December 2016 Update: New grants & PWS Research

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FOUNDATION FOR PRADER-WILLI RESEARCH

Today's webinar

- Update on FDA visit – Commissioner's Listening Session
- New Grants for Fall 2016
- Examples of Returns on Investment - Research Advances in PWS

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FDA Visit

Commissioner's Listening Session

- FDA Leadership: Commissioner, Directors of CDER, CBER, CDRH, Orphan Drugs

- Rheumatology, Infectious Disease, Rare Disease

NORD, Everylife, Cystic Fibrosis Foundation, Parent Project Muscular Dystrophy, Cure SMA

Priorities and Concerns for discussion

FDA Visit

Commissioner's Listening Session

- 21st Century Cures Act – signed into law Dec.13, 2016 – will formalize and strengthen the voice of the patient in the drug development process
  - Support modernization of Clinical Trial design
  - Make data sharing required for NIH investigators
  - New funding for Cancer Moonshot, BRAIN Initiative, Precision Medicine Initiative, Regenerative Medicine
- http://blogs.fda.gov/fdavoice/index.php/2016/12/21st-century-cures-act-making-progress-on-shared-goals-for-patients/ (FDA)
- http://www.nejm.org/doi/full/10.1056/NEJMp1615745 (NIH)

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FDA Visit

Commissioner's Listening Session

FPWR Concerns and Priorities:

- Priority*: Improve institutional knowledge of PWS at the FDA, and maintain an ongoing dialog as we accumulate new data on the patient perspective*. (PWS-CTC)
- Priority: *Improve interaction and meaningful engagement with FDA, throughout the drug development process, with particular emphasis on time-sensitive issues*
- Priority: *Work with the FDA to provide additional clarity on the FDA's thinking re: PWS drug development.*
- Concern: *Perception of Conflict of Interest*.

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FDA Visit

Commissioner's Listening Session

Other 'take aways' relevant to rare disease:

- Importance of Patient Registries for understanding natural history and monitoring long term safety; having the registry center on the patient (rather than a clinical study or drug) is ideal
- Challenges for patient groups in navigating the FDA offices and divisions
- Discussion on the use of biomarkers as endpoints in clinical trials
- Conflict of interest challenges (in all directions)

Advancing FPWR's Mission

Mission: ***To eliminate the challenges of PWS through the advancement of research***

General Grants Program: Investigator-Initiated Research

Supports innovative research that will significantly advance the understanding of PWS and/or develop and evaluate new therapeutic interventions for PWS

Directed Research Programs and Research Tools

PWS Research Plan https://www.fpwr.org/5-year-plan/

Directed research: Clinical Care, Fundamental Knowledge, Therapeutic development

Research Tools: Global PWS Registry, PWS Clinical Trials Consortium, Preclinical Animal Network, PWS cellular network, data sharing, biobank

Key accomplishments of the Grant Program

- Supported >$8 million in PWS research, >125 projects, > 75 Investigators
- Supported >100 papers published in the peer-reviewed medical literature
- FPWR support has brought new scientists into the PWS field and helped young investigators get established; broad portfolio of projects
- FPWR has funded the development of key resources for use across the scientific community (new animal models, cellular models, bioinformatics)
- Multiple avenues to promote interaction and collaboration among scientists

http://www.fpwr.org/fpwr-funded-projects/

http://www.fpwr.org/fpwr-research-outcomes/

http://www.fpwr.org/therapeutics-in-development-for-pws/

FOUNDATION FOR PRADER-WILLI RESEARCH

Spring 2016 – 9 grants >$850,000

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

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

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

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

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

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

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

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

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

FOUNDATION FOR PRADER-WILLI RESEARCH

Fall 2016 – 8 grants $745,000

GHRELIN: IS IT DETRIMENTAL, BENEFICIAL, OR INCONSEQUENTIAL IN PRADER-WILLI SYNDROME? (Year 2) Jeffrey Zigman, MD, PhD, University of Texas Southwestern Medical Center.

WAKE PROMOTING EFFECTS OF OXYTOCIN (year 2) Thomas Scammell, MD, Harvard Medical School.

UNDERSTANDING MULTIPLE HORMONE SECRETION DEFICITS IN PRADER-WILLI SYNDROME Robert Nicholls, PhD, University of Pittsburgh Medical Center

RECAPITULATING OBESITY AND HYPERPHAGIA IN NOVEL ADULT-ONSET MOUSE MODELS OF SNORD116 DELETION Giles Yeo, PhD, University of Cambridge.

PHYSIOLOGICAL AND GENETIC DETERMINANTS ON HYPERTHERMIA AND HYPERPHAGIA IN PWS Valter Tucci, PhD, Italian Institute of Technology.

THE MOLECULAR MECHANISM OF SNORD116 ACTION AND POSSIBLE SNORD116 SUBSTITUTION STRATEGIES Stefan Stamm, PhD, University of Kentucky

SMALL MOLECULE ALLOSTERIC MODULATORS OF THE MELANOCOTIN-4 RECEPTOR FOR THE TREATMENT OF PRADER-WILLI SYNDROME Roger Cone, PhD, University of Michigan.

