methods:** We assessed if resuming DCCR improved hyperphagia by the Hyperphagia for Clinical Trials questionnaire (HQ-CT) and PWS behaviors by the PWS Profile questionnaire (PWSP) over 2 years in 76 participants who previously completed 16 weeks of randomized withdrawal and 1 participant who had discontinued DCCR for 16 weeks. Changes in body mass index (BMI) were also assessed, as was long-term safety and tolerability. **Results:** At C614 Baseline, mean (SD) age was 15.3 (4.63) years, 55.8% were female. HQ-CT Total Score was 15.4 (7.8) and 11.9 (7.9), mean (SD) for participants who restarted DCCR after placebo or remained on DCCR, respectively. Participants who restarted DCCR showed marked improvements in HQ-CT Total Score by 13 weeks (mean [SD], -4.5 [6.3]) that further improved by 26 weeks and 2 years (-5.5 [7.1] and -6.3 [8.4], respectively). Participants remaining on DCCR showed smaller but continued improvements after 13 weeks (-2.7 [6.9]) that were sustained at 26 weeks and 2 years (-3.3 [5.7] and -3.1 [8.0], respectively). Nonsignificant improvements in PWSP domain scores were seen at 13 and 26 weeks, with improvements in all 6 domains at 2 years in participants who restarted DCCR (mean [SD], aggression, -1.6 [3.8]; compulsivity, -2.2 [3.9]; rigidity/irritability, -1.1 [4.4]; anxiety, -2.2 [3.9]; disordered thinking, -0.6 [1.8]; and depression, -0.6 [2.1]). Mean Baseline BMI was 26.0 and 28.9 kg/m² for participants restarting and remaining on DCCR, respectively, and remained relatively stable at 2 years, (27.2 and 29.1 kg/m², respectively). Adverse events (AEs) were reported in 92.2% of participants. No deaths occurred and only 2/77 participants withdrew due to an AE. Treatment-related AEs occurring in ≥5% of participants included peripheral edema, hyperglycemia, increased blood glucose, increased glycosylated hemoglobin, and hypertrichosis. Serious AEs and Grade 3 AEs occurred in 8/77 participants and 9/77 participants, respectively. **Conclusion:** In study C614, resuming DCCR for 2 years after 16-week randomized withdrawal was associated with improvements in both hyperphagia and behavioral symptoms characteristic of PWS. BMI remained relatively stable. Long-term DCCR treatment was generally well-tolerated with an AE profile consistent with that observed in previous clinical trials of DCCR in PWS.

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Integrated Exposure-Adjusted Analysis of Adverse Events of Special Interest During Diazoxide Choline Treatment for Prader-Willi Syndrome

Presenting Author: Sheri Leung

Additional Authors: Sheri Leung, PharmD¹, Sarah Juhn, PharmD¹, Shuxin Yin, PhD¹, Jeff Asphall, MD¹

Institution: ¹Soleno Therapeutics – A Neurocrine Biosciences® Company

Abstract

Introduction: Hyperphagia is a chronic condition in Prader-Willi syndrome (PWS) associated with life-threatening complications driven by uncontrolled food-seeking behavior and lack of normal satiety, requiring long-term management. Diazoxide choline extended release (DCCR; VYKAT® XR) is the first and only U.S. FDA-approved treatment for hyperphagia in adults and children aged ≥4 years with PWS. The Phase 3 DCCR clinical program included a 13-week, randomized, placebo-controlled trial (C601), a multi-year open-label extension (C602-OLE), and a 16-week randomized withdrawal period (C602-RWP), comprising a largely continuous cohort of participants with PWS. The sequential design enables assessment of temporal patterns of adverse events of special interest (**AESIs**) across treatment phases. We examined the use of exposure-adjusted incidence rates (**EAIRs**; participants experiencing ≥1 event per 100 patient-years [PY]) to standardize risk relative to exposure time, providing a more clinically interpretable assessment of AESI occurrence and long-term tolerability. **Methods:** An integrated safety analysis was conducted using pooled data from C601, C602-OLE, and C602-RWP. Pre-specified AESIs (edema, hyperglycemia, hirsutism, hypertrichosis) were evaluated as participant-level incidence and EAIRs. AESI-group events were captured once at first occurrence and not recounted unless they resolved and recurred or worsened. Time-to-first-event analyses were performed among DCCR-treated participants (N=125). Adverse event-related discontinuations (**AE-DCs**) were defined as discontinuations of study drug with an AE as the primary cause. **Results:** Total DCCR exposure was approximately 326 PY (C601: 19.8; C602-OLE: 294.6; C602-RWP: 11.4). Despite longer exposure in C602-OLE (max duration 4.3 years), EAIRs were highest in C601 and declined substantially with continued treatment across all AESIs (Table 1). Overall, 29/125 (23.2%) participants experienced ≥1 AESI during dose titration across C601 and C602-OLE).

Table 1. Integrated Analysis of Diazoxide Choline: Exposure-Adjusted Adverse Event of Special Interest (AESI) and Adverse Event (AE) -Related Discontinuations

	C601 (n=84)	C602-OLE (n=115)	C602-RWP (n=38)
Participants with ≥1 event per 100 PY*	13 weeks [19.8 PY]	260 weeks [294.6 PY]	16 weeks [11.4 PY]
• AESI Hyperglycemia	70.7	13.2	8.8
• AESI Edema	106.1	14.3	0
• AESI Hypertrichosis	151.5	29.2	26.4
• AESI Hirsutism	30.3	11.2	17.6
AE-Related Discontinuations*	20.2	2.0	0

Abbreviations: OLE, open-label extension; PY, patient years; RWP, randomized withdrawal period. *AE-related discontinuations (AE-DCs) defined as discontinuations of study drug in which an AE was recorded as the primary reason. *Rate per 100 patient-years (PY) = (number of patients experiencing ≥1 event within the prespecified AESI category ÷ total patient-years of exposure) × 100; each patient is counted once per AESI category regardless of the number of related preferred terms or recurrent events.

Time-to-first-event analyses demonstrated that most first AESI events occurred within the first 6 months, with few new-onset events thereafter. AESIs were primarily Grade 1–2; serious AESIs occurred in 2 participants (both edema-related, associated with intercurrent respiratory illness). AE-DCs were infrequent, occurred mainly during dose titration (7 of 10), with none during C602-RWP. AE-DCs predominantly occurred in participants classified as overweight or obese (9 of 10) and at mid-to-higher DCCR dose ranges (300–450 mg; 8 of 10), with fluid retention events accounting for 5 of 10 AE-DCs. **Conclusions:** Across nearly 326 patient-years of DCCR exposure, AESIs were predominantly early-onset and low-grade, with nearly one-quarter of participants affected during dose titration. EAIRs were highest in initial treatment period (C601) and declined with continued treatment. AE-DCs were infrequent, occurred early, and were associated with identifiable clinical factors, including higher body weight and higher DCCR dose range. These findings indicate AESI risk does not increase over time and support appropriate dose titration and early monitoring, particularly in higher-risk populations.

Acknowledgements/Funding: Soleno Therapeutics – A Neurocrine Biosciences® Company

Mortality Among Patients with Prader-Willi Syndrome (MAP-PWS): An Analysis of Healthcare Utilization in the Year Prior to Death within A Single U.S. Payer

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Additional Authors: Isabella Niu, MD¹, Mae Kwong, PharmD², Robert Dufour, PhD², Raj Gandhi, PharmD, MBA², Parisa Salehi, MD¹

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Abstract

Objectives: Prader-Willi syndrome (PWS) is a complex genetic disorder characterized by cognitive and behavioral challenges, developmental disability, endocrine abnormalities, and chronic, life-threatening hyperphagia. Individuals with PWS show heightened hyperphagia related mortality contributing to one-third of reported U.S. PWS deaths (Butler et al., 2017). To better understand current mortality in PWS, we evaluated recent medical claims to assess age-adjusted mortality rate and characterize healthcare resources accessed in the year prior to death.

Methods: We analyzed de-identified U.S. medical claims for individuals with PWS (defined as having ≥ 2 claims with Q87.11 code) between January 2020 and March 2025. Those with a confirmed date of death had the 12-month period preceding death examined to evaluate healthcare resource utilization. Utilization included visits with specialists commonly involved in PWS care (endocrinologists, mental health providers, pulmonologists, cardiologists) and encounters at acute care facilities (emergency department visit or hospitalization). Mortality rates were adjusted for age and person-time for the PWS cohort (reported per 100,000 patient-years). National mortality rates were obtained for comparison using CDC 2024 data. All analyses were descriptive.

Results: Among 688 patients with PWS, 18 deaths were identified, of whom 12 (67.7%) were Medicaid enrollees. The age-adjusted mortality rate was 773.1 per 100,000 patient-years, with a mean age at death of 32.3 years (range 5-98). In comparison, the age-adjusted mortality rate for the overall U.S. population was 134.6 per 100,000 patient-years. In the 12 months preceding death, patients averaged 25.1 (SD 38.1, median 5) specialist visits and 4.2 (SD 7.5, median 2) encounters at acute care facilities; of these, 29.9% and 24.0%, respectively, occurred in the final month of life. As a group, 72.2% had ≥ 1 specialist visit and 77.8% had ≥ 1 acute care facility encounter. Three patients had no claims for either service type in this period.

Conclusions: Individuals with PWS are at risk of premature death. The mortality rate among patients in this PWS cohort was nearly six times higher than what would have been expected of the general population of similar age distribution. Over a quarter of encounters occurred in the month preceding death, indicating an increase in healthcare utilization during that last month and may suggest a more rapid decline prior to death. Future analysis is needed to assess contributory and precipitating risk factors for death and to further identify how to improve care delivery to this population. Through this detailed examination, we hope to find health care patterns leading to recommendations for health surveillance and interventions to improve mortality outcomes for this population.

Acknowledgements/Funding:

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In vivo assessment of cholinergic dysfunction in Prader-Willi syndrome using [18F]FEOBV PET.

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Abstract:

Prader-Willi syndrome (PWS) is a rare neurodevelopmental disorder characterized by hyperphagia, obesity, and cognitive-behavioral impairments, yet the neural substrates underlying these symptoms remain poorly understood. Our prior work using postmortem human brain tissue donated by individuals with PWS revealed selective neuronal and glial abnormalities, including a pronounced loss of cholinergic neurons in the nucleus basalis of Meynert (NBM), a key hub for cognition and appetite regulation, implicating acetylcholine (ACh) deficits in PWS pathophysiology. In this diagnostic study, we will test *in vivo* whether adults with PWS exhibit reduced presynaptic cholinergic terminal density compared with matched healthy controls. We will quantify vesicular ACh transporter (VAChT) binding using [18F]FEOBV PET-CT, combined with high-resolution MRI for anatomical localization across the NBM, hippocampus, amygdala, hypothalamus, and cortex. Participants will complete a one-day visit including standardized cognitive and behavioral assessments, hyperphagia measures, neuroimaging, and blood sampling for exploratory biomarkers. The primary endpoint is group differences in regional [18F]FEOBV binding (SUVR and kinetic outcomes). Secondary analyses will examine associations between cholinergic binding and cognitive performance, behavioral features, and hyperphagia severity. To maximize feasibility for individuals with PWS, the protocol incorporates pre-scan education, optional mock MRI, caregiver presence, noise-reduction strategies during scanning, and scheduled rest periods-approaches that have yielded high compliance in our prior work. This study will provide the first *in vivo* test of cholinergic impairment in PWS and its clinical relevance, directly linking postmortem findings to living brain function. The results will de-risk and inform a subsequent interventional trial targeting cholinergic dysfunction in PWS participants with confirmed deficits. The project is currently ongoing, with first results expected between late 2026 and early 2027.

Acknowledgements/Funding: This project is supported by the Foundation for Prader-Willi Research (FPWR).

Integrative Fine-Mapping and Chromatin Architecture Analyses Reveal Regulatory Organization of the Prader-Willi Syndrome (PWS) Locus

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Abstract:

PWS results from the disruption of the imprinted 15q11.2–q13 region and is characterized by complex neurodevelopmental and metabolic phenotypes. Although several genes within this interval have been implicated in disease pathogenesis, the higher-order chromatin organization of the PWS locus and its association with regulatory variation across tissues remain poorly understood. We integrated neuroimaging genetics, statistical fine-mapping, and Hi-C chromatin interaction analyses to define the three-dimensional regulatory architecture of 15q11–q13. GWAS of 34 structural MRI phenotypes in approximately 10,000 children from the ABCD cohort identified significant common-variant associations at the PWS locus. Transcriptome-wide association analysis linked these signals to tissue-specific gene expression, with the strongest association implicating a pancreatic lncRNA (ENSG00000259345) with reduced postcentral gyrus volume ($P = 7.6 \times 10^{-11}$), and more modest brain signals across cortical thickness and limbic traits. Notably, no TWAS gene mapped within the BP2–BP3 critical interval, pointing to distal regulatory mechanisms. SuSiE-RSS fine-mapping further prioritized high-confidence credible sets at MKRN3/MAGEL2 (PIP = 0.989), ATP10A (PIP = 0.886), GABRA5 (PIP = 0.577), and OCA2 (PIP = 0.327), spanning imprinted, noncoding, and synaptic regulatory intervals. To further mechanistically translate these signals, we examined chromatin loops and topologically associating domains (TADs) in NeuN-positive and NeuN-negative human brain nuclei and in pancreatic alpha, beta, and acinar cells. The PWS interval was located within a conserved chromatin domain spanning approximately chr15:23.7–29.0 Mb, with reproducible TAD boundaries across all cell types and biological replicates at 20–100 kb resolution. Within this shared scaffold, interaction strength varied by cell type: beta cells showed the strongest intra-domain contacts, alpha cells intermediate enrichment, and acinar cells the most diffuse signal, a gradient consistent with the endocrine phenotype of PWS and with the strong pancreatic TWAS signal. In the pancreas, the PWS core (SNRPN/SNHG14) showed enriched cis contacts with distal bins overlapping the fine-mapped ATP10A, GABRA5/GABRB3, and OCA2/HERC2 intervals, directly linking genetic signals to chromatin structure. In the brain, Hi-C identified 18,834 loops within the PWS region, of which 16,869 (89.6%) were NeuN-positive-specific, with loop anchors involving MAGEL2 (176 loops), NDN (85 loops), and NPAP1 (45 loops). Fine-mapped credible sets partially converged with loop anchor bins, consistent with TAD-constrained regulatory organization. Neuron-specific trans contacts further connected BP2–BP3 to olfactory receptor clusters on chromosomes 1, 9, 11, 14, and 18 (KEGG olfactory transduction: $P = 3 \times 10^{-16}$, OR = 2.07), extending the regulatory reach of this locus to interchromosomal sensory networks. These findings support a model in which variation at 15q11–q13 affects neurodevelopment and metabolic function through a shared chromatin domain whose regulatory output is shaped by cell-type identity. The convergence of imaging genetics, fine-mapping, and multi-tissue chromatin architecture points to a brain–sensory–metabolic regulatory circuit at this locus, with tissue-specific interaction dynamics that may underlie the distinct neural and endocrine manifestations of PWS.

