

# HYPERPHAGIA

The Mechanism The Research The Treatment

2nd International Conference on Hyperphagia October 17-20, 2012  
Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, LA, USA

2<sup>ND</sup> INTERNATIONAL  
CONFERENCE ON  
HYPERPHAGIA

[WWW.HYPERPHAGIA.ORG](http://WWW.HYPERPHAGIA.ORG)

Hunger

GNAWING, RELENTLESS, PERPLEXING.

26<sup>TH</sup> ANNUAL  
PWSA (USA)  
Scientific Day &  
Professional  
Providers Conference

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USA  
PRADER-WILLI  
SYNDROME  
ASSOCIATION | *Still hungry  
for a cure.*

October 17-20, 2012  
Baton Rouge, Louisiana, USA

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**Hunger**, the drive to eat, is a critical factor in the worldwide problem of **Obesity**.

**Hyperphagia** is the extreme unsatisfied drive to consume food.

Hyperphagia is a hallmark characteristic of **Prader-Willi** syndrome and several other disorders.

## Conference Theme

- Expand your understanding of hyperphagia
- Generate points of contact and collaboration
- Create research initiatives for hyperphagia

## About the Conference

The Hyperphagia Conference will feature top international scientists in the field of appetite and obesity research. Over the three day conference, participants will present the latest information on various aspects of appetite control including:

- Intracellular nutrient control of hunger
- Common and novel genetic causes of hyperphagia
- Animal and cell models of hyperphagia
- Addictive behavior and hyperphagia
- Novel investigative approaches to study hyperphagia

The conference will also feature panel discussions of the pros and cons of certain treatment avenues for hyperphagia. Finally, the scientists will address "Challenge Questions" and develop recommendations for the research agenda.

**We're hungry for a solution to obesity.** Imagine that one source could provide breakthrough insight with Prader-Willi syndrome as that "Window of Opportunity". As the most common known genetic cause of life-threatening obesity, Prader-Willi syndrome features extreme problems related to genetics, hormones, brain structures, psychology, and appetite control. Research on the extremes of PWS is the "Window of Opportunity" for breakthroughs applicable to the general population.

## -- Best Idea Grant --

PWSA (USA) is challenging the research community to develop ideas for projects that explore practical solutions to the hyperphagia problem in PWS and certain other uncommon disorders and cut across disorders and disciplines to create urgency in attaining answers and solutions. In collaboration with the Foundation for Prader-Willi Research (FPWR), PWSA (USA) will also make funds available for "**Best Idea Grant**" opportunities.

# CONFERENCE ORGANIZING SPONSORS



## **Prader-Willi Syndrome Association (USA)**

For over 25 years PWSA (USA) has taken the lead, internationally, in raising vital funds, promoting key advocacy, encouraging collaborating research in support of Prader-Willi syndrome and providing support and educational materials for families and caregivers.



## **Pennington Biomedical Research Center**

Since 1988, PBRS has served as the catalyst for a team of scientists dedicated to pursuing a mission of healthier lives through nutrition and preventative medicine. The Center's strategy is to address nutrition from every angle- cellular, molecular, genetic and behavioral. Working through the world's largest assembly of 80 faculty members and 600 physicians, scientists and technicians dedicated to the problems of obesity, appetite control and nutrition, PBRS is an established international leader in the fight to solve the complex factors of appetite control.



## **Foundation for Prader-Willi Research**

Established in 2003, the mission of FPWR is to eliminate the challenges of Prader-Willi syndrome through the advancement of research. FPWR is dedicated to fostering and supporting research that will advance the understanding