IMPROVING SOCIAL FUNCTIONING IN PRADER-WILLI SYNDROME Elisabeth Dykens, PhD, Vanderbilt University

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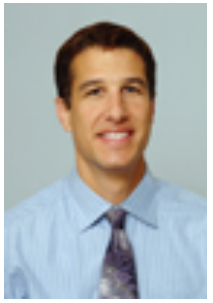
Renewals

GHRELIN: IS IT DETRIMENTAL, BENEFICIAL, OR INCONSEQUENTIAL IN PRADER-WILLI SYNDROME? Jeffrey Zigman, MD, PhD, University of Texas Southwestern Medical Center.

It's critical to understand the role of high levels of ghrelin in PWS. This project will explore whether ghrelin plays a protective role in PWS with regards growth hormone deficiency, hypoglycemia and mental health issues, but a detrimental role with regards to extreme food-seeking behaviors and obesity. This information is key for future therapies designed to target the ghrelin system in PWS.



WAKE PROMOTING EFFECTS OF OXYTOCIN Thomas Scammell, MD, Harvard Medical School.

Dr. Scammell is studying the role of reduced oxytocin/orexin signaling in PWS sleep disorders, using advanced photoactivation techniques. This project will improve our understanding of how hypothalamic dysfunction impairs sleep and wakefulness in PWS, and provide potential targets for intervention.

Watch the update + other insights into PWS & Sleep:
http://research.fpwr.org/blog/sleep-issues-in-pws-presentation-by-dr-thomas-scammell-video

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Improving Mouse Models for Drug Development

RECAPITULATING OBESITY AND HYPERPHAGIA IN NOVEL ADULT-ONSET MOUSE MODELS OF SNORD116 DELETION Giles Yeo, PhD, University of Cambridge.

Rationale

- The Snord116 PWS mouse eats a lot but does not get obese
- It's hard to study weight loss drugs if your mouse never gets obese
- Dr. Yeo's group has initial data suggesting an approach to allow PWS mice to become obese
- Identify therapies that are readily available and could be used in the clinic

PHYSIOLOGICAL AND GENETIC DETERMINANTS ON HYPERTHERMIA AND HYPERPHAGIA IN PWS Valter Tucci, PhD, Italian Institute of Technology

- Dr. Tucci has studied sleep disruptions in the Snord116 mouse model of PWS
- He will investigate the impact of environmental temperature on sleep architecture, food intake, body weight and energy expenditure in Snord116 del mice.
- The goal is to have a robust and well characterized model for drug development.

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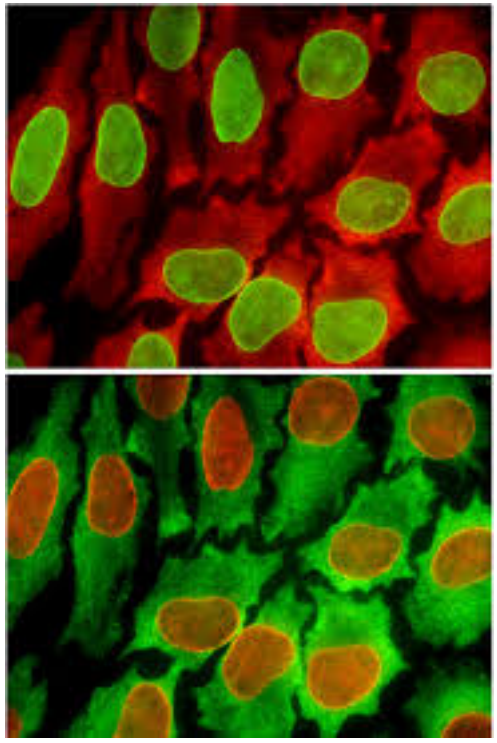
UNDERSTANDING MULTIPLE HORMONE SECRETION DEFICITS IN PRADER-WILLI SYNDROME

Robert Nicholls, PhD, University of Pittsburgh Medical Center



PWS is associated with multiple hormone deficiencies, and there is some evidence of cellular dysfunction in secreting hormones.

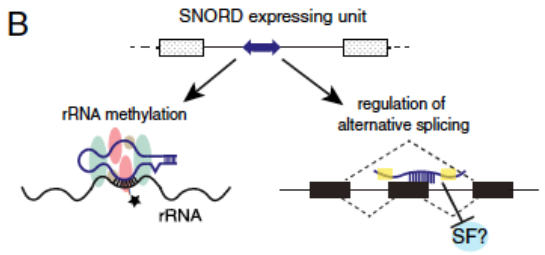
Dr. Nicholls has developed novel PWS cells in which secretory function can be readily visualized and quantified.

This study will advance our understanding of PWS cell dysfunction, and could serve as a platform for drug screening studies.

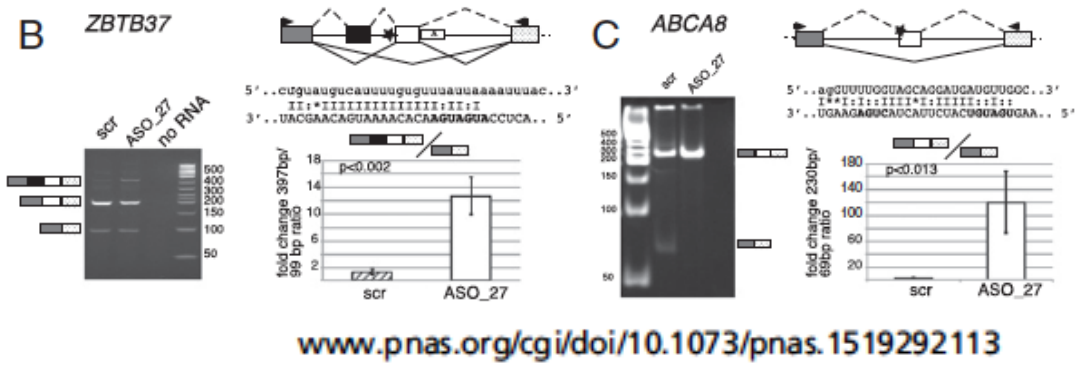
THE MOLECULAR MECHANISM OF SNORD116 ACTION AND POSSIBLE SNORD116 SUBSTITUTION STRATEGIES