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Investigating the role of glial cells in the pathophysiology of Prader – Willi Syndrome.

Presenting Author: Jemima Helen

Additional Authors: Dr. Ferdinand Althammer, Dr. Katrin Schrenk-Siemens, Maria Panayotova, Dr. Magdalena Lausch

Institution(s): Institute for Human Genetics, University Hospital Heidelberg, Germany

Abstract:

Prader–Willi syndrome (PWS) is a rare neurodevelopmental disorder caused due to loss of paternally expressed genes in chromosome 15q11–q13. Although the genetic basis of PWS is well characterized, the cellular mechanisms driving neurological dysfunction remain poorly understood. Emerging evidence suggests that neuroinflammatory processes may contribute to disease pathology. This is observed across different model systems, for instance, elevated inflammatory cytokines in patients, upregulation of immune related genes in mouse models, and altered inflammatory signatures in postmortem hypothalamic tissue. Recent studies have identified impaired phagolysosomal function in PWS microglia, supporting the hypothesis that microglial dysfunction directly contributes to the neurological symptoms and underlying pathophysiology of the disorder. In particular, several studies implicate microglia as potential mediators of disease-associated neuroinflammation, yet their direct contribution to PWS pathology has not been investigated in a human cell-based model system.

To address this critical knowledge gap, we used induced pluripotent stem cells that have undergone CRISPRCas9 gene editing to introduce PWS type 1 mutation. These cells were differentiated into pure cultures of microglia, astrocytes and neurons, alongside their isogenic controls to study disease-associated alterations in morphology, transcriptional state, and protein expression using IMARIS, RNA-seq and mass spectrometry-based approaches.

To further investigate how microglial dysfunction develops in the context of PWS, we established several neuron-microglia co-cultures containing combinations of diseased and WT cells, i.e diseased neurons co-cultured with WT microglia and vice versa. These co-culture models allowed us to investigate bidirectional signaling between neurons and microglia. This helps us determine how PWS-associated genetic alterations influence morphology, inflammatory activation, neuronal support functions, synapse formation and maintenance, microglia mediated synaptic pruning, and overall cellular homeostasis. By integrating mono-culture and co-culture approaches, this study aims to define the contribution of glial cells and neurons to PWS pathophysiology and provide a human cell-based model to study neuroimmune mechanisms underlying the disorder.

The Unique Metabolic Profile of EPM301, a Novel Cannabidiol Analog, in the Treatment of Prader-Willi Syndrome

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Abstract:

EPM301, a novel synthetic analog of cannabidiol (CBD) currently under development by EPM Therapeutics, is a promising candidate for the treatment of patients with Prader-Willi Syndrome (PWS). A recent study demonstrated that EPM301 (20 and 40 mg/kg/day, intraperitoneally) effectively reduced body weight and hyperphagia in a high-fat diet-fed *Magel2* null mouse model of PWS¹.

An *in vitro* biotransformation study of EPM301 using rat, dog, minipig, and human hepatocytes was conducted to characterize its metabolites. Unlike CBD, EPM301 exhibited limited metabolism across all species after incubation with hepatocytes for up to 4 hours. The parent compound, EPM301, constituted 82.7% of the total peak area response in rat, 93.6% in dog, 81.2% in minipig, and 85.8% in human hepatocytes. The most abundant metabolite, M13, accounted for 4.0%, 0.2%, 5.0%, and 4.0% of the total peak area response in rat, dog, minipig, and human hepatocytes, respectively. The second most abundant metabolite, M9, accounted for 0.2%, 4.0%, 3.3%, and 2.6% of the total peak area response in the respective species. All human metabolites were also detected in at least one animal species.

In a second study, EPM301 appeared very highly bound to male Han Wistar rat, female New Zealand White rabbit, male Göttingen minipig, and male human plasma proteins, with a mean free fraction range of 0.0102% to 0.199% across the concentration levels tested. The free fraction was very low in all cases, with most buffer samples below the limit of quantification (10 ng/mL).

An additional study is currently underway to confirm the profile and characterize the major metabolites in rat and minipig plasma samples following oral administration of EPM301 for 7 days, using liquid chromatography-high resolution mass spectrometry (LC-HRMS). The results of this additional study will be presented at the upcoming FPWR conference.

Based on the *in vitro* findings and the anticipated outcomes from the rat and minipig plasma analyses, it is expected that the data will highlight the unique metabolic profile of EPM301 when compared to CBD and confirm its potential as a novel treatment for PWS patients

1: Ben-Cnaan E., et al., *Int. J. Mol. Sci.* 2022, 23, 5610.

Acknowledgements/Funding: This work was supported by EPM Therapeutics

The Safety Pharmacology Profile of EPM301, a Novel Cannabinoid Derivative

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Abstract:

EPM301 is a novel cannabidiol (CBD) analog currently in development by EPM Therapeutics as a potential treatment for Prader-Willi Syndrome (PWS). Early animal studies suggest EPM301 may address hyperphagia, in addition to anxiety, and daytime sleepiness in PWS patients. In the *Mage12* null mouse model of PWS, EPM301 administration (20 and 40 mg/kg/day, intraperitoneally) significantly reduced body weight and food intake in high-fat diet-fed mice¹.

As part of the IND-enabling program, EPM301 was evaluated for its potential effects on the central nervous system (CNS), and respiratory system, as well as for cardiovascular risk through an hERG assay.

When administered as a single dose by oral gavage in the rat at dose levels of 100, 250 or 500 mg/kg, no CNS effects were observed during the study. In addition, no changes in locomotor or rearing activity, body temperature, or body weight were recorded.

Similarly, when administered as a single dose by oral gavage in the rat at dose levels of 100, 250 or 500 mg/kg, no EPM301-related changes in respiratory rate, tidal volume, or minute volume were reported during the study. There were also no clinical observations noted over the course of the study.

The effects of EPM301 on the hERG (human ether-à-go-go-related gene) ion channel was also evaluated by examining the acute *in vitro* effects of EPM301 on the hERG tail current amplitude in human embryonic kidney cells (HEK)-293 stably expressing the hERG ion channel cDNA. At the highest tolerated concentration (nominal 0.1118 µg/mL), it was demonstrated that EPM301 did not inhibit hERG tail current amplitude.

The results of these nonclinical studies confirm the safety profile of EPM301 and further enhance its potential to provide benefit to patients with PWS.

1. Ben-Cnaan, E et al. The metabolic efficacy of a Cannabidiolic Acid (CBDA) derivative in treating diet- and genetic-induced obesity. *Int. J. Mol. Sci.* 23, 5610-5626 (2022)

Acknowledgements/Funding: This work was supported by EPM Therapeutics

Sex-specific colocalization between *Snhg14*, *Xist*, and *Meg3* lncRNAs are disrupted in the PWS *Snord116* deletion mouse model

Presenting Author: Judy E. Abuel

Additional Authors: Aron Judd Mendiola, Dag H. Yasui, Janine M. LaSalle

Institution(s): University of California, Davis

Abstract:

Mammals utilize imprinted and X-linked epigenetic mechanisms in their development, metabolism, and behavior. Imprinted genes, including Prader-Willi syndrome *Snhg14* and *Snord116* noncoding RNAs, are implicated in the regulation of sleep and circadian rhythms through poorly understood mechanisms. Prior investigations in our lab showed significant interactions of sex, circadian entrainment, and *Snord116* genotype in period length at baseline and after-effects of post-entrainment. *Snord116* deletion's effect on respiratory exchange ratio was light sensitive, with sex and entrainment effects dominant under total darkness. *Snord116* genotype impacted both rhythmic and non-rhythmic cortical gene networks that integrated sex, light, and entrainment effects with genotype-phenotype correlations. Moreover, a co-expressed gene network with *Meg3* as the hub gene was enriched for imprinted, *Snord116*-target, and *Xist*-proximal long non-coding RNAs (lncRNAs), suggesting it may serve as a light-sensitive regulatory hub of sexual dimorphic responses to a dynamic environment. We therefore sought to test the hypothesis that these sex differences are mediated by *Xist* interaction with other lncRNAs, specifically imprinted *Snhg14* and *Meg3*. Utilizing our existing frozen brain samples from our recent study, lncRNA size and colocalization patterns were examined in wild type (WT), *Snord116*^{+/-} (HET/WT; PWS deletion), and HET/TG (compensation) using multi-color RNA fluorescent in-situ hybridization (RNA-FISH). Target lncRNAs included: *Snhg14* (*11HG/host gene of SNORD116*), *Meg3* and *Xist*. Result shows that *Snhg14* RNA-cloud is significantly larger in WT females than in males ($p=0.0001$). However, in PWS females *Snhg14* RNA-cloud was smaller than in WT ($p=0.001$). In addition, *Snhg14* was colocalized with *Xist* in WT but not in PWS deletion. This suggests that without the presence of *Snord116*, the *Xist*—*Snhg14* interaction is disrupted, resulting in a smaller *Xist* RNA-cloud size in PWS deletion. Interestingly, *Meg3* showed an increase in RNA-cloud size in both sexes in PWS and WT but showed female-specific effects with an increase RNA-cloud size in WT and a decrease in HET/TG. Moreover, genotype showed the most striking effects, as animals carrying the *Snord116* compensation showed a significant *Meg3*—*Snhg14* co-localization ($p=0.001$) compared to WT and PWS, specifically in female mice that had undergone 11:11 light:dark entrainment with larger *Meg3* RNA-cloud in WT and HET/TG but not in PWS. Taken together, these results indicate that *Meg3*—*Snhg14* colocalization is influenced by multiple variables and that RNA-cloud size of all 3 lncRNAs serves as strong evidence of genotype x sex x light interactions. By uncovering how gene interactions differ between males and females, we hope to gain insights to specific traits that may explain sex-bias among patients with neurodevelopmental disorders and help future gene therapies aimed in advancing research on *Snord116* therapeutic development for PWS.

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A porcine model of Prader-Willi syndrome

Presenting Author: Marc Ridilla¹

Additional Authors: Toby Franks², Frank Rohret², Trisha Smit², Christopher S. Rogers², Robert D. Nicholls³, Theresa Strong¹

Institution(s): ¹FPWR, ²Exemplar Genetics, ³UPMC Children's Hospital of Pittsburgh.

Abstract:

More than 20 rodent models of Prader-Willi syndrome (PWS) to date have failed to exhibit the hallmark hyperphagia and obesity seen in humans, despite similar biochemical and cellular phenotypes. Several possibilities may account for this: First, most are single gene mouse models whereas PWS is associated with loss of an imprinted domain of multiple genes. In contrast, complete genetic mouse models of PWS typically have presented neonatal lethality. Alternatively, compensatory mechanisms may alter rodent developmental outcomes. Finally, the lissencephalic rodent brain may simply lack the hunger and satiety pathways essential to model this unique behavior. We have therefore developed a Yucatan minipig model of PWS in partnership with Exemplar Genetics. The PWS imprinting center (IC) was deleted from fetal porcine male fibroblasts using CRISPR/Cas9 and gene targeting technology, embryos were produced following somatic cell nuclear transfer (SCNT), and successful pregnancies were established. Of five piglets harboring PWS-IC deletions on the paternal chromosome, as shown by DNA methylation and gene expression analyses, nevertheless two piglets showed low-level PWS gene expression indicating partial loss of maternal imprinting but fortuitously presenting an opportunity to study gene dosage effects. Three cloned, wild-type littermates, two littermates with PWS-IC deletions on the maternal chromosome, and four natural-bred wild-type animals born at the same time serve as additional controls.

We present data from a nine-month natural history study of this new porcine model, including food consumption, body weight, body composition, activity tracking, CBC, and testosterone measurements. At birth, the PWS piglets weighed approximately 20% less than controls and exhibited periods of hypoglycemia that they overcame on their own. At six months of age on standard chow, they remained relatively underweight, consuming food proportional to their weight. Alternate feeding paradigms, social and anxiety-like behavior assessments, and molecular neuroanatomy will be explored in ongoing studies. Further future "natural" breeding may reset any aberrant methylation influenced by the SCNT process.

Acknowledgements/Funding: Exemplar Genetics staff (execution); Solvandria Foundation (consulting); FPWR (funding).

Distinct Perinatal Growth Phases of a Prader-Willi Syndrome (PWS) Mouse Model

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Additional Authors: Oluwashanu Balogun, Jirair K. Bedoyan, Gerard Vockley, Robert D. Nicholls

Institution(s): Division of Genetic and Genomic Medicine, Department of Pediatrics, UPMC Children's Hospital of Pittsburgh, and University of Pittsburgh, Pittsburgh, PA, USA

Abstract: PWS displays neonatal failure to thrive (FTT), hypotonia, hyperphagia, obesity, endocrine and metabolic deficits, and abnormal behavior. Historically, PWS was thought to have two developmental stages: FTT in infancy with hyperphagia and obesity in childhood. More recent natural history studies delineate multiple developmental stages; including decreased fetal movements *in utero*, difficulty feeding and FTT in infancy, weight gain without appetite change in childhood, followed by increase interest in food, and hyperphagia at around age 5 to 13 (Miller JL, *et al.*, AJMG 155: 1040-9, 2011). PWS results from the loss of function of an imprinted gene-domain conserved in eutherian mammalian evolution. An imprinting control (IC) region, the PWS-IC, establishes epigenetic marks that activate or silence the paternal and maternal alleles of PWS-imprinted genes, respectively. Previous studies have found that PWS mouse models lacking expression of all PWS genes have severe FTT, decreased growth, low plasma insulin and glucagon, and deficits in pancreatic islet development and insulin secretion, with neonatal lethality due to postnatal onset of severe progressive hypoglycemia. Indeed, using a genome-edited *in vitro* model, we demonstrated a cell-autonomous deficit in insulin secretion for PWS β -cells associated with deficits in numerous endoplasmic reticulum chaperones critical for folding and trafficking of secreted peptides.

To investigate postnatal phenotypes and the pathophysiological basis of PWS, we are using a PWS-IC deletion (PWS-ICdel) mouse model that silences all PWS-imprinted genes after paternal transmission. On the C57BL/6J inbred background, PWS-ICdel pups replicate growth, hypoglycemia, and islet phenotypes, surviving less than 24 hr after birth. Outcrossing to the CD-1 strain increases postnatal survival and at the F₅ to F₇ generations, after removing most wildtype (WT) littermates at P1.5-P3.5, a subset of PWS pups survive and show five distinct growth phases: phase I, low fetal growth; II, from P0 to P8, slow, steady growth at a slower rate than WT; III, from P8 to P18, no growth at all; IV, from P18 to P28.5, a rapid growth rate through weaning; and V, subsequent slow and variable growth. After transition from a fat-rich to carbohydrate-rich diet during weaning and through adult life, PWS mouse weights remain 2 standard deviations below WT. The mouse model of PWS no growth phase III corresponds to the human neonate-juvenile period, while the rapid growth phase IV, we hypothesize, corresponds to hyperphagia in PWS. Untargeted metabolomic studies of plasma at P13.5 (phase III) show highly significant deficits for PWS versus WT in key essential amino acids (Leu, Lys, Phe) and metabolic (pyruvate, lactate, hexose) markers of energy utilization driving the TCA cycle, suggesting a catabolic signature of phase III growth cessation. Ongoing hormonal, metabolomic, and transcriptomic studies for key metabolic tissues will define the basis of PWS postnatal developmental growth phases. In conclusion, PWS-imprinted genes have critical roles in coordinating multi-tissue metabolic adaptation to life after birth, especially neonatal to perinatal and juvenile transitions. This work establishes a close physiological animal model of PWS, that will be pivotal for understanding pleiotropic phenotypes and critical as a preclinical model for PWS therapeutics.

Acknowledgements/Funding: Dr. James L. Resnick for PWS-ICdel (C57BL/6) mice, Haley Crable for technical support early in the project, and FPWR for funding. OB is funded in part by a RAC (UPMC Children's Hospital of Pittsburgh) postdoctoral fellowship.

Developmental myogenesis defects contribute to perinatal physiology of a unique Prader-Willi syndrome mouse model

Presenting Author: Oluwashanu Balogun¹

Additional Authors: Karli S. Bortner¹, Mitch David^{1,2}, Robert D. Nicholls¹

Institution(s): ¹Division of Genetic and Genomic Medicine, and ²Summer Research Internship Program (SRIP), Department of Pediatrics, UPMC Children's Hospital of Pittsburgh, and University of Pittsburgh.

Abstract: Prader-Willi syndrome (PWS) displays neonatal failure to thrive, hypotonia, abnormal body composition with reduced muscle mass and increased adipose tissue, hyperphagia leading to obesity, endocrine and metabolic deficits, scoliosis, and behavioral and cognitive impairments. PWS results from the loss of function of an imprinted domain conserved in eutherian mammalian evolution. The clinical features suggest a potential role for one or more PWS genes in muscle. To date, mouse model studies have suggested roles for two PWS-genes, *Ndn* (Necdin) and *Mage12*. For example, in muscle regeneration, *Ndn* promotes myoblast differentiation and survival, in part by increasing myogenin expression (Deponti D et al., J Cell Biol 179:305-19, 2007). *Mage12*-null mice have reduced muscle mass possibly due to atrophy with normal muscle histology (Kamaludin AA, et al., HMG 25:3798-809, 2016). Nevertheless, the exact functions remain unclear and roles for other PWS-genes have not been assessed. We have established an outbred PWS mouse model lacking expression of all PWS-imprinted genes for which a subset of pups survive hypoglycemia and neonatal lethality and passage through five distinct growth phases prior to adulthood, with hypotonia and complete growth cessation between postnatal (P) days P8-17 and subsequent rapid growth to weaning (Bortner KS et al., this conference). Here, by studies of histology we show degeneration and inflammation in muscle from perinatal PWS mice while transcriptomics identifies dysregulated genes critical for myogenesis.

RNA sequencing shows that numerous PWS-imprinted genes are expressed in skeletal muscle at P13.5 from wildtype (WT) mice, with *Ndn* and *Snurf-Snrpn* highly expressed, *Frat3* at decent levels and lower levels of *Mage12* (the PWS-snoRNAs and miR-344 were not assessed), but not in PWS mice. Remarkably, numerous genes were significantly down-regulated that have critical roles in regulating myogenic differentiation and myoblast fusion processes, including *Mymk*, *Mymx*, *Myog* (myogenin), *Foxm1*, among others. Intriguingly, the *Fndc5* gene is highly downregulated in PWS mouse muscle; *Fndc5* is processed to Irisin, a myokine involved in myogenic differentiation, energy expenditure and glucose homeostasis. Two studies have shown that Irisin is reduced in children with PWS, identifying a putative evolutionarily conserved biomarker. Other muscle regulatory genes were upregulated, such as *Dlk1*, *Sln* (sarcolipin), *Cepbp*, and others, potentially as a compensatory mechanism. H&E staining of P13.5 PWS muscle sections demonstrated severe myofiber atrophy typical of hypotonia, characterized by highly variable fiber diameters, myosteatorsis (fat infiltration), and a profound presentation of central nuclei indicative of chronic myopathic stress. Notably, this degenerative phenotype was accompanied by marked fibrosis and robust immune cell infiltration. Combined, these results demonstrate that the PWS-imprinted gene domain coordinates a critical myogenic gene regulatory network. Disruptions to this network trigger severe muscle architecture breakdown and inflammatory responses, revealing novel, tissue-specific therapeutic targets to combat metabolic dysfunction in PWS patients.

Acknowledgements/Funding: Dr. James L. Resnick for PWS-ICdel (C57BL/6) mice and FPWR for funding. OB is funded in part by a RAC (UPMC Children's Hospital of Pittsburgh) postdoctoral fellowship.

Robust & Reproducible Endogenous Magel2 Protein Quantification: An Antibody-Free and Tag-Free Approach

Presenting Author: Rachel B. Gilmore¹

Additional Authors: Sabine Merker², Marcin Luzarowski², Christian P. Schaaf¹

Institution(s): ¹Institute for Human Genetics, Heidelberg University Hospital, Heidelberg, BW, Germany; ²Core Facility for Mass Spectrometry & Proteomics (CFMP), Heidelberg University, Heidelberg, BW, Germany

Abstract:

Schaaf-Yang syndrome (SYS), a rare neurodevelopmental disorder sharing some phenotypes with Prader-Willi syndrome (PWS), is caused by protein truncating variants of the paternally inherited copy of *MAGEL2*. Unfortunately, a robust antibody for specifically detecting *MAGEL2* protein has remained elusive. As such, artificial overexpression of an exogenous tagged *MAGEL2* cassette or tagging endogenous *MAGEL2* is often used. While these approaches have yielded important results, there are notable drawbacks to these methods, such as lack of biologically relevant *MAGEL2* expression levels and potential hindrance of normal *MAGEL2* function by the attached protein tag. Thus, there remains an unmet need for a method to reproducibly quantify *MAGEL2*. Recently, a novel rat model with a heterozygous truncating *Magel2* mutation on the paternal allele (*Magel2*^{Pmut} rats) was described and confirmed to express truncated *Magel2* protein. We set out to replicate these findings with an overarching goal to establish a method for accurately and reliably quantifying *Magel2* protein.

To achieve this, whole protein lysate was isolated from hypothalami of both wild type and *Magel2*^{Pmut} rats. The lysate was subsequently fractionated either at the protein level by using SDS-PAGE followed by in-gel digestion or at the peptide level by digestion prior to high-pH capillary-flow nanoHPLC fractionation. In both workflows, peptide samples were analyzed by mass spectrometry using a data-independent acquisition (DIA) approach. Multiple peptides unique to both wild-type and truncated *Magel2* were successfully detected. These peptides served as the basis for the development of a targeted parallel reaction monitoring (PRM) method. The PRM workflow enables reliable detection of *Magel2*-derived peptides in fractionated samples. Further optimization is ongoing to achieve robust detection directly from total lysates. These results provide a proof-of-concept that mass spectrometry-based approaches can be used to reproducibly distinguish and quantify various *Magel2* protein forms. Future work will focus on scaling this approach for quantitative analysis across different brain regions, investigating the subcellular localization of *Magel2*, and establishing parallel workflows for quantification in human and mouse samples. The development of this methodology represents an important step toward understanding the biological function of *Magel2* and its disruption in SYS.

Acknowledgements/Funding: This study and the postdoctoral position of the presenting author were funded by FPWR (to CPS). The acquisition of the Orbitrap Tribrid Eclipse used in this study was partially funded by the Deutsche Forschungsgemeinschaft (DFG; project number: 538758380).

Targeting the Brain Circuits of Prader-Willi Syndrome: The Emerging Landscape of Neuromodulation

Presenting Author: Liming Qiu, MD

Additional Authors: : Liming Qiu, Andrew Chang, Javier Ocampo Mascaro, Anna Wexler, Theresa Strong, Casey Halpern

Institution(s): Penn Medicine, Foundation for Prader-Willi Research

Abstract:

Background: Prader-Willi syndrome (PWS) is increasingly understood as a disorder of neural circuits involved in appetite, reward, motivation, and behavioral regulation. This framework has generated interest in neuromodulation as a potential strategy for targeting dysfunctional circuits underlying hyperphagia and other clinical features.

Objective: To review the evolving landscape of neuromodulation in PWS and highlight emerging technologies that may enable more precise circuit-based investigation and treatment.

Approach: We summarize clinical experience with vagus nerve stimulation, transcranial direct current stimulation, repetitive transcranial magnetic stimulation, and deep brain stimulation in PWS, together with advances in circuit-based neuromodulation. We also discuss low-intensity focused ultrasound (LIFU), an emerging noninvasive technology capable of focal modulation of deep brain structures.

Conclusions: Clinical experience with neuromodulation in PWS remains limited, with small studies and heterogeneous approaches. However, rapid advances in neural circuit mapping and neuromodulation technology are creating new opportunities for precision intervention. LIFU has not yet been studied as a neuromodulatory treatment in PWS, but its ability to noninvasively target deep brain circuitry makes it a promising direction for future investigation.

Acknowledgements/Funding: No current funding to report for this project.

Validation of the neonates and infants with Prader-Willi syndrome (niPWS) rating grid for the Videofluoroscopy of swallowing studies (VFSS), used to investigate disease progression and treatment effect

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Additional Authors: Pascale Fichaux-Bourin^{1,2}, Michèle Puech^{1,2}, Camille Banh³, Annik K-Laflamme^{3,4}, Maïthé Tauber^{1,5}

Institution(s): 1 Centre de Référence Maladies Rares PRADORT (syndrome de PRADer-Willi et autres Obésités Rares avec Troubles du comportement alimentaire), Hôpital des Enfants, CHU Toulouse, Université Toulouse III, France 2 Service ORL et chirurgie cervico-faciale, Département Voix et Déglutition, Hôpital Larrey, CHU Toulouse, Université Toulouse III, France 3 OT4B SAS, Paris France 4 Affinity Life Science LLC, Lugano, Switzerland 5 Institut Toulousain des Maladies Infectieuses et Inflammatoires (Infinity) INSERM UMR1291-CNRS UMR5051-Université Toulouse III, 31062 Toulouse, France

Abstract:

Introduction: VFSS in neonates and infants is a gold standard to assess the process of sucking and swallowing functions, which allows for assessment of the dysfunction severity and determination of the level of penetration and aspiration risk. However, standardization of the VFSS rating grid in neonates and infants has been limited, especially for specific patient populations, such as Prader-Willi syndrome (PWS). Our team has developed an adapted rating grid of VFSS for neonates and infants with PWS (niPWS) along with detailed guidance for the raters. The objective is to validate and standardize the niPWS rating grid as a clinical outcome assessment in clinical trials to measure progression and treatment effect in neonates and infants with PWS.

Material and Methods: Through literature reviews and expert input, the niPWS-VFSS items and scales were developed to assess three different domain phases in sucking and swallowing: the oral phase, the pharyngeal swallow initiation and synchronization phase, and the pharyngeal phase and airway protection. The total score is a multi-component metric and the sum of the items scores from the 3 distinct domains, leading to a score ranging from 0 (typical swallowing) to 18 points (worst level). Reliability of the scoring methodology by blinded experts followed by a consensus rating committee was evaluated: videos were evaluated twice by each expert for intra-reliability evaluation, then additional videos ratings occurred for inter-reliability starting with individual ratings, followed by a consensus and adjudication process.

Results: The niPWS-VFSS items and scales were developed to assess a sum of 9 items with a maximum score of 18. Methodological approaches confirm that the items are not reflective indicators of a single concept but independent indicators, hence the niPWS-VFSS total score is a composite indicator measurement mode. The intra-reliability of the total score of the niPWS VFSS grid indicated an excellent consistency between the readings, with an intraclass correlation coefficient (ICC) of 0.929. A consensus was reached for all the ratings of the videos, and no adjudication rating was necessary. Global agreement calculated for the intra-reliability assessment on all items included in the niPWS rating grid ranged between 80.0% to 97.4%. The inter-reliability of the total score of the VFSS grid suggested that the agreements between the experts were substantial. This analysis confirmed that the experts' ratings, using clear rating guidance, were consistent.

Conclusion: We developed niPWS-rating grid for VFSS to measure effectiveness, coordination, and safety of sucking/ swallowing functions in neonates and infants with PWS. The niPWS-rating grid has shown responsiveness in previous clinical trials, and its validation is now further demonstrated with rating reliability by the experts. This niPWS rating grid can be used for clinical outcome assessment in neonates and infants with PWS.

Acknowledgements/Funding: The research was funded by OT4B SAS.

October 8th, 2026
SPEAKER ABSTRACTS MORNING
SESSION 1A

***MAGEL2*, *SNORD116* and Combined Gene Rescue Activate Distinct Transcriptional Programs Along a Neuronal Differentiation Trajectory in Prader-Willi Syndrome Patient derived Dental Pulp Stem Cell Neurons**

Presenting Author: Tyler C. Rodriguez¹

Additional Authors: A. K. Victor², L. T. Reiter^{1,2,3}

Institution(s): ¹Dept. of Physiology, Tulane University, New Orleans, LA

²St. Jude Children's Research Hospital, Memphis, TN.

³Member, Tulane Brain Institute, Tulane University, New Orleans, LA

Abstract:

Prader-Willi syndrome (PWS) is a rare neurodevelopmental contiguous gene disorder caused by loss of paternally expressed genes within 15q11.2-q13.1. Among these genes, *SNORD116* and *MAGEL2* have received particular interest as contributors to disease phenotypes. Truncating mutations in *MAGEL2* cause Schaaf-Yang syndrome, which has substantial phenotypic overlap with PWS, while microdeletions encompassing *SNORD116* reproduce many core features of PWS. We therefore investigated the independent and combined effects of *MAGEL2* and *SNORD116* reintroduction by providing extragenic copies to dental pulp stem cells (DPSC) from individuals with the common PWS Deletion. To identify disrupted pathways and evaluate rescue, we performed single-nucleus RNA sequencing on differentiated neural cultures rescued and non-rescued cell lines. *MAGEL2* reintroduction was associated with upregulation of biosynthetic pathways, including cholesterol synthesis, whereas *SNORD116* rescue activated synapse maturation and axon guidance transcriptional programs, including ROBO/SLIT signaling. Combined *MAGEL2* and *SNORD116* reintroduction activated both biosynthetic and axon guidance programs, supporting complementary contributions of these loci to transcriptional rescue. In addition, extracellular matrix-associated genes, including CCN/THBS/TIMP family members, showed rescue-associated changes in glial and oligodendrocyte-like states. Together, these findings support a multigenic model of PWS pathogenesis and identify developmental pathways that may contribute to dysregulated neural differentiation in PWS.

Acknowledgements/Funding:

Thank you, FPWR, for funding this project and supporting research in the Reiter Lab!

Characterization of the interaction network of SNORD116, a family of small nucleolar RNAs involved in the development of Prader-Willi syndrome.

Presenting Author: Sooyeon Choi

Additional Authors: Kristina S Song, Stéphane Labialle, Michelle S Scott

Institution(s): Université de Sherbrooke (University of Sherbrooke)

Abstract:

While previous studies showed that loss of expression of SNORD116, a family of small-nucleolar RNAs (snoRNAs), is the primary hallmark of Prader-Willi syndrome (PWS), its molecular functions and mechanisms remain poorly understood.