Stefan Stamm, PhD, University of Kentucky

Addresses a fundamental question in PWS: What does SNORD116 normally do, and how does loss of SNORD116 alter the mRNAs in a PWS cells, leading to the symptoms of PWS?



SNORD27



www.pnas.org/cgi/doi/10.1073/pnas.1519292113

SNORDs may influence RNA splicing
Define SNORD116 targets

Can you engineer ‘oligonucleotides’ to replace SNORD116 function?

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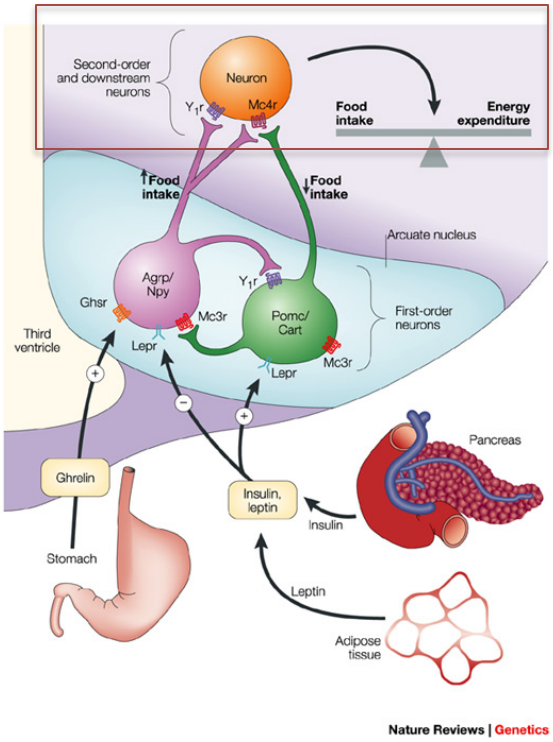
SMALL MOLECULE ALLOSTERIC MODULATORS OF THE MELANOCOTIN-4 RECEPTOR FOR THE TREATMENT OF PRADER-WILLI SYNDROME Roger Cone, PhD, University of Michigan



Novel drugs for obesity, targeting the MC4R pathway

May enhance efficacy of existing drugs (eg, setmelanotide)

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IMPROVING SOCIAL FUNCTIONING IN PRADER-WILLI SYNDROME

Elisabeth Dykens, PhD, Vanderbilt University

Dr. Dykens and Elizabeth Roof at Vanderbilt have a long history of studying the social impact of PWS, and developing ways to improve social interaction and reduce stress in people with PWS and their families.

Need: *Adolescents/young adults struggle to adjust, and it is a vulnerable time for depression, social isolation*

Goals

- Develop a program to improve social skills, perceptions and thinking
- Pilot an online study
- Long term – transferable program

* Funded in partnership with FPWR Canada

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Why we are excited about this grant!

- The study addresses a vulnerable and under-served demographic – young adults with PWS.
- Applies long distance intervention – more feasible
- Will develop a program that can be extended broadly to those with PWS

Potential long-term contributions

- Proof of concept on whether a tele-health intervention can positively impact young adults with PWS
- Program that can be transferred to many settings

2017 – Plans – FPWR grant program

Continue to fund cutting edge PWS research through our investigator-initiated grant program (~30 new grants currently in review)

Continue to facilitate collaboration and interaction among scientists and clinicians in PWS, and continue to get input from families.

Capitalize on advances coming out of the grant program for our translational research efforts.

Advance fundamental knowledge to identify new therapeutic targets; serve as the “farm team” for development of new therapies.

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Your funds at work –
Two recent advances in PWS Research