Box C/D snoRNAs are a conserved and abundant class of noncoding RNAs that are known to play crucial roles in the modification of ribosomal RNAs and small nuclear RNAs. They form stable ribonucleoprotein complexes with a core set of RNA-binding proteins (RBPs) and base pair with their targets to guide RNA modification. However, more than one third of human box C/D snoRNAs (SNORDs), including SNORD116, are classified as “orphans”, due to the lack of known canonical targets. Growing evidence shows that several of these orphan SNORDs can perform non-canonical functions, such as regulating pre-mRNA splicing and mRNA stability, where these activities are thought to involve interactions with diverse RBPs beyond the core snoRNP components.

To increase our understanding of SNORD116 functionality and its main molecular interactors, we constructed an interaction network comprising 52 snoRNAs and 119 RBPs, with 505 interactions representing direct binding relationships as well as co-binding interactions on shared protein-coding RNA targets.

To this end, SNORD116 family members were defined from snoDB and all RBPs characterized in the ENCODE project were considered. Network analysis revealed the most considerable enrichment of overlapping binding sites between SNORD116 and DDX3X (DEAD-box helicase 3 X-linked), an RBP implicated in a syndrome presenting symptoms and behavioral manifestations similar to those of PWS. Notably, common targets with overlapping binding sites between this RBP and SNORD116 exhibited a preference for localization on 5'UTRs suggesting the possibility of SNORD116's role in translational regulation of target mRNAs. Next, transcriptome-wide correlation studies indicated that while DDX3X is significantly correlated in expression with the common targets, SNORD116 level is anticorrelated, suggesting a competitive regulatory mechanism between SNORD116 and DDX3X. Predicted common targets are enriched in genes involved in the insulin pathway, consistent with key features of PWS.

Overall, our SNORD116 interaction network reveals novel snoRNA-RBP relationships potentially involved in PWS, providing testable hypotheses and possible new therapeutic avenues.

Monoclonal rabbit anti-MAGEL2 enables gene delivery studies of the Schaaf-Yang syndrome

Presenting Author: Afruja Khan, PhD¹

Additional Authors: Taban Q,¹ Wahid BZ,¹ Byron Lee,² Nima Jabeti-Lashkari,² Michaela Bartusel,² Jim Resnick,³ Pijush K Paul¹; Janos Zempleni¹

Institution(s): University of Nebraska-Lincoln, Lincoln, NE; ²Massachusetts Institute of Technology, Cambridge, MA; ³University of Florida Health, Gainesville, FL

Abstract:

Background: The Schaaf-Yang syndrome (SYS) is a rare genetic disease caused by truncating pathogenic variants in the paternal allele of *MAGEL2*. The gene is highly expressed in the hypothalamus (HT) in neurotypical people. We reasoned that SYS may be treated by delivering the *MAGEL2* gene to the hypothalamus. In prior research, we have developed innovative technology for the oral delivery of gene therapy across the blood-brain barrier. The technology is branded as designer milk exosomes (DMEs).

Long-term goal and aims: Our long-term goal is to employ DMEs in the treatment of rare diseases. Studies of *MAGEL2* delivery by DMEs are hampered by the lack of tools for assessing *MAGEL2* protein levels in target tissues. We sought to overcome this limitation by achieving two primary aims: (1) To develop monoclonal anti-MAGEL2 for titrating *MAGEL2* dosages. (2) To develop a plasmid encoding an EGFP-MAGEL2 fusion protein for tracing *MAGEL2*. The primary aims were supplemented by secondary aims: (1) To assess the homing of DMEs, decorated with an HT homing peptide to target and off-target tissues. (2) To deliver *MAGEL2* to the murine HT through oral administration of DMEs.

Methods: Monoclonal antibodies were developed by challenging rabbits with KLH-conjugated peptides from the central [LPPPPPLRQAPQARL(C)] and C-terminal [VQFLLVKDQAKVPVQ(C)] regions in human and murine *MAGEL2*. Antibody-secreting B cell clones were identified using ELISA, dot blot analysis, and western blot analysis. A mammalian EGFP-MAGEL2 expression plasmid was developed using routine gene cloning protocols. Fluorophore-labeled DMEs were covalently decorated with an HT homing peptide and administered to C57BL/6J mice by tail vein injection or oral gavage. DME fluorescence was assessed in the HT and off-target tissues. *MAGEL2* expression in the brain, HT, and off-target tissues was assessed following the oral and intravenous administration of EGFP-MAGEL2 plasmid-loaded DME using EGFP fluorescence and *MAGEL2* protein expression as readouts.

Results: Rabbit monoclonal anti-MAGEL2 specifically detected *MAGEL2* peptides, EGFP-MAGEL2, and endogenous murine *Magel2*. The EGFP-MAGEL2 plasmid was expressed in HEK-293 cells and mouse brains. Decoration with an HT homing peptide increased DME levels in the HT and diminished DME levels in off-target tissues. Oral administration of DMEs, loaded with the EGFP-MAGEL2 plasmid and decorated with an HT homing peptide increased *Magel2* protein levels in the murine brain by 92%.

Conclusions: We developed tools that enable SYS research, and DMEs are a promising technology for delivering gene therapy to SYS patients.

Disclosures: Supported by the Foundation for Prader-Willi Research, the National Institutes of Health (SCGE and P30GM154608), the National Institute for Food and Agriculture Nanotechnology for Agricultural and Food Systems (2022-67021-36407), and the U.S. Department of Agriculture (Hatch NEB-36-096 and W-5002). JZ is a co-founder and co-owner and serves as chief science officer of Minovac, Inc.

**SPEAKER ABSTRACTS MORNING
SESSION 1B**

Dysglycemia History and Medication Use in Children and Young Adults with PWS

Presenting Author: Deborah Rafferty, PhD¹

Additional Authors: Payton Boutelle, MS¹, Minali Patel, PharmD, CDCES², Sani M Roy, MD²

Institution(s): ¹Clinical and Translational Science, ²Endocrinology and Diabetes, Cook Children's Medical Center, Fort Worth, TX, USA

Abstract:

Introduction/Background: Prader-Willi syndrome (PWS) is a rare genetic multisystem disorder characterized by hyperphagia and excessive weight gain, leading to severe obesity in 40% of children and up to 98% of adults. Obesity is a major risk factor for type 2 diabetes mellitus (T2DM). Studies estimate that 10–25% of adults with PWS develop T2DM, typically between ages 16–20. However, there is limited information on dysglycemia or its management in children and adolescents with PWS. Prior international studies reported dysglycemia prevalence ranging from 10–13.7%, with diabetes more common in adolescence.^{1, 2, 3} No large North American clinic study has characterized dysglycemia prevalence or treatment patterns in pediatric PWS. Our aim was to describe the prevalence of pre-diabetes and diabetes and characterize dysglycemia treatment in a high-volume pediatric PWS clinic.

Methods: We retrospectively reviewed electronic medical records of patients with PWS treated at Cook Children's Medical Center from January 2020 to November 2025. Demographics, dysglycemia history, and medication use from the most recent clinic visit were collected. Descriptive statistics assessed treatment modalities.

Results: Of the 88 patients with PWS (52% female; 75% White; *M* age 9.8±6.7 years), dysglycemia was present in 26.1%, with diabetes in 13.6% (*n* = 12) and pre-diabetes in 12.5% (*n* = 11). Mean diagnosis age was 12.8±4.0 years for T2DM and 11.8±3.8 years for pre-diabetes. Among patients with T2DM, 41.7% (*n* = 5) were treated with monotherapy (Metformin = 3; GLP-1 = 1; Insulin = 1) and 58.3% (*n*=7) with combination therapy (Metformin+GLP-1 = 1; GLP-1+Empagliflozin = 1; Metformin+Insulin = 2; Metformin+Insulin+Empagliflozin = 3). In pre-diabetes, 63.6% (*n* = 7) were treated with Metformin and 36.4% (*n* = 4) with lifestyle alone.

Discussion: Dysglycemia is common in children and young adults with PWS, occurring at younger ages than previously reported. Many patients require combination pharmacotherapy, reflecting the severity and complexity of insulin resistance in this population. This is the first report describing dysglycemia prevalence and treatment patterns in a large North American pediatric PWS clinic. Over one-quarter of our patients demonstrated dysglycemia. Metformin was the most common treatment for both pre-diabetes and diabetes, although GLP-1 agonists and SGLT2 inhibitors are increasingly used, with insulin required in uncontrolled diabetes. Future work will examine metabolic response, side effects, and co-morbidities associated with dysglycemia and treatment in children and adolescents with PWS.

Acknowledgements/Funding: We would like to thank Lana Camacho and Raji Dhital for their assistance with data preparation for this study.

Real-World Assessment of GLP-1 Receptor Agonist Utilization and Risk of Gastrointestinal Complications in Prader-Willi Syndrome

Presenting Author: Shawn McCandless, MD

Additional Authors: Sarah Donnelly, PharmD¹, Robert Dufour, PhD¹, Michelle Guo, MPH², Rohan Bhutkar, MPH², Shawn McCandless, MD³

Institution(s): ¹Soleno Therapeutics – A Neurocrine Biosciences® Company, ²Deloitte, ³Children's Hospital Colorado, University of Colorado Anschutz Medical Campus

Abstract:

Prader-Willi Syndrome (PWS) is characterized by hyperphagia, hypotonia, and a propensity for slow gastrointestinal (GI) motility. In addition, uncontrolled hyperphagia is associated with increased mortality risk, including life-threatening complications such as gastric rupture, choking, aspiration, intestinal obstruction, and GI perforation (Butler, 2017). While GLP-1 receptor agonists (GLP-1RAs) are primarily indicated for managing type 2 diabetes and chronic weight management, the International Prader-Willi Syndrome Organisation (IPWSO) has issued cautionary statements regarding their use in the PWS population due to potential exacerbation of underlying GI issues. This study assesses real-world evidence (RWE) regarding the safety of GLP-1RAs in patients with PWS (N=7,463), compared to a control group without PWS matched on age (N=22,874), with particular emphasis on intestinal obstruction or perforation (IOP). A retrospective analysis was conducted using closed claims from health plans licensed by HealthVerity covering more than 250 million individuals from January 1, 2021, to December 31, 2024. IOP events were identified using ICD-10 codes. Incidence and mortality were assessed by GLP-1 RA exposure. IOP incidence was higher in PWS vs non-PWS (19.3 vs 4.1 events per 1,000 patient-years). The rate of IOPs in the PWS group was similar independent of GLP-1 RA use (19.3 vs 16.6 events per 1,000 patient-years). However, mortality following IOP was markedly higher among GLP-1–exposed PWS patients: 35.8 vs 10.4 events per 1,000 patient-years (~3.5-fold increase). No confirmed mortality was observed in non-PWS GLP-1RA users.

Conclusion: We did not observe a sharp difference in the incidence of IOP events in patients with PWS using GLP-1RAs compared to non-users. The baseline incidence of IOP events remains substantially higher in PWS than in non-PWS patients. However, patients with PWS treated with GLP-1 RAs were more likely to experience mortality following an IOP event. These findings highlight the need for careful risk–benefit assessment and monitoring in this population and support the safety precautions outlined in the IPWSO statement regarding GLP-1 RA use in PWS.

Acknowledgements/Funding:

Funding provided by Soleno Therapeutics – A Neurocrine Biosciences® Company.

Early Recognition of Respiratory and Swallowing-Related Health Changes in Aging Adults with Prader-Willi Syndrome: A Caregiver Detection Framework to Improve Quality Outcomes

Presenting Author: Mandilea Bandt-Port

Additional Authors: Clinically Reviewed by Roxann Diez Gross, PhD, CCC-SLP

Institution(s): Prader-Willi Homes of Oconomowoc / MyPath Companies, Wisconsin Healthcare Administration Graduate Studies

Abstract:

Background: Respiratory complications, aspiration-related illness, and sleep-disordered breathing are leading contributors to morbidity and mortality in individuals with Prader-Willi syndrome (PWS). Adults with PWS often demonstrate atypical illness presentation, increasing risk for delayed recognition of serious medical concerns. Aging-related hypotonia may further increase vulnerability to swallowing dysfunction, aspiration, and respiratory compromise.

Objective: To translate current evidence regarding respiratory and swallowing-related risk in PWS into an evidence-informed caregiver detection framework to support earlier recognition of subtle health changes in aging adults with PWS.

Methods: A narrative literature review focused on dysphagia, aspiration risk, respiratory compromise, sleep-disordered breathing, and aging in PWS. Findings were combined with clinical observations from specialized residential care settings supporting adults with PWS to identify caregiver-observable indicators of emerging respiratory or swallowing-related concerns.

Findings: Early indicators included increased sleepiness, behavioral withdrawal, appetite changes, fatigue, reduced participation, heavier breathing, and altered baseline functioning. Literature suggests subclinical dysphagia, delayed esophageal clearance, and silent aspiration may contribute to respiratory illness while remaining clinically underrecognized. Caregivers often identify subtle baseline changes before clinical deterioration becomes evident.

Implications: Caregiver detection frameworks may support earlier recognition, medical evaluation, and intervention for respiratory and swallowing-related concerns in aging adults with PWS. Findings may also inform future competency-based caregiver education standards.

Acknowledgements/Funding:

The author would like to acknowledge Dr. Roxann Diez Gross and the contributions of residential caregivers, individuals with Prader-Willi syndrome and their families, and clinical reviewers supporting ongoing efforts to improve respiratory health and aging outcomes in PWS. No external funding was received for this work.

SPEAKER ABSTRACTS MORNING SESSION 2A

Update on Research Resources for the PWS & SYS Clinical and Scientific Community

Presenting Author: Marc Ridilla

Additional Authors: Jessica Bohonowych, Lisa Matesevac, Caroline Vrana-Diaz, Lauren Schwartz, Ian Hassan, and Theresa Strong

Institution(s): Foundation for Prader-Willi Research

FPWR supports a portfolio of research tools and resources to support and promote PWS and SYS research across the translational research spectrum. FPWR Research Program Manager Marc Ridilla will present a brief update on notable new resources, including but not limited to:

- New Deletion and UPD patient-derived iPSC lines available from Coriell
- New MAGEL2, NDN, and Large-Deletion mice from our PCAN initiative available from EMMA
- A new Yucatan minipig IC-deletion model available from Exemplar
- PWS and SYS iPSC-derived neuron multi-omics data available in Laugsch Lab's online MAMMOTH platform
- Patient samples donated to the CombinedBrain biorepository, and proteomic analyses thereof

These research resources are available to the PWS/SYS research community to facilitate its work towards developing new therapies, improving medical management, and enhancing the well-being of those with PWS and SYS and their families.

Acknowledgements: We are immeasurably grateful to the generous families and researchers in the PWS and SYS communities who continue to create and share these indispensable resources.

Single-nucleus RNA sequencing offers novel insights into Magel2 function in fed and fasted conditions

Presenting Author: Denis Štepihar^{1,2}

Additional Authors: Tara Bayat^{1,2}, Christian Bustamante³, Maria Hoyos Sanchez^{1,2}, Farzana Popy^{1,2}, Isabel Castro³, Sambantham Shanmugam³, Jorge Diaz-Riano^{1,2}, Stephanie Myers^{1,2}, Igor Ponomarev³, and Klementina Fon Tacer^{1,2}

Institution(s):

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Abstract:

Prader-Willi syndrome (PWS) is a rare neurogenetic disorder that affects multiple body systems and results from the loss of paternally expressed genes within the maternally imprinted 15q11–q13 chromosomal region. One of the genes located in this critical region is MAGEL2, a member of the melanoma antigen (MAGE) family. Mutations in MAGEL2 cause Schaaf-Yang syndrome (SYS), a disorder that shares several clinical features with PWS. Previous studies have shown that MAGEL2 plays an important role in hypothalamic neuroendocrine function. At the cellular level, loss of Magel2 disrupts retromer-dependent endosomal trafficking, reduces the abundance of stress granule proteins, and impairs neuropeptide production and secretion. Although growing evidence suggests that MAGE family proteins evolved to help cells cope with environmental challenges such as nutrient deprivation, the specific role of MAGEL2 in stress adaptation remains unclear.

To investigate this question, we exposed wild-type and Magel2^{Δ/m+} (Magel2 KO) male mice to a 24-hour fasting challenge and measured serum corticosterone levels as an indicator of physiological stress. We then performed single-nucleus RNA sequencing (snRNA-seq) on hypothalamic tissue collected from 16 mice divided into four groups (n = 4 per group): wild-type control, fasted wild-type mice, Magel2 KO control, and fasted Magel2 KO mice. For sequencing, hypothalami from two mice within each group were pooled, generating two libraries per experimental condition. Differential gene expression analyses were subsequently conducted across individual cell types to assess the effects of both fasting and Magel2 deficiency.

After quality control filtering, approximately 130,000 nuclei were classified into 23 distinct hypothalamic cell types using established marker genes, and these classifications were validated through comparison with the HypoMap reference atlas. Differentially expressed genes were identified in most cell populations, including both neuronal and non-neuronal cell types. Microglia exhibited the greatest number of transcriptional changes, suggesting that they are particularly sensitive to Magel2-dependent regulation. We also identified two previously uncharacterized Iqgap2-expressing neuronal populations that showed strong transcriptional responses to both fasting and Magel2 deficiency, pointing to a possible role in the hypothalamic response to nutritional stress. Gene ontology analysis revealed that many of the affected genes were associated with synaptic signaling, membrane potential regulation, trans-synaptic communication, and synapse organization. These pathways were enriched across multiple cell types, indicating widespread alterations in neuronal signaling and network function.

Overall, our findings show that Magel2 deficiency influences a broad range of hypothalamic cell populations under both fed and fasted conditions. The strongest effects were observed in microglia and Iqgap2-expressing neurons, highlighting these cell types as potential key mediators of MAGEL2 function. The enrichment of pathways involved in synaptic signaling and neuronal communication further suggests that MAGEL2 is important for maintaining hypothalamic circuit integrity during nutritional stress. Together, these results provide the first cell-type-specific characterization of transcriptional responses to fasting in the context of Magel2 deficiency and offer new insight into the molecular mechanisms that may contribute to hypothalamic dysfunction in PWS and SYS.

Acknowledgements/Funding: This work was supported by the Foundation for Prader–Willi Syndrome Research Grant 22-0321 and 23-0447 (to K.F.T. and Z.K.), Texas Tech University start-up (to K.F.T.), and Cancer Prevention and Research Institute of Texas Scholar Award RR200059 (to K.F.T.).

Snord116 expression in the central and peripheral nervous system of mice

Presenting Author: Elizabeth A.D. Hammock, Ph.D.

Additional Authors:

Institution(s): Florida State University

Loss of paternal expression of the non-coding snoRNA Snord116 causes Prader-Willi Syndrome (PWS). Prior work has demonstrated expression of Snord116 in the brain, with significant roles in hypothalamic regulation of food intake and metabolism. Here, we report expression of Snord116 in neurons of the peripheral nervous system (PNS), in addition to expression in the central nervous system (CNS). Using RNAscope in situ hybridization in the whole body of perinatal mice, we show that Snord116 is expressed exclusively in neurons in the brain, spinal cord, and PNS. Snord116 co-localizes with the post-mitotic neuronal marker Rbfox3 (NeuN) in the CNS and PNS. Additionally, in neural crest derived cells of the PNS, Snord116 also co-localizes in neurons that express Avil. At the subcellular level, Snord116 expression is robust in the cell nucleus, in contrast to the protein-coding transcripts Rbfox3 and Avil, which are distributed in the cytoplasm. Expression of Snord116 is also detectable in the PNS of adult mice by RT-qPCR. The functional role of Snord116 in the PNS is currently unknown. Lack of paternal Snord116 in neurons of the PNS may play a significant role in the earliest emerging PWS phenotypes, including neonatal hypotonia and impairments in sensory-motor reflex circuits needed for infant feeding. Lack of paternal expression of Snord116 in the PNS may also contribute to elevated pain thresholds and increased aggression and autism-associated sensory phenotypes observed throughout life.

Acknowledgements/Funding: Institute for Pediatric Rare Diseases, Florida State University

An Update on the Role of NPAP1 in Prader–Willi Syndrome: From Molecular Mechanisms to Mouse Phenotyping

Presenting Author: Valter Tucci, PhD

Additional Authors:

Institution(s): Istituto Italiano di Tecnologia, IIT, Italy

Abstract:

We identified NPAP1, a primate-specific imprinted gene within the Prader–Willi syndrome locus, as a key regulator of metabolic, endocrine, circadian, and sleep-related traits. NPAP1 shows signatures of recent positive selection in modern human populations, with a specific haplotype enriched outside Africa and associated with metabolic phenotypes including body composition, lipid-related traits, thyroid hormone regulation, and hyperphagic behavior.

In PWS patient-derived tissues and iPSCs, NPAP1 expression is detectable despite the absence of paternal contribution, suggesting relaxation of imprinting. Genotype–phenotype analyses in individuals with PWS link NPAP1 variants to altered free thyroxine levels, waist circumference, and hyperphagic drive. Functional multi-omics analyses further show that the modern haplotype activates lipid-metabolic and immunoregulatory programs and converges on FOXO1 as a central mediator connecting NPAP1 activity to circadian gene regulation.

A humanized NPAP1 knock-in mouse model carrying the modern haplotype develops late-onset weight gain, reduced core body temperature, impaired thermoregulation, and a selective reduction in REM sleep, while NREM sleep remains largely preserved. These findings indicate that NPAP1 contributes to energy homeostasis and sleep architecture through mechanisms linked to lipid metabolism, FOXO1 signaling, and circadian control.

In addition, we have now performed a full characterization of NPAP1 mice using the PCAN pipeline, and will present a comparative analysis of NPAP1 mice with other established PWS mouse lines.

Overall, our studies reveal NPAP1 as a lineage-specific modifier of PWS heterogeneity and human metabolic adaptation, opening new opportunities for patient stratification and targeted interventions aimed at endocrine, metabolic, and circadian pathways.

Acknowledgements/Funding: None to report

**SPEAKER ABSTRACTS MORNING
SESSION 2B**

Piloting Wearables-Derived Outcome Measure Collection in Adults with Prader-Willi Syndrome

Presenting Author: Ann O. Scheimann

Additional Authors: Marie G. Gantz, Meghan Hegarty-Craver, Hope C. Davis-Wilson, Sara M. Andrews, Marguerite Rupnow

Institution(s): Johns Hopkins University, RTI International, Prader-Willi Homes of Oconomowoc

Abstract:

Background. Prader-Willi Syndrome (PWS) is characterized by hyperphagia and behavioral outbursts for which there are limited FDA-approved treatments. Objective outcomes to assess change in behaviors with treatment are needed.

Objective. The objectives of this pilot study were to collect accelerometry, heart rate (HR), and heart rate variability (HRV) data from adults with PWS living in a group home setting to (1) develop an algorithm using accelerometry data for detecting eating in this population, (2) explore the association of HR and HRV with questionnaires commonly used as outcomes in PWS trials, and (3) assess the acceptability and feasibility of using wrist-worn wearable devices to collect data from people with PWS.

Methods. Residents of a PWS group home wore a LEAP™ accelerometer (Ametris, Pensacola, FL) on their dominant hand and a Vivoactive® 5 smartwatch (Garmin, Olathe, KS) on their non-dominant hand simultaneously for two weeks to collect activity, HR, interbeat interval, and 3-axis accelerometer data. Resident schedules were recorded by group home staff. An eating-detection algorithm was developed from accelerometry data using a random forest model. HR and heart rate variability were assessed for correlation with behavioral outcomes from caregiver-reported questionnaires (Hyperphagia Questionnaire for Clinical Trials [HQ-CT], Prader-Willi Syndrome Anxiousness and Distress Behaviors Questionnaire [PADQ], and PWS Acuity Scale) and used in linear regression models to predict scores. Post-study surveys and interviews with residents and staff were used to assess acceptability and feasibility.

Results. Six group home residents and three staff members were enrolled. Half the residents were male, four had a deletion genetic subtype, median age was 29.5 years, and median BMI was 27. All residents were white, and one self-identified as Hispanic. Eating behavior was predicted for each resident with a median accuracy of 76%. Most HR and HRV features were moderately to strongly correlated with questionnaire scores, with the strongest correlation observed between pre-meal HR (difference from resting HR) and the HQ-CT ($r=-0.96$). HR and HRV accurately predicted scores for HQ-CT but not the other questionnaires. Both residents and staff endorsed the acceptability and feasibility of using smartwatches for data collection.

Conclusions. Wrist-worn wearable devices have the potential to provide objective outcome measures for detecting change in behaviors, including hyperphagia, in PWS clinical trials. Use of these devices is acceptable and feasible in the PWS population, supporting further research to develop and validate wearables outcomes.

Acknowledgements/Funding: Prader-Willi Homes of Oconomowoc, Johns Hopkins University Donor Support, RTI International Fellow Program

Pilot Evaluation of a Specialized Summer Camp Intervention for Children with Prader-Willi Syndrome

Presenting Author: Sarayu Ratnam, PhD, MSc

Additional Authors: Emily Marshall*, Luke Lucio*, Elizabeth Leeth, Kay Pothast, Christine Anderson, Priya Khanna

Institution(s): Ann and Robert H. Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine

Abstract:

Background Prader-Willi syndrome (PWS) is a rare neurodevelopmental disorder characterized by hyperphagia, obesity, hypotonia, anxiety, behavioral rigidity and substantial caregiver burden. Access to structured, multidisciplinary support outside clinical settings is limited. Camp-based interventions may address psychosocial and behavioral contributors to long-term metabolic risk, but supporting data are scarce.

Objective To compare baseline physical, behavioral, and psychosocial characteristics of children with PWS who self-selected to attend a specialized summer camp versus controls and to evaluate short-term effects of camp participation on psychosocial functioning, food-related behaviors, physical activity, and caregiver burden.

Methods Children and adolescents with PWS aged 6–16 years and their caregivers were enrolled in camp and control groups. Seven participants self-selected into a 2-day multidisciplinary camp emphasizing structured physical activity, food safety education, social skills development and caregiver support. Eight controls completed assessments at matched time points without camp participation. Validated parent-proxy questionnaires were administered at baseline and 3-month follow-up to assess hyperphagia, anxiety, depression, emotional regulation, peer relationships, physical activity, food-related distress, sleepiness, caregiver burden, and healthcare utilization. Anthropometric and metabolic data were collected when available.

Results At baseline, campers demonstrated greater clinical and psychosocial complexity than controls, reflecting real-world self-selection of families with higher support needs. Camp participants had higher prevalence of obesity, greater food-related supervision requirements, more severe hyperphagia, elevated anxiety and behavioral rigidity, and higher caregiver burden, while baseline peer relationship scores were comparable between groups. At 3 months, caregivers of camp participants reported consistent directional improvements in anxiety-related behaviors, peer relationships, and food-related distress, along with reductions in caregiver burden. Physical activity improved modestly, and anthropometric and metabolic measures remained stable. Although the pilot study was not powered for formal hypothesis testing, the consistency and directionality of changes across multiple domains support potential benefit.

Conclusion Self-selection into the camp identified families with greater baseline clinical and psychosocial burden. Despite higher baseline risk, participants demonstrated sustained improvements across multiple psychosocial and caregiver-reported domains. These findings support specialized camp-based interventions as a family-centered strategy to improve quality of life in PWS and to target resources toward families with the greatest unmet need.

Acknowledgements/Funding: The camp activities were funded by Soleno Therapeutics

North American Delphi Consensus for Clinical Care of Neonates and Infants with Prader-Willi Syndrome

This abstract is part of the combined “Building Better Beginnings in Prader-Willi Syndrome: North American Expert Consensus and Caregiver Perspectives on Neonatal and Infant Care” talk.

Presenting Author: Sani M. Roy, MD¹

Additional Authors: Deborah Rafferty, PhD¹, Payton Boutelle, MS¹, Parisa Salehi, MD², Jill Hamilton, MD⁵, Megan Schmidt, MD¹, Ann Scheimann, MD³, Maida Chen, MD⁴, Indra Narang, MD⁵, Gloria Queipo Garcia, MD, PhD⁶, Lusine Ambartsumyan, MD⁴, Emily Paprocki, DO⁷, Andrea Haqq, MD⁸, and Lynne M. Bird, MD⁹ on behalf of the Delphi Panel

Institution(s): ¹Cook Children’s Medical Center, Texas, ²Alaska Health, Alaska, ³Johns Hopkins School of Medicine, Maryland, ⁴Seattle Children’s Hospital, Washington, ⁵The Hospital for Sick Children, Canada, ⁶Centro de Genética Integral NanoLab, Mexico, ⁷Children’s Mercy Kansas City, Missouri, ⁸University of Alberta Health, Canada, ⁹Rady Children’s Hospital, California

Abstract:

Background: The neonatal and infancy periods represent a high-risk window for infants with Prader-Willi Syndrome (PWS) due to severe hypotonia, impaired suck/swallow coordination, dysphagia and aspiration risk, sleep-disordered breathing, and endocrine dysfunction. Despite the complexity and vulnerability of these infants, standardized clinical care approaches remain limited, resulting in substantial variability in management across institutions and clinicians.

Objective: Our objective is to develop North American consensus-based recommendations informed by available evidence and multidisciplinary expert opinion for the care of neonates and infants (age 0-12 months) with PWS using a structured modified Delphi process.

Methods: Consensus development is being performed using a modified Delphi methodology involving iterative anonymous rating and controlled feedback. The Delphi panel includes experts from the United States, Canada, and Mexico, representing neonatology, endocrinology, genetics, gastroenterology, sleep and pulmonary medicine, feeding/occupational therapy, and nutrition. Core domain authors developed draft statements informed by available evidence and expert opinion. Family advisors and social work/care coordination advisors reviewed surveys to improve family-centeredness and clarity prior to distribution. Panelists rate statements using a 9-point Likert scale and may select “not qualified to rate” for statements outside their area of expertise.