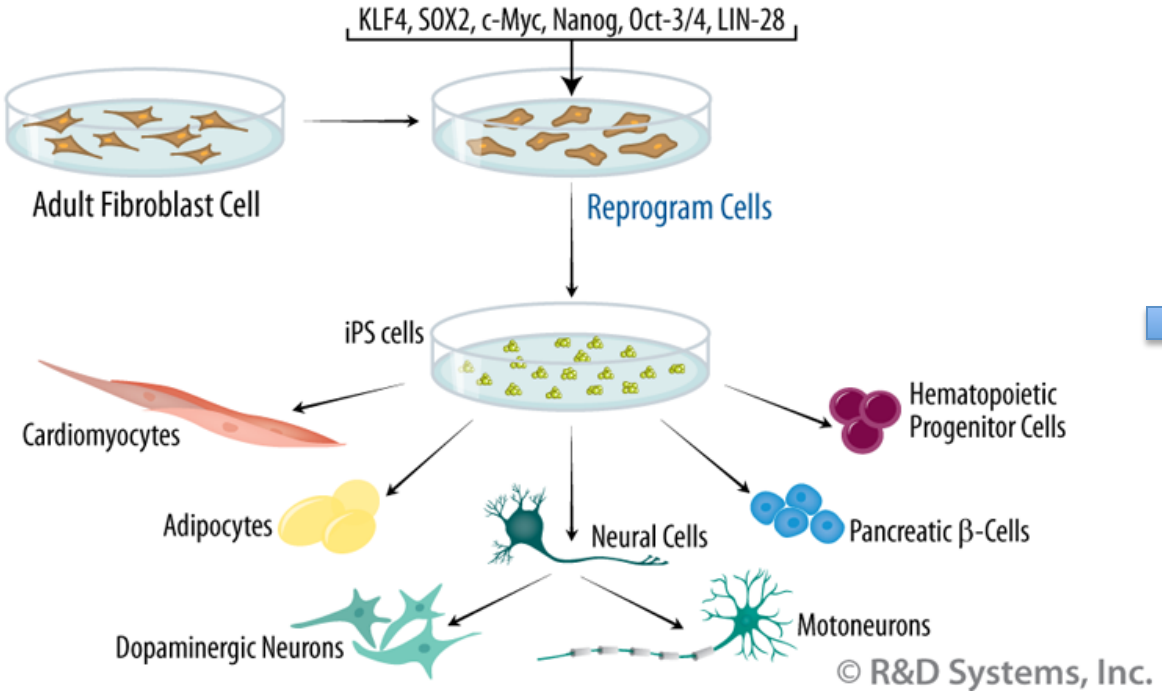
FOUNDATION FOR PRADER-WILLI RESEARCH

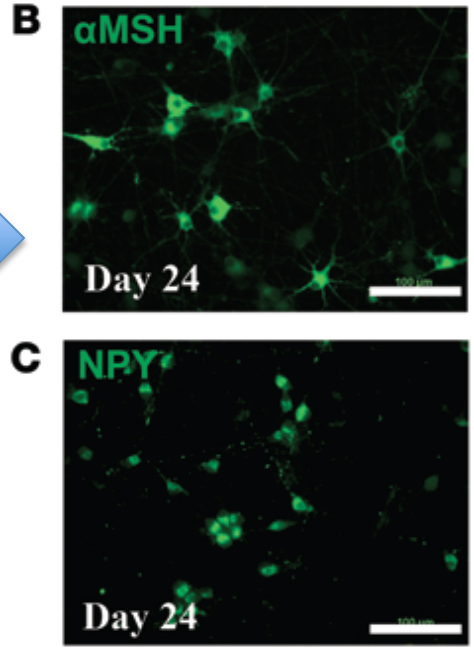
Deficiency in prohormone convertase PC1 impairs prohormone processing in Prader-Willi syndrome

Lisa C. Burnett,[1,2,3] Charles A. LeDuc,[2,3,4] Carlos R. Sulsona,[5] Daniel Paull,[6] Richard Rausch,[2,3] Sanaa Eddiry,[7] Jayne F. Martin Carli,[2,3,8] Michael V. Morabito,[2,3] Alicja A. Skowronski,[1,2,3] Gabriela Hubner,[9] Matthew Zimmer,[6] Liheng Wang,[2,3] Robert Day,[10] Brynn Levy,[11] Ilene Fennoy,[12] Beatrice Dubern,[13] Christine Poitou,[13] Karine Clement,[13] Merlin G. Butler,[14] Michael Rosenbaum,[2,3] Jean Pierre Salles,[7,15] Maithe Tauber,[7,15,16] Daniel J. Driscoll,[5,17] Dieter Egli,[2,3,6] and Rudolph L. Leibel[2,3,4]

The Journal of Clinical Investigation

iPS cells: "Disease in a Dish"





Differentiation of hypothalamic-like neurons from human pluripotent stem cells. J Clin Invest. Feb 2015

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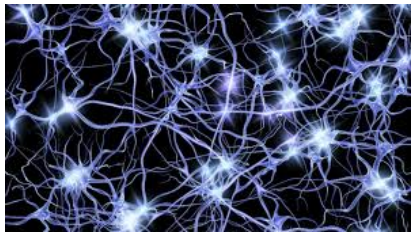
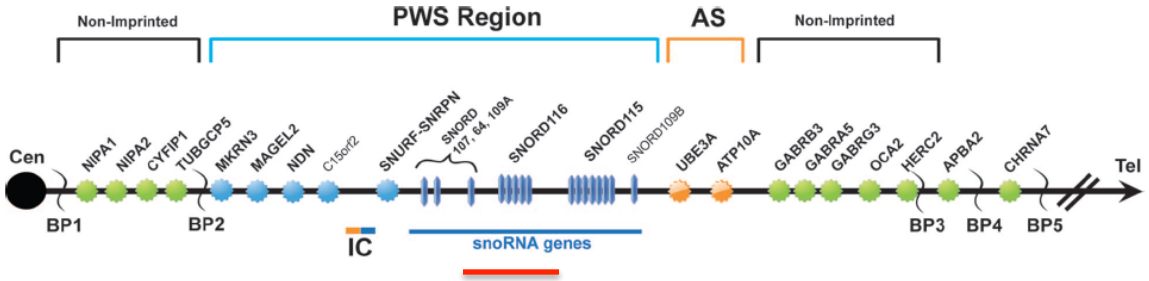
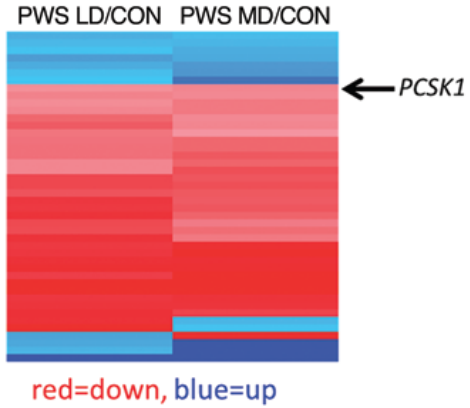
Highly restricted deletion of the SNORD116 region is implicated in Prader–Willi Syndrome

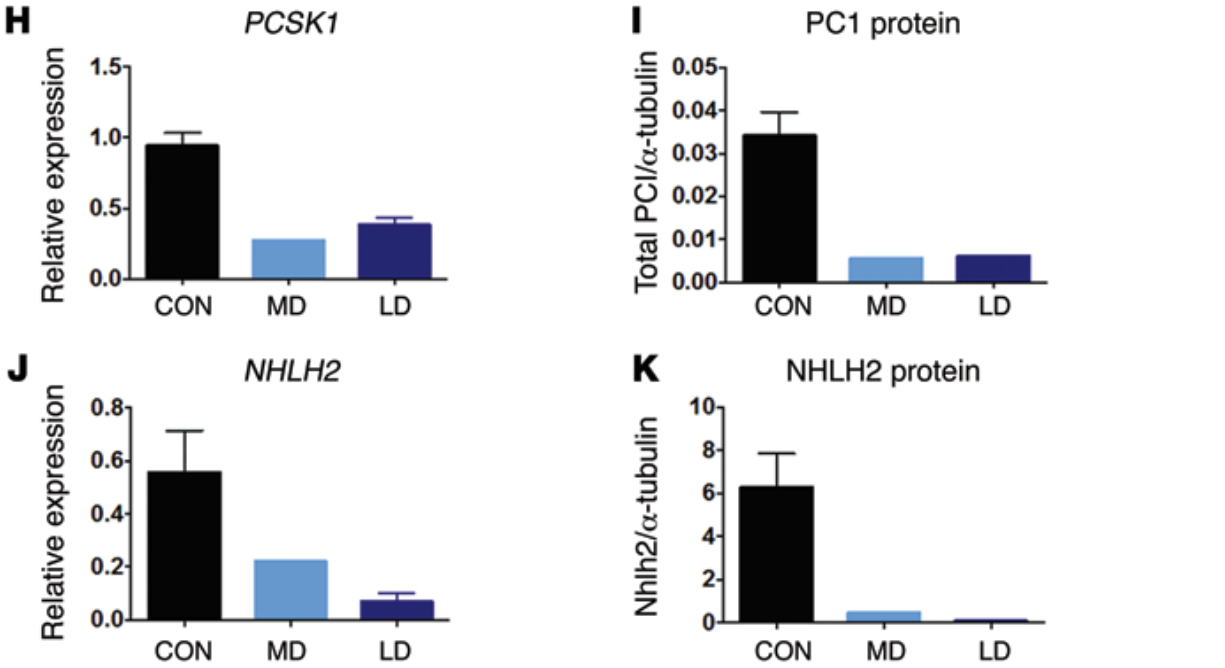
Eric Bieth*[,1,8], Sanaa Eddiry[2,8], Véronique Gaston[1], Françoise Lorenzini[3,4], Alexandre Buffet[1], Françoise Conte Auriol[2], Catherine Molinas[2,4], Dorothée Cailley[5], Caroline Rooryck[5], Benoit Arveiler[5], Jérome Cavaillé[6], Jean Pierre Salles[2,7] and Maïthé Tauber[2,4,7]





What genes have lower or higher expression in PWS compared to control?





https://doi.org/10.1172/JCI88648

Reduced NHLH2 and PC1 are associated with hyperphagia, obesity in mice and humans