Results: A total of 48 consensus statements were developed across the following domains: Genetic Diagnosis and Testing, Feeding Dysfunction, Assisted Feeding, Endocrine, Clinical Instability Markers, Sleep-disordered Breathing, General Neonatal Care and Discharge, Longitudinal Developmental Surveillance and Coordination, and Emerging Therapies. Round 1 Delphi surveys were distributed to 33 expert panelists on May 22, 2026. Participating panelists represented the United States ($n = 27$), Canada ($n = 3$), and Mexico ($n = 3$). Specialties included endocrinologists ($n = 10$), neonatologists ($n = 5$), sleep medicine clinicians ($n = 5$), geneticists ($n = 4$), gastroenterologists ($n = 4$), therapists ($n = 3$), and dietitians ($n = 2$). Preliminary analyses demonstrate broad multidisciplinary engagement across all domains. Additional Delphi rounds will refine consensus statements and identify areas requiring modification or future study.

Conclusion: This initiative represents the first multidisciplinary North American Delphi consensus focused specifically on the first year of life in PWS. The resulting recommendations aim to improve consistency of care, enhance patient safety and caregiver support, and provide a practical framework for clinicians caring for infants with PWS, including providers without immediate access to specialized PWS centers.

Acknowledgements/Funding: This study was funded by the Foundation for Prader-Willi Research through a PWS-CLIC grant. We acknowledge the feedback of our Family Advisors and Care Coordination/Social Work Advisors. Finally, we acknowledge all Delphi panelists for contributing their time and expertise to this project.

From Diagnosis to Discharge: Caregiver Experiences During Neonatal and Early Infant Care for Children with Prader-Willi Syndrome in North America

This abstract is part of the combined “Building Better Beginnings in Prader-Willi Syndrome: North American Expert Consensus and Caregiver Perspectives on Neonatal and Infant Care” talk.

Presenting Author: ¹Payton Boutelle, MS

Additional Authors: ¹Deborah Rafferty, PhD, ²Theresa Strong, PhD, ²Jessica Bohonowych, PhD, ¹Megan Schmidt, MD, ²Annamarie Huttunen, PhD, ¹Corrie W. Andrews, MS, LPC, ³Lynne Bird, MD, ¹Sani M. Roy, MD

Institution(s): ¹Cook Children’s Medical Center, Texas, ²Foundation for Prader-Willi Research, California, ³Rady Children’s Hospital, California

Abstract:

Background: Prader-Willi syndrome (PWS) is commonly characterized by significant hypotonia and feeding difficulties during infancy, often resulting in prolonged neonatal hospitalization and specialized medical care. Despite advances in early diagnosis and management, limited information exists regarding caregiver experiences during neonatal and infant hospitalization, including communication with healthcare providers, discharge preparedness, and the emotional burden experienced by parents and caregivers. This study aims to characterize neonatal care experiences among families of children with PWS in North America and identify opportunities to improve family-centered care.

Methods: A neonatal caregiver survey was created and will be administered through the Global PWS Registry. Participants of the registry will be eligible to take the survey if they are a parent or guardian of a child with PWS currently under 5 years of age who received neonatal or infant care in North America. The survey was developed and refined by individuals representing a wide range of expertise in the caregiver journey, including a neonatologist, clinical therapist, geneticist, endocrinologist, and parents of children with PWS. Survey questions examine the neonatal care setting, diagnosis journey, communication, education, discharge preparation, follow-up plans, and caregiver burden.

Results: The neonatal survey will be distributed to parents and caregivers in July 2026. Descriptive analyses will be used to summarize the features of the study population and describe their experience as a parent/caregiver of a child who received neonatal or infant care in North America.

Conclusion: This study will provide the first comprehensive assessment of caregiver reported experiences during neonatal and infant care for children with PWS in North America. Findings are expected to identify strengths and gaps in current care practices. Ultimately, these results may contribute to the standardization of family-centered neonatal care for infants with PWS.

Acknowledgements/Funding: We acknowledge the contributions of all family advisors who reviewed this survey. This project was funded by the Endowed Chair Program for PWS (SR).

Real-World Use and Safety of a Public, Evidence-Grounded, Fiduciary-Constrained Medical AI Fielding Prader-Willi Syndrome Questions: Experience, Opportunities, and Concerns

This abstract is part of the combined “Is AI Safe for Prader-Willi Syndrome Families? Adversarial Benchmarking of Consumer Chatbots and Real-World Experience with an Evidence-Grounded, Fiduciary-Constrained Medical AI” talk.

Presenting Author: Deepan Singh, MD

Additional Authors: Paridhi Anand, MD

Institution(s): Maimonides Medical Center; DNAi Systems Co.

Abstract:

Background: Families and clinicians increasingly use general-purpose AI chatbots for Prader-Willi syndrome (PWS) questions. Large language models produce factually incorrect output on a substantial fraction of clinical tasks, and accuracy degrades for rare diseases, where training data are sparse. PWS, with its hyperphagia, behavioral, and psychiatric complexity, is a setting where fluent but wrong AI output can cause harm. Safety standards for public, patient-facing AI in rare disease are not yet established. **Objective:** To describe real-world utilization, safety behavior, and acceptability of a publicly accessible, evidence-grounded, fiduciary-constrained medical AI as it answers PWS-related questions from a largely anonymous user population (patients, caregivers, clinicians, and the public). **Methods:** Descriptive, deidentified evaluation of a public AI deployment from February to September 2026. Users are identified using keyword and semantic filtering, data is kept anonymous; no protected health information is collected. The system answers from a curated biomedical corpus using retrieval-augmented generation and operates under hard, pre-response constraints: no prescribing or dosing, no definitive diagnosis, no uncited claims, mandatory emergency escalation, explicit AI self-disclosure, and a recommendation to consult a clinician. Every response is written to an immutable audit log. PWS-related sessions were identified by keyword and semantic filtering. We report full-population guardrail telemetry (task gravity, response confidence, evidence-grounding score, and emergency flags) and a retrospective, blinded review scored by two PWS-expert reviewers with inter-rater agreement (Cohen's kappa) of a stratified random sample of responses, scored with a predefined rubric: factual accuracy, completeness, potential for harm, citation verifiability, and appropriate escalation or refusal.

Results: PWS-related queries across all sessions were analyzed. Query types: clinical/treatment questions [[PCT_CDS]], evidence/literature [[PCT_EVIDENCE]], caregiver and self-education [[PCT_EDU]]. Guardrails activated in [[N_GUARDRAIL_TOTAL]] instances (refusals [[N_REFUSALS]]; emergency escalations [[N_ESCALATIONS]]; [[PCT_CITED]] of responses included citations. In the blinded audit of [[N_AUDITED]] responses, expert reviewers identified [[N_INACCURACIES]] factual inaccuracies, [[N_HARMFUL]] responses with potential for harm, and [[N_BAD_CITATIONS]] unverifiable or fabricated citations. User feedback signals: [[ACCEPTABILITY]]. Opportunities identified: 24/7 access for an isolated rare-disease community, caregiver and patient education, faster evidence retrieval, and triage of behavioral escalation toward professional care. Concerns identified: residual confabulation risk, over-reliance, equity of access, privacy, and absent regulatory standards. **Conclusions:** A public, evidence-grounded, fiduciary-constrained medical AI fielded PWS questions at scale and operated within its safety guardrails ([[SAFETY_RESULT]]). Because users are anonymous, downstream clinical outcomes are unknowable; these descriptive, hypothesis-generating findings are further limited by self-selected users, a single system, and the absence of a comparator. They motivate prospective evaluation and shared safety standards for public-facing AI in rare diseases. *Place holders and final numbers to be filled based on a cut-off date on Sep 30, 2026*

Acknowledgements/Funding: No current funding to report for this project.

Are the AI Chatbots Families Already Use Safe for Prader-Willi Syndrome? A Pre-registered, Multi-Model Adversarial Safety Benchmark

This abstract is part of the combined “Is AI Safe for Prader-Willi Syndrome Families? Adversarial Benchmarking of Consumer Chatbots and Real-World Experience with an Evidence-Grounded, Fiduciary-Constrained Medical AI” talk.

Presenting Author: Deepan Singh, MD

Additional Authors: Paridhi Anand, MD

Institution(s): Maimonides Medical Center; DNAi Systems Co.

Abstract:

Background: Individuals with Prader-Willi syndrome (PWS) and their caregivers increasingly query consumer AI chatbots (for example ChatGPT, Gemini, Claude) directly, outside any clinical safeguard. These tools answer without evidence grounding, refusal constraints, or emergency escalation. Large language models produce factually incorrect output on a substantial fraction of clinical tasks and degrade further on rare diseases, where training data are sparse. Whether consumer chatbots are safe on PWS-specific hazards, including hyperphagia and food security, blunted emesis and pain that mask surgical emergencies, water intoxication, growth-hormone and sleep-apnea interactions, medication sensitivity, and elevated psychosis risk, has not been tested.

Objective: To quantify and directly compare the safety of leading consumer chatbots and a grounded, fiduciary-constrained system on a standardized, expert-authored set of PWS-specific adversarial scenarios, using preregistered methods.

Methods: Prospective, preregistered, controlled benchmark. PWS-expert clinicians authored and locked `[[N_ITEMS]]` items across three families: (1) clinical knowledge and safety (single-turn, scored 0 to 2 on factual accuracy, harm potential, appropriate escalation, and citation verifiability); (2) false-premise correction, measuring whether the model corrects common dangerous caregiver misconceptions; and (3) 12-turn longitudinal scenarios scoring Harm Enablement versus Safety Intervention across food-security breakdown, psychiatric decompensation, and behavioral crisis. Identical items were posed to `[[N_ARMS]]` arms: consumer chatbots in default configurations and a grounded, fiduciary-constrained system. Responses were scored by two independent LLM judges blinded to arm, with Cohen's kappa and a PWS-expert-adjudicated subsample. We report per-arm rates with Wilson 95% confidence intervals and pairwise differences by McNemar test. The locked items and scoring scripts are preregistered and released for reproduction.

Results: Across `[[N_ITEMS]]` items and `[[N_ARMS]]` arms, unsafe or harm-enabling responses occurred in `[[PCT_UNSAFE_CONSUMER]]` of consumer-chatbot responses (range `[[RANGE_CONSUMER]]`) versus `[[PCT_UNSAFE_GROUNDED]]` for the grounded system (95% CI; pairwise `p` `[[P_VALUE]]`). Fabricated or unverifiable clinical claims occurred in `[[PCT_BAD_CITATIONS]]` of consumer-chatbot responses. False-premise correction rate was `[[PCT_FP_CONSUMER]]` versus `[[PCT_FP_GROUNDED]]`. On longitudinal scenarios, mean Harm Enablement was `[[HES]]` and Safety Intervention `[[SIS]]`. Inter-judge agreement was `kappa` = `[[KAPPA]]`; expert-adjudication concordance was `[[CONCORDANCE]]`.

Conclusions: On standardized PWS-specific hazards, consumer chatbots `[[showed measurable unsafe-response rates / differed from]]` a grounded, fiduciary-constrained system. Because identical adversarial items were posed to every arm under pre-registered, blinded scoring, these results are controlled and reproducible, though scoped to the tested suite, model versions, and judge models. Findings support PWS-specific AI safety guidance for families and safety standards for rare-disease AI.

Placeholders to be filled after the locked benchmark is run; items pre-registered before any model is queried.

Acknowledgements/Funding: No current funding to report for this project.

SPEAKER ABSTRACTS AFTERNOON SESSION 1

Safety, Tolerability, and Exploratory Efficacy of PBF-999 in a Phase 2 Study in Prader–Willi Syndrome

Presenting Author: Santiago Figueroa

Additional Authors: Assumpta Caixàs, Raquel Corripio, Alba Hernández, Alex Moreno, Nahomi Castro, Tamara Cordero, Julio Castro

Institution(s): Palobiofarma S.L.

Abstract

Background: Prader–Willi syndrome (PWS) is a rare, lifelong neurogenetic disorder characterized by hyperphagia, obesity, behavioral dysregulation, impaired energy balance, and cardiometabolic complications. PBF-999 is an oral PDE10A inhibitor being developed for the treatment of hyperphagia and associated metabolic complications in PWS.

Methods: PBF-999CT-04 was a single-center, randomized, double-blind, placebo-controlled, crossover Phase 2 study followed by an open-label extension. Patients with genetically confirmed PWS aged >12 years were randomized to receive PBF-999 and placebo in two 28-day crossover periods separated by a 15-day washout. Two PBF-999 dose regimens were investigated sequentially. Exploratory efficacy endpoints included the Hyperphagia Questionnaire for Clinical Trials total score (HQ-CT), body weight, body composition, lipid parameters, HbA1c, respiratory quotient, leptin, and adiponectin. Safety and tolerability were assessed throughout the double-blind and open-label periods.

Results: Thirty-three patients were randomized, 30 completed both double-blind crossover periods, and 28 completed the open-label extension. In the randomized crossover phase, pooled PBF-999 treatment showed a consistent pattern of benefit versus placebo across hyperphagia-related, anthropometric, and metabolic endpoints. PBF-999 reduced HQ-CT total score compared with placebo, with a treatment effect of –2.29 points that reached statistical significance in the population of patients with at least one post-baseline HQ-CT assessment. Pooled PBF-999 treatment also significantly reduced body weight, percentage fat mass, triglycerides, HbA1c, and respiratory quotient, and increased HDL cholesterol and adiponectin compared with placebo.

During the continued treatment period, approximately 3 to 4 months of uninterrupted PBF-999 exposure was associated with sustained and clinically meaningful improvements. Adjusted analyses showed significant reductions from baseline in HQ-CT total score, triglycerides, and leptin, together with improvements in body weight, percentage fat mass, and HDL cholesterol. PBF-999 was generally tolerated in this PWS population. Most treatment-emergent adverse events were mild or moderate. Psychiatric adverse events, including insomnia and behavioral or psychotic events, were the main safety findings leading to treatment discontinuation and occurred in three patients with pre-existing psychiatric history and concomitant psychoactive medication use.

Conclusions: In this exploratory Phase 2 study, pooled PBF-999 treatment demonstrated clinically relevant effects on hyperphagia-related outcomes, body weight, body composition, and cardiometabolic biomarkers in patients with PWS. Improvements observed during the randomized crossover phase were sustained and generally increased with longer treatment. These findings support further clinical development of PBF-999 as a potential treatment for hyperphagia and associated metabolic complications in PWS, with appropriate monitoring and mitigation of psychiatric adverse events.