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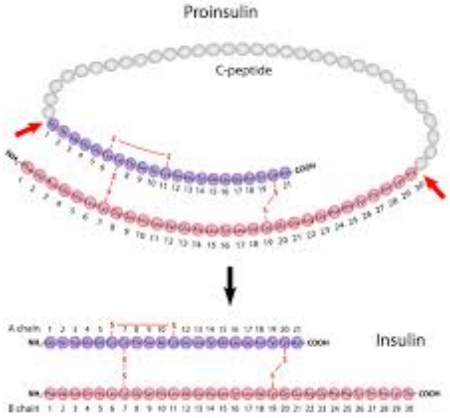
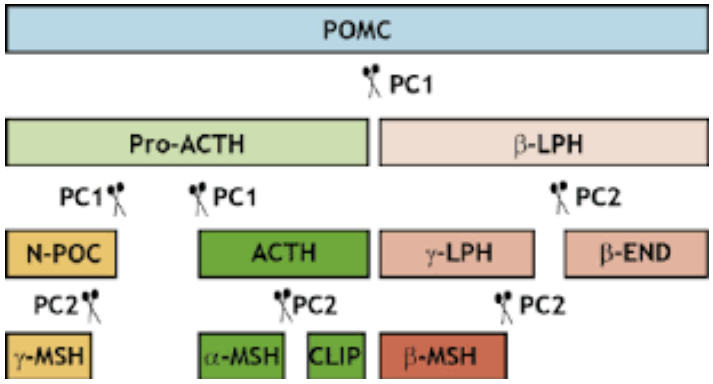
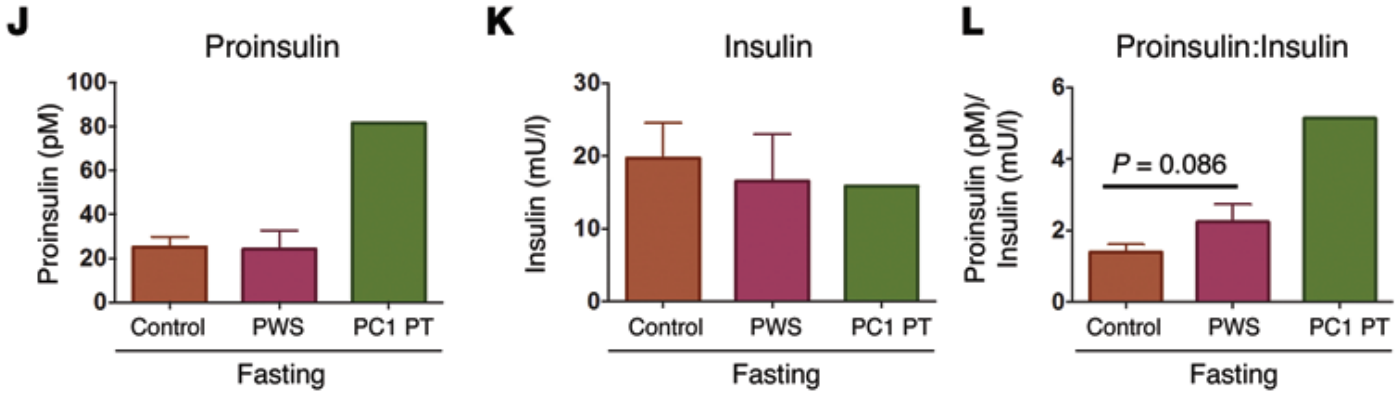
Normal function of PC1:
Cuts a “prohormone” into a hormone





Change in hormone processing compared to normal, more subtle than PC1 deficient patients



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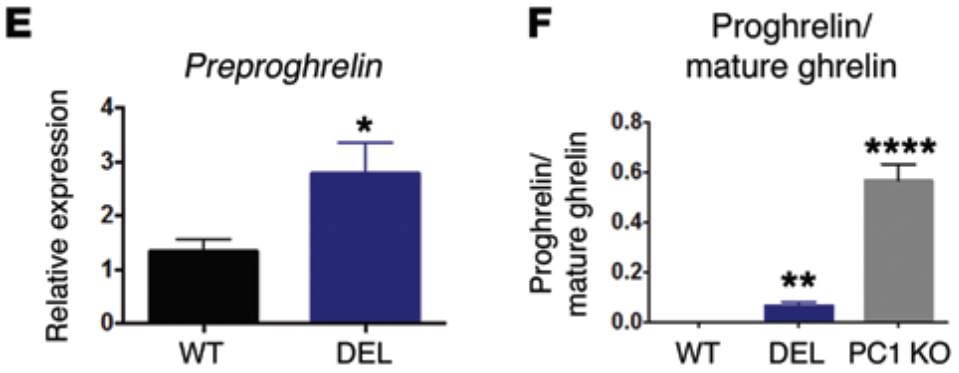
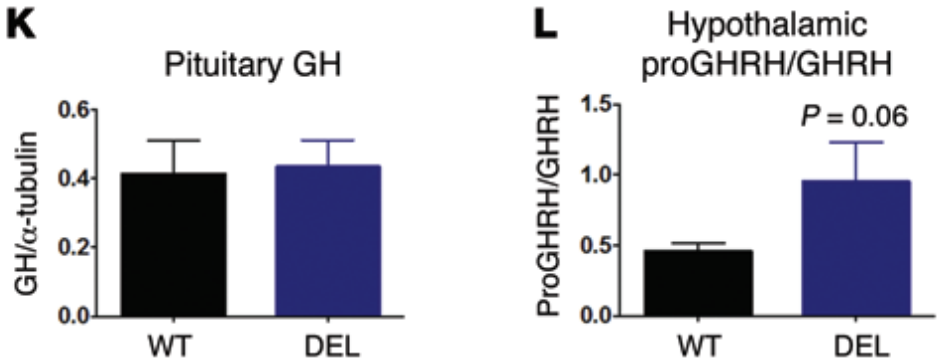


Snord116 deletion mouse



?impaired release of GH? (Nicholls)

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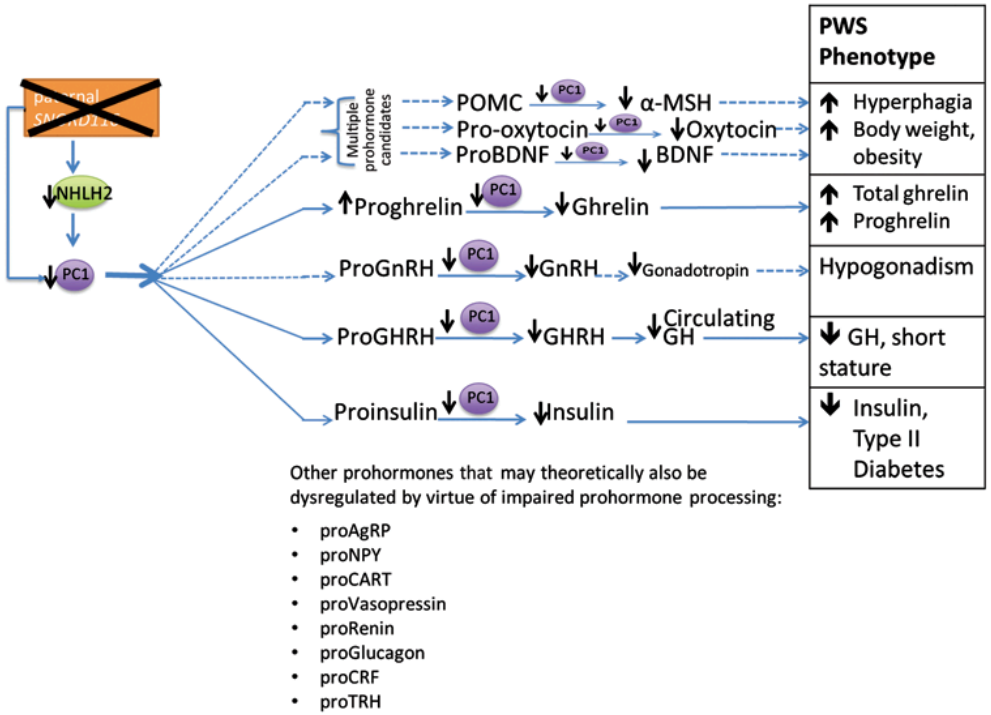

Potential for a global deficiency in fully processed hormones

Many remaining questions:

If NHLH2/ PC1 expression is recovered to normal levels, will many/most of the symptoms associated with PWS improve? (does this pathway account for the major features of PWS, or is it just one of many contributing factors)

How exactly does loss of SNORD116/IPW lead to decreased NHLH2 and PC1? (are there targets further upstream?)

How much do other genes up/down regulated contribute to the PWS symptoms?

What is the best way to restore PC1 expression?

Levo Therapeutics

When, where and how much will expression have to be recovered to make a difference?

FOUNDATION FOR PRADER-WILLI RESEARCH

Targeting the endocannabinoid/CB1 receptor system for treating obesity in Prader–Willi syndrome

Ibrahim Knani [1], Brian J. Earley [2], Shiran Udi [1], Alina Nemirovski [1], Rivka Hadar [1], Asaad Gammal [1], Resat Cinar [2], Harry J. Hirsch [3], Yehuda Pollak [3], Itai Gross [3], Talia Eldar-Geva [4], Daniela P. Reyes-Capo [5], Joan C. Han [5,6,7], Andrea M. Haqq [8], Varda Gross-Tsur [3], Rachel Wevrick [9], Joseph Tam [1,*]

MOLECULAR METABOLISM 5 (2016) 1187–1199
www.molecularmetabolism.com

- Endocannabinoids are important in appetite regulation
- Cannabinoid-1 Receptor (CB1R) blockage looked like a promising target for weight loss (Rimonobant), potentially in PWS
- Access to brain was associated with psychiatric side effects [**Psychiatric adverse effects of rimonobant in adults with Prader Willi syndrome**, Angoulo & colleagues]
- JD5037 – peripheral endocannaboid receptor blocker

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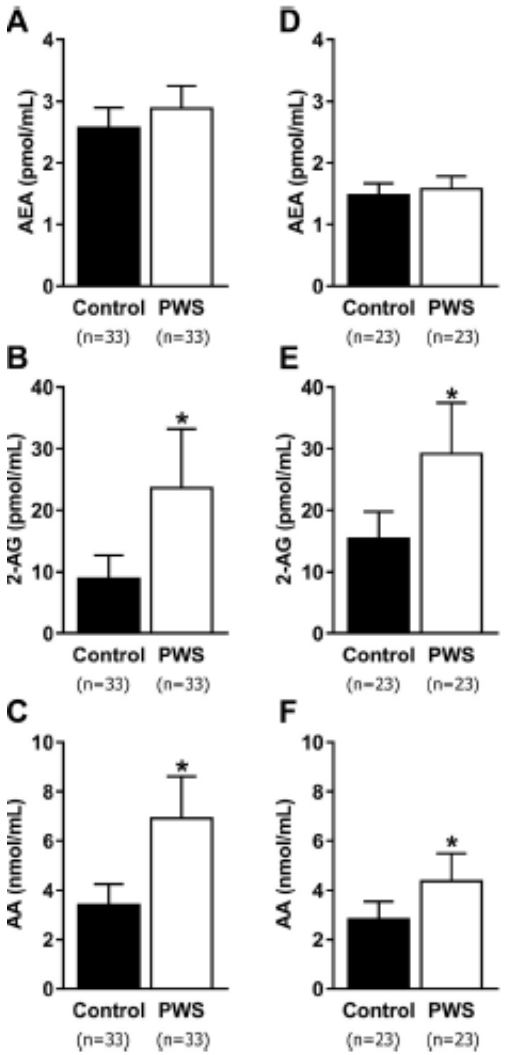
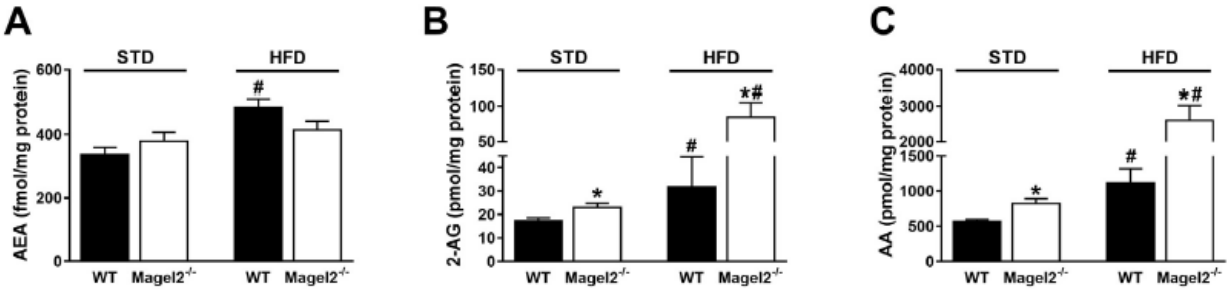