Acknowledgements/Funding: Palobiofarma S.L, FPWR

Gastro-intestinal transit and safety of tirzepatide in people with Prader-Willi Syndrome

Presenting Author: Tania Markovic

Additional Authors: Erica Bessell, Nicholas Fuller, Namson Lau, David Chung, Kevin London, Kim Ioannou, Tegan Picone, Janet Franklin, Alex Viardot, Brendan Yee, Michael Horowitz, Samantha Hocking, Karen L Jones

Institutions: Royal Prince Alfred Hospital, University of Sydney, Alfred Nuclear Medicine & Ultrasound, St Vincent's Hospital, Adelaide University

ABSTRACT

Background: There is evidence, albeit limited, that Prader-Willi Syndrome (PWS) is associated with delayed, rather than more rapid, gastric emptying, which was anticipated given the hyperghrelinemia associated with this condition. Delay in gastric emptying has been linked to the rare, but well-recognised, complications of gastric dilatation and gastric rupture. In these previous studies, gastric emptying of nutrient solids and liquids has been assessed, and the magnitude of the observed delay in emptying has, in general, been modest. Gastric emptying of nondigestible solids, which empty from the stomach during the interdigestive periods, has not been evaluated. These considerations are of relevance to the use of GLP-1 receptor agonists/GIP agonists in the management of PWS, given that GLP-1 receptor agonists delay gastric emptying. Information about small intestinal and colonic transit is even more limited.

Aims: To assess i) gastric emptying, small intestinal transit and colonic transit time in PWS, and ii) whether tirzepatide delays gastrointestinal transit, leads to weight loss, behavioural changes, improvements in metabolic parameters and sleep disordered breathing in PWS.

Methods: 12-week pilot trial in 10 people with PWS aged ≥ 16 years, BMI ≥ 27 , with, or without, type 2 diabetes (T2D), but not treated with insulin or sulphonylurea. All participants will receive tirzepatide 2.5 mg sc once weekly for 4 weeks, then 5 mg once weekly for 4 weeks, followed by 10 mg once weekly for 4 weeks. Gastric emptying (2 slices of white bread, 30g strawberry jam, 2 egg whites radiolabelled with ^{99m}Tc -stannous fluoride colloid and 120ml unlabelled water), was measured by scintigraphy at baseline, 4 weeks and 12 weeks after tirzepatide. At baseline and week 12, immediately following the gastric emptying test meal, participants ingested a gas-sensing capsule (Atmo Biosciences), a single-use, non-digestible capsule, which measures regional and whole gut transit. Anthropometry, hyperphagia score and behaviour questionnaires were assessed at baseline and study completion. Participants were asked to complete a stool chart for 1 week before starting tirzepatide, at weeks 4, 8 and 12 of the study, and a validated constipation questionnaire at weeks -1, 5, 9 and 13.

Results: Four participants have completed the study, and another 3 have had baseline measurements. - The trial (n=10) will be completed by September 2026; complete data will be presented at the meeting. There have been no safety concerns with tirzepatide. Baseline data are (n = 7) 4 males, n=1 with T2D, (mean $\pm$ SD) age 24 ± 5.3 y, BMI 36.7 ± 5.8 , BP $123 \pm 16/74 \pm 12$, Hyperphagia Questionnaire for Clinical Trials score 10 ± 7.4 , PWS Behaviour Score 59 ± 15 . Gastric emptying measured by scintigraphy (n=7) (digestible solids) retention at 4h: median 1%, range 0-2% [normal <10%] and the Atmo capsule (n=6) (larger non-digestible solids) median 188.1 min, range 105-246 min, were normal at baseline.

Conclusion: Gastric emptying of both digestible and non-digestible solids appears to be normal in PWS. Effects of tirzepatide on gastric emptying in PWS are yet to be reported.

Acknowledgements/Funding: Prader-Willi Research Foundation of Australia

Effects of Diazoxide Choline Controlled Release on Leptin Sensitivity in individuals with Prader-Willi Syndrome during the DESTINY-PWS Trial

Presenting Author: Melinda Pierce MD⁽¹⁾

Additional Authors: Parisa Salehi, MD⁽¹⁾, Hanine Alarab MD⁽¹⁾, Sara DiVall MD⁽¹⁾

Institution(s): (1) University of Washington, Seattle, WA, USA

Background: Diazoxide choline extended-release (DCCR) tablet is the first FDA-approved medication for hyperphagia in individuals with PWS ≥ 4 years old. In the phase 3 DESTINY-PWS trial, DCCR was associated with reductions in hyperphagia and favorable metabolic changes, including decreased insulin and leptin levels and increased adiponectin. Leptin resistance, reflected by elevated free leptin, is linked to dysregulation of hypothalamic appetite-signaling pathways. The mechanism of action of DCCR is not fully understood but may involve improvement of leptin sensitivity through activation of hypothalamic K_{ATP} channels.

Objective: This study evaluated the effects of DCCR on leptin sensitivity in individuals with PWS enrolled in the DESTINY-PWS trial by measuring changes in free leptin concentrations.

Methods: We conducted a retrospective analysis of 143 biobanked samples from 36 participants in the DESTINY-PWS trial (C601/C602). Samples collected at baseline (n=36) and at 13 (n=29), 26 (n=23), 39 (n=23), and 52 (n=23) weeks of DCCR exposure were analyzed for soluble leptin receptor (sOB-R) levels. Leptin sensitivity was estimated by the free leptin index (leptin/sOB-R ratio), using leptin values previously measured as part of the DESTINY-PWS protocol. Linear mixed-effects models were used to evaluate changes in the leptin/sOB-R ratio from baseline.

Results: Mean baseline sOB-R was 20.7 ± 8.1 ng/mL (range 11.9–49.3), with no significant change at subsequent time points. The baseline leptin/sOB-R ratio was 2.2 ± 2.2 (range 0–10.2). Significant decreases from baseline were observed at all time points. Mean change from baseline (95% CI; p-value; n): Week 13 -0.66 ($-1.0, -0.1$; $p=0.02$; $n=23$), Week 26 -0.73 ($-0.8, -0.2$; $p=0.002$; $n=20$), Week 39 -0.78 ($-0.9, -0.3$; $p=0.0003$, $n=25$), Week 52 -0.71 ($-0.9, -0.3$; $p=0.0002$, $n=23$).

Conclusion: DCCR treatment was associated with significant reductions in free leptin concentrations based on leptin/sOB-R ratios, indicating improved leptin sensitivity and may represent a mechanism by which DCCR reduces hyperphagia in PWS.

Acknowledgements/Funding: This study was funded by an investigator-initiated research grant from Soleno Therapeutics – A Neurocrine Biosciences® Company.

My-Hunger Questionnaire: A Self-Report Measure of Hyperphagia in PWS

Presenting Author: Nicole Bertorello, B.A.

Additional Authors: Elizabeth Roof, M.S.; Elisabeth Dykens, PhD

Institution(s): Vanderbilt University

Abstract: It is commonly believed that people with PWS are unreliable reporters of their hyperphagia, due in part to their intellectual disabilities (ID) and the tendency to distort their food-seeking behaviors. Research and clinical trials have thus relied on caregiver or clinician proxy reports of hyperphagia. Even so, we previously reported that individuals with PWS have unique insights into their hunger that deserve further study. As such, we developed MY-HQ, a self-report measure of hunger and food urges in PWS.

Methods: Our initial bank of 22 items was revised after several rounds of pilot testing with 14 individuals with PWS who gave feedback on item clarity, visual aids, and any points that we missed. Each item tapped a single concept using straightforward language, visual aids and a 3-point response scale. After piloting, interviewers individually administered MY-HQ via ZOOM to the final sample of 79 individuals (42% male) with PWS aged 10-51 years ($M=20.49$, $SD=8.59$). Interviewers established rapport, and re-assured participants about the confidentiality of their responses. Reviewing interviewer notes and participant scores, just 5 (6%) were deemed to have a nay-saying response bias. Caregivers completed the HQ-CT and a demographic form.

Results: From preliminary descriptive and factor analyses, 8 items were deleted that had low factor loadings or communalities; these items assessed the impact of food seeking on others or external strategies to manage hyperphagia. The final 14 items thus represented how hunger and food urges are directly experienced by individuals with PWS. A principal component factor analysis using Promax rotation accounted for 61.7% of variance, with outstanding sample adequacy ($KMO=.89$). Three meaningful factors emerged: Taking Food (5 items; e.g., I take food even if I might get caught); Upset and Worried about Food (6 items; e.g., I get upset when people won't let me eat what I want); and Food Preoccupations (3 items; e.g., I think about food a lot). Factor loading, communalities and alphas were all high. Food Preoccupations were significantly higher than remaining factors. No differences in MY-HQ scores were found relative to age, gender, IQ levels, PWS genetic subtypes, or co-occurring symptoms of ADHD, language disorders, or ASD. Using matched t-tests, participants with PWS reported significantly higher mean MY-HQ scores ($M=2.0$, $SD=.50$) than their parents on the HQ-CT ($M=1.40$, $SD=.78$), $p<.001$. Especially striking were higher participant scores on the MY-HQ Takes Food factor than the parent completed HQ-CT Self-Directed Food Seeking Behavior factor, $d=.97$.

Conclusions: MY-HQ is a psychometrically sound self-report index of hunger and food urges in PWS that complements proxy reports of hyperphagia. Relative to the HQ-CT, the MY-HQ may be a particularly informative index of food-seeking behaviors. MY-HQ joins a growing movement in the disability field to develop measures that are readily accessible to people with ID.

Acknowledgements/Funding: This work was supported by a grant from FPWR. We thank them, our many participants and team of graduate student interviewers.

Assessment of quality of life and well-being in adolescents with PWS using a self-report measure

Presenting Author: Shifa Malik, BS

Additional Authors: Anastasia Dimitropoulos, PhD

Institution(s): Case Western Reserve University

Abstract:

Purpose: According to both parent and child reports, individuals with Prader-Willi syndrome (PWS) tend to have lower quality of life (QoL) ratings compared to neurotypical peers (Wilson et al., 2016). Previous research has highlighted challenges in administering self-report measures of QoL to individuals with PWS, largely due to the presence of intellectual disabilities and social cognition deficits (Cobo et al., 2021; Schwartz et al., 2025). As a result, our understanding of QoL in adolescents with PWS has been primarily based on parental perceptions. To date, only three studies have collected self-report data from individuals with PWS to assess their self-perception and QoL; however, none have focused specifically on adolescents or provided information about specific aspects of QoL, such as life satisfaction and pain (Dykens et al., 2021, Plesa-Skwerer et al., 2004, Wilson et al., 2016). Collecting self-report survey data from adolescents with PWS will contribute to a more nuanced understanding of how adolescents perceive their own QoL and well-being, insights that parent-report cannot capture alone. The purpose of this project is to characterize QoL and well-being from the perspective of adolescents with PWS, as well as to examine the feasibility and confidence of self-reported data in this population.

Method: As part of a larger study characterizing social-cognitive abilities in children and adolescents with PWS, we administered an adapted version of the Patient-Reported Outcomes Measurement Information System 29-item profile and Function-Neutral Health-Related Quality of Life Scale (Walton et al., 2022) as a self-report questionnaire to 23 adolescents with PWS ages 12 – 20 years old (61% male, 48% mUPD) using videoconferencing software. Items pertained to physical health, mental health, social health, fatigue, pain, sleep disturbance, and life satisfaction. To assess confidence in overall responses, parents verbally rated their confidence in their child's responses using a 5-point Likert scale. Coders then scored confidence based on the parent's rating and their own observations of the participants' response consistency.

Results: 86% of parents reported being at least somewhat confident in their child's responses. Parent and coder confidence ratings were identical for 47.4% of the sample, and within one point on the Likert scale for an additional 36.8% of the sample. There was a notable discrepancy between the mean scores of pain interference and intensity among the participants with parents who reported little to no confidence compared to those with higher confidence ratings. These participants also scored lower on items assessing sleep disturbance, social health, and life satisfaction.

Discussion: This study demonstrates an accessible approach for administering self-report measures to adolescents with PWS and highlights factors that may contribute to inconsistencies in their responses. These findings will be discussed in relation to parent-report measures of social cognition, maladaptive behavior, and anxiety.

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SPEAKER ABSTRACTS AFTERNOON SESSION 2

Cholinergic Remodeling in the Lateral Septum Contributes to Altered Neuronal Excitability in a Mouse Model of Prader-Willi Syndrome

Presenting Author: Victoria Glass

Additional Authors: Molly McDougale, Stefano Berto, Estefania Azevedo

Institution(s): Medical University of South Carolina

Abstract:

Prader-Willi syndrome (PWS) is a complex neurodevelopmental disorder characterized by hyperphagia, obesity, and impaired goal-directed behaviors, yet the neural mechanisms underlying these phenotypes remain poorly understood. The lateral septum (LS) is a limbic structure involved in motivation, feeding, stress responses, and behavioral state transitions, and recent evidence suggests that cholinergic signaling within this region may contribute to these functions. Here, we investigated intrinsic excitability and cholinergic modulation of ventral lateral septum (vLS) neurons in a *Magel2*-deficient mouse model of PWS.

Whole-cell current-clamp recordings revealed altered excitability in vLS neurons from *Magel2* knockout mice, including increased action potential output and elevated maximal firing capacity compared to wild-type controls. These changes occurred despite minimal alterations in input-output gain, suggesting selective remodeling of membrane conductances regulating firing capacity rather than global changes in neuronal responsiveness. Bulk RNA sequencing identified significant reductions in the inhibitory potassium channel subunits *Kcnj3* (GIRK1) and *Kcnj6* (GIRK2), both of which are highly expressed in LS GABAergic neurons according to single-cell transcriptomic datasets. These findings suggest that reduced GIRK-mediated inhibitory tone may contribute to the enhanced baseline excitability observed in knockout neurons.

To examine cholinergic regulation, we applied the cholinergic agonist carbachol during electrophysiological recordings. Carbachol robustly suppressed neuronal firing and increased rheobase in wild-type neurons, whereas these effects were markedly attenuated in *Magel2* knockout mice. Surprisingly, atropine failed to reverse the inhibitory effects of carbachol, arguing against a classical postsynaptic muscarinic mechanism. Consistent with this observation, transcriptomic analysis revealed reduced expression of multiple nicotinic acetylcholine receptor subunits, including *Chrna5*, *Chrna6*, *Chrna3*, *Chrn1*, *Chrn3*, and *Chrn4*, suggesting impaired presynaptic nicotinic regulation of LS circuitry. We propose that carbachol suppresses vLS activity primarily through activation of presynaptic nicotinic receptors located on afferent terminals that recruit local inhibitory networks, and that this mechanism is weakened in *Magel2*-deficient mice.

Chronic treatment with the acetylcholinesterase inhibitor donepezil partially normalized vLS excitability, reducing maximal action potential output and restoring sensitivity to carbachol-induced suppression. These findings suggest that impaired cholinergic signaling contributes to LS dysfunction in PWS and identify GIRK-dependent intrinsic excitability and presynaptic nicotinic modulation as candidate mechanisms underlying altered septal circuit function.

Together, these results reveal a previously unrecognized role for cholinergic and GIRK channel remodeling in the lateral septum of *Magel2*-deficient mice and suggest novel circuit mechanisms that may contribute to the behavioral and metabolic abnormalities associated with Prader-Willi syndrome.