Found eCB “tone” was abnormal in individuals with PWS,
and in a PWS mouse model



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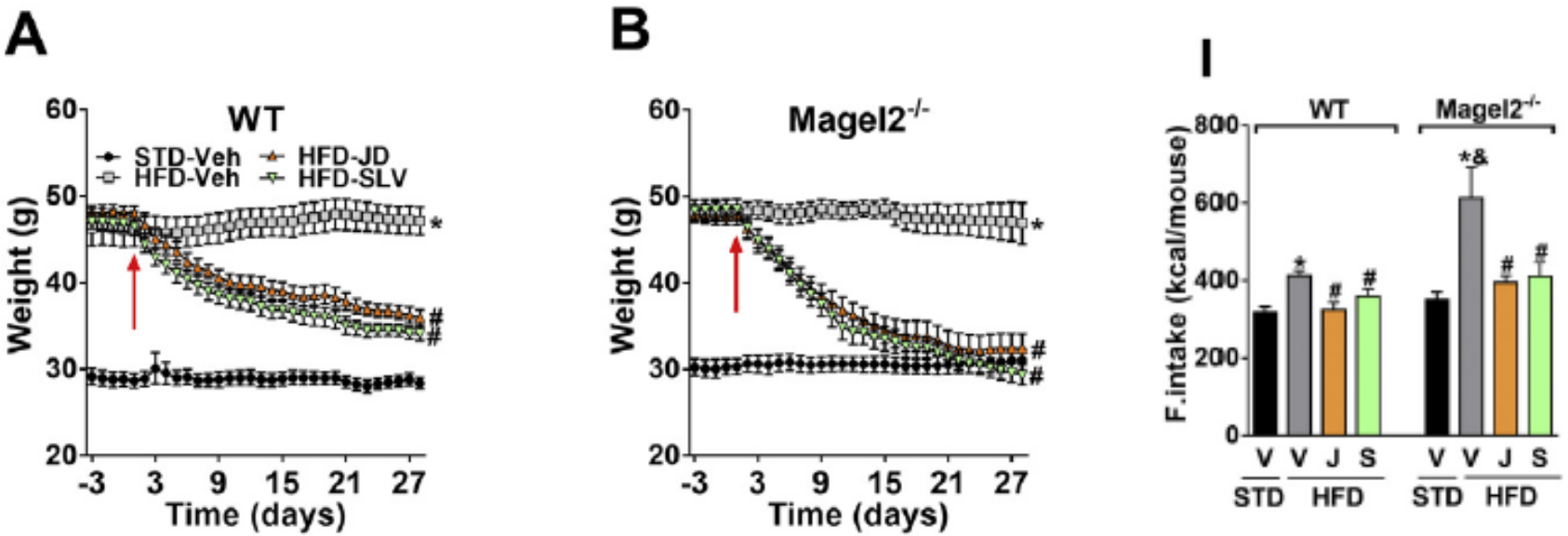

Treating overweight normal or PWS mice with JD5037 effectively reduces weight (fat mass), decreases hyperphagia, and improves metabolic parameters, and energy profile

Provides the rationale for testing JD5037 in PWS

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Opportunities to contribute – please consider participating!

PREDICTORS OF PSYCHOSIS IN PRADER WILLI SYNDROME

Carrie Bearden, PhD, UCLA.

- Early identification of those at highest risk and those showing early warning signs to allow for early intervention
- Goal of preventing or mitigating psychotic illness in PWS – clinical intervention

12+

PLASTIC TASTER: A SWITCHING TRAINING GAME FOR PEOPLE WITH PWS THAT ADAPTS TO INDIVIDUAL NEEDS

Kate Woodcock, Ph.D. Queens University, Belfast)

Goals

- Build upon the software prototype
- Adapt/tailor to individual needs
- Improve ability to handle changes in routines and decrease temper outbursts

5-16

https://www.fpwr.org/category/clinical-trials

GLOBAL PRADER-WILLI SYNDROME REGISTRY

www.pwsregistry.org

- >1,000 enrolled
- Using with ongoing research projects, recruitment
- Working with NORD to expand analytics
- Looking at ways to incorporate real world data
- Sharing data and implementing in PWS research

Natural History Studies for Rare Diseases

Please complete your surveys!

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Thank you!

It takes a village – FPWR partners in 2016:

FPWR- Canada

FPWR UK

Prader-Willi France

PWSA – UK

OSS Hosts

All of our amazing fundraisers and donors !

Advocate reviewers

One SMALL Step for Prader-Willi Syndrome