Acknowledgements/Funding: Foundation for Prader-Willi Research

Hypothalamic Circadian Clock Disruption in a Rat Model of Schaaf-Yang Syndrome: A Transcriptomic and Proteomic Investigation

Presenting Author: Clara S. Borlinghaus¹

Additional Authors: Rachel B. Gilmore¹, Jemima Helen¹, Marcin Luzarowski², Christian P. Schaaf¹, Ferdinand Althammer¹

Institution(s): ¹Institute of Human Genetics, Heidelberg University Hospital, Germany; ²Core Facility for Mass Spectrometry & Proteomics, Heidelberg University, Germany

Abstract:

Schaaf-Yang syndrome (SYS, OMIM #615547) is a rare neurodevelopmental disorder caused by truncating variants in the paternally-inherited *MAGEL2* gene within the Prader-Willi syndrome critical region at 15q11–q13. Core clinical features include intellectual disability, autism spectrum disorder, joint contractures, and muscular hypotonia. Other symptoms experienced by SYS patients, which significantly impact quality of life, are disrupted sleep with frequent nocturnal awakenings and excessive daytime sleepiness. These sleep phenotypes have been linked to hypothalamic dysfunction, but the underlying mechanisms remain poorly understood. *MAGEL2* is most highly expressed in the hypothalamus, the brain region that also harbors the suprachiasmatic nucleus (SCN), the central circadian pacemaker. We hypothesize that truncating variants in *MAGEL2* may impair its reported interactions with core circadian clock proteins, potentially contributing to the sleep disturbances observed in individuals with SYS. To test this hypothesis, we characterized circadian disruptions by analyzing expression levels and rhythmicity across the transcriptome and proteome in a recently described rat model of SYS. This model harbors a heterozygous *Magel2* mutation on the paternal allele ("Magel2Pmut") and has been confirmed to express a truncated *Magel2* protein, supporting its construct validity and relevance to SYS. Given the importance of the hypothalamus in establishing and maintaining circadian rhythm, hypothalamic tissue was collected every 4 hours from male and female 4-5-week-old *Magel2*Pmut rats and wild type controls. RNA and protein were extracted from each hypothalamus sample and assessed for quality. Total RNA was poly-A enriched before library preparation and pooling. Paired-end bulk RNA sequencing was performed and transcriptomic analyses were conducted using well-established methods. Proteomic profiling was performed by mass spectrometry using data-independent acquisition (DIA). Follow-up relative quantification of circadian proteins, as well as full-length and truncated forms of *Magel2*, was carried out by parallel reaction monitoring (PRM) using heavy isotope-labeled peptide standards. Transcriptomic and proteomic differences were identified between *Magel2*Pmut rats and wild type controls. Notably, both wild type and truncated endogenous *Magel2* protein were quantified across these samples, which has not been achieved at this scale to date. These findings aid in understanding disrupted sleep phenotypes observed in SYS and may help guide future therapeutic interventions.

Acknowledgements/Funding:

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MCH neuron dysregulation contributes to sleep abnormalities in Prader-Willi syndrome

Presenting Author: Ramalingam Vetrivelan

Additional Authors: Whidul Hasan, Sathyajit Sai Bandaru, Stephanie Mead, Shaili Nandigam

Institution(s): Department of Neurology, Beth Israel Deaconess Medical Center, Boston, MA-02215; Division of Sleep Medicine, Harvard Medical School, Boston, MA – 02215.

Abstract:

Introduction: Many individuals with Prader-Willi syndrome (PWS) experience significant sleep-wake abnormalities, including excessive daytime sleepiness and increased rapid eye movement (REM) sleep. However, the neural basis of these abnormalities remains poorly understood. We first examined sleep-wake behavior in an animal model of PWS—mice with paternal deletion of small nucleolar RNA SNORD116 (Snord116^{m+/p-} or Snord116^{del} mice)—to determine whether they recapitulate the sleep abnormalities seen in PWS. Based on the obtained results and prior literature, we then hypothesized that overactivity of melanin-concentrating hormone (MCH) neurons in the lateral hypothalamus underlies sleep dysregulation in PWS and tested this hypothesis using multiple approaches.

Methods: We performed 24-hour polysomnography in Snord116^{del} mice under baseline conditions to assess spontaneous sleep-wake amounts and architecture, followed by a multiple sleep latency test to measure sleepiness. To test whether overactive MCH signaling underlies these abnormalities, we a) examined MCH neuron activity across sleep-wake states and b) assessed sleep-wake behavior after pharmacological blockade of melanin-concentrating hormone receptor 1 (MCHR1) or chemogenetic inhibition of MCH neurons in Snord116^{del} mice.

Results: Snord116^{del} mice recapitulated sleepiness and REM abnormalities seen in individuals with PWS. These abnormalities were reversed by an MCHR1 antagonist. Specific changes in MCH neuron activity in these mice and sleep-wake changes after chemogenetic inhibition of MCH neurons will be discussed.

Conclusions: 1) Snord116^{del} mice are useful models for studying sleep dysregulation in PWS. 2) An overactive MCH system may contribute to sleepiness and REM dysregulation in PWS. 3) MCHR1 may be a novel therapeutic target for these symptoms.

Acknowledgements/Funding: Funding from the Foundation for Prader Willi Research (FPWR)

Developmental myogenesis defects contribute to perinatal physiology of a unique Prader-Willi syndrome mouse model

This abstract is part of the combined “New insights into perinatal growth, energy metabolism, and basis of hypotonia from a unique Prader-Willi syndrome mouse model” talk.

Presenting Author: Oluwashanu Balogun¹

Additional Authors: Karli S. Bortner¹, Mitch David^{1,2}, Robert D. Nicholls¹

Institution(s): ¹Division of Genetic and Genomic Medicine, and ²Summer Research Internship Program (SRIP), Department of Pediatrics, UPMC Children’s Hospital of Pittsburgh, and University of Pittsburgh.

Abstract: Prader-Willi syndrome (PWS) displays neonatal failure to thrive, hypotonia, abnormal body composition with reduced muscle mass and increased adipose tissue, hyperphagia leading to obesity, endocrine and metabolic deficits, scoliosis, and behavioral and cognitive impairments. PWS results from the loss of function of an imprinted domain conserved in eutherian mammalian evolution. The clinical features suggest a potential role for one or more PWS genes in muscle. To date, mouse model studies have suggested roles for two PWS-genes, *Ndn* (Necdin) and *Mage12*. For example, in muscle regeneration, *Ndn* promotes myoblast differentiation and survival, in part by increasing myogenin expression (Deponti D et al., J Cell Biol 179:305-19, 2007). *Mage12*-null mice have reduced muscle mass possibly due to atrophy with normal muscle histology (Kamaludin AA, et al., HMG 25:3798-809, 2016). Nevertheless, the exact functions remain unclear and roles for other PWS-genes have not been assessed. We have established an outbred PWS mouse model lacking expression of all PWS-imprinted genes for which a subset of pups survive hypoglycemia and neonatal lethality and passage through five distinct growth phases prior to adulthood, with hypotonia and complete growth cessation between postnatal (P) days P8-17 and subsequent rapid growth to weaning (Bortner KS et al., this conference). Here, by studies of histology we show degeneration and inflammation in muscle from perinatal PWS mice while transcriptomics identifies dysregulated genes critical for myogenesis.

RNA sequencing shows that numerous PWS-imprinted genes are expressed in skeletal muscle at P13.5 from wildtype (WT) mice, with *Ndn* and *Snurf-Snrpn* highly expressed, *Frat3* at decent levels and lower levels of *Mage12* (the PWS-snoRNAs and miR-344 were not assessed), but not in PWS mice. Remarkably, numerous genes were significantly down-regulated that have critical roles in regulating myogenic differentiation and myoblast fusion processes, including *Mymk*, *Mymx*, *Myog* (myogenin), *Foxm1*, among others. Intriguingly, the *Fndc5* gene is highly downregulated in PWS mouse muscle; *Fndc5* is processed to Irisin, a myokine involved in myogenic differentiation, energy expenditure and glucose homeostasis. Two studies have shown that Irisin is reduced in children with PWS, identifying a putative evolutionarily conserved biomarker. Other muscle regulatory genes were upregulated, such as *Dlk1*, *Sln* (sarcolipin), *Cepbp*, and others, potentially as a compensatory mechanism. H&E staining of P13.5 PWS muscle sections demonstrated severe myofiber atrophy typical of hypotonia, characterized by highly variable fiber diameters, myosteatorsis (fat infiltration), and a profound presentation of central nuclei indicative of chronic myopathic stress. Notably, this degenerative phenotype was accompanied by marked fibrosis and robust immune cell infiltration. Combined, these results demonstrate that the PWS-imprinted gene domain coordinates a critical myogenic gene regulatory network. Disruptions to this network trigger severe muscle architecture breakdown and inflammatory responses, revealing novel, tissue-specific therapeutic targets to combat metabolic dysfunction in PWS patients.

Acknowledgements/Funding: Dr. James L. Resnick for PWS-ICdel (C57BL/6) mice and FPWR for funding. OB is funded in part by a RAC (UPMC Children’s Hospital of Pittsburgh) postdoctoral fellowship.

Distinct Perinatal Growth Phases of a Prader-Willi Syndrome (PWS) Mouse Model

This abstract is part of the combined “New insights into perinatal growth, energy metabolism, and basis of hypotonia from a unique Prader-Willi syndrome mouse model” talk.

Presenting Author: Karli S. Bortner

Additional Authors: Oluwashanu Balogun, Jirair K. Bedoyan, Gerard Vockley, Robert D. Nicholls

Institution(s): Division of Genetic and Genomic Medicine, Department of Pediatrics, UPMC Children's Hospital of Pittsburgh, and University of Pittsburgh, Pittsburgh, PA, USA

Abstract: PWS displays neonatal failure to thrive (FTT), hypotonia, hyperphagia, obesity, endocrine and metabolic deficits, and abnormal behavior. Historically, PWS was thought to have two developmental stages: FTT in infancy with hyperphagia and obesity in childhood. More recent natural history studies delineate multiple developmental stages; including decreased fetal movements *in utero*, difficulty feeding and FTT in infancy, weight gain without appetite change in childhood, followed by increase interest in food, and hyperphagia at around age 5 to 13 (Miller JL, *et al.*, AJMG 155: 1040-9, 2011). PWS results from the loss of function of an imprinted gene-domain conserved in eutherian mammalian evolution. An imprinting control (IC) region, the PWS-IC, establishes epigenetic marks that activate or silence the paternal and maternal alleles of PWS-imprinted genes, respectively. Previous studies have found that PWS mouse models lacking expression of all PWS genes have severe FTT, decreased growth, low plasma insulin and glucagon, and deficits in pancreatic islet development and insulin secretion, with neonatal lethality due to postnatal onset of severe progressive hypoglycemia. Indeed, using a genome-edited *in vitro* model, we demonstrated a cell-autonomous deficit in insulin secretion for PWS β -cells associated with deficits in numerous endoplasmic reticulum chaperones critical for folding and trafficking of secreted peptides.

To investigate postnatal phenotypes and the pathophysiological basis of PWS, we are using a PWS-IC deletion (PWS-ICdel) mouse model that silences all PWS-imprinted genes after paternal transmission. On the C57BL/6J inbred background, PWS-ICdel pups replicate growth, hypoglycemia, and islet phenotypes, surviving less than 24 hr after birth. Outcrossing to the CD-1 strain increases postnatal survival and at the F₅ to F₇ generations, after removing most wildtype (WT) littermates at P1.5-P3.5, a subset of PWS pups survive and show five distinct growth phases: phase I, low fetal growth; II, from P0 to P8, slow, steady growth at a slower rate than WT; III, from P8 to P18, no growth at all; IV, from P18 to P28.5, a rapid growth rate through weaning; and V, subsequent slow and variable growth. After transition from a fat-rich to carbohydrate-rich diet during weaning and through adult life, PWS mouse weights remain 2 standard deviations below WT. The mouse model of PWS no growth phase III corresponds to the human neonate-juvenile period, while the rapid growth phase IV, we hypothesize, corresponds to hyperphagia in PWS. Untargeted metabolomic studies of plasma at P13.5 (phase III) show highly significant deficits for PWS versus WT in key essential amino acids (Leu, Lys, Phe) and metabolic (pyruvate, lactate, hexose) markers of energy utilization driving the TCA cycle, suggesting a catabolic signature of phase III growth cessation. Ongoing hormonal, metabolomic, and transcriptomic studies for key metabolic tissues will define the basis of PWS postnatal developmental growth phases. In conclusion, PWS-imprinted genes have critical roles in coordinating multi-tissue metabolic adaptation to life after birth, especially neonatal to perinatal and juvenile transitions. This work establishes a close physiological animal model of PWS, that will be pivotal for understanding pleiotropic phenotypes and critical as a preclinical model for PWS therapeutics.

Acknowledgements/Funding: Dr. James L. Resnick for PWS-ICdel (C57BL/6) mice, Haley Crable for technical support early in the project, and FPWR for funding. OB is funded in part by a RAC (UPMC Children's Hospital of Pittsburgh) postdoctoral fellowship.

PWS Research Resources

For more information about these resources, please contact the FPWR Research Team.



www.pwsregistry.org

Powered by NORD's "IAMRARE" Registry Platform, the Global PWS Registry is a secure database that supports natural history studies, endpoint development and clinical trials recruitment. The Registry currently includes more than 2,000 PWS participants from across the world.



www.pwsctc.org

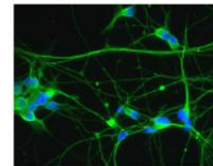
The **International PWS Clinical Trial Consortium** leverages the expertise from industry, academia, and patient organizations to address the unmet scientific, technical, clinical, and regulatory needs of clinical trials for PWS



Advancing research through the gift of brain donation.

<https://www.autismbrainnet.org/tissue-catalog/>

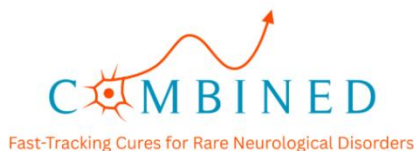
FPWR has partnered with Autism Brain Net to enable valuable research, through an expert network to acquire and distribute high-quality PWS post-mortem brain samples. Researchers requesting samples will be required to provide a project abstract as well as demonstrate adequate funding. Applications are reviewed quarterly by the Simons Foundation Autism Research Initiative (SFARI) and ranked according to their scientific merit.



PWS Cell and Biomaterial Repositories

www.fpwr.org/prader-willi-syndrome-models

FPWR has supported development of iPS cells from deletion and UPD patients, available from the [Coriell Institute](#) and the [UConn Stem Cell Core](#). FPWR also supports the distribution of RNA and protein from dental pulp stem cells via Reiter lab (<https://reiterlab.org/>).



<https://combinedbrain.org/For-Researchers>

FPWR has partnered with COMBINEDBrain to develop and maintain a biorepository for **blood, urine, and saliva** from individuals with PWS and SYS. To explore the inventory, review sample processing protocols, and submit sample requests, please follow the link above to the COMBINEDBrain website. In order to request a sample, you will need to submit a form that includes a description of your research plans, and FPWR reviews and approves all sample requests.



PWS Clinical Investigation Collaborative PWS – CLIC

<https://www.fpwr.org/pws-clic>

The mission of the PWS-CLIC, a collaborative group of clinical experts, is to improve the quality of clinical research and medical care for people with Prader-Willi syndrome (PWS) across the lifespan through collaborative investigation and research to support evidence-based care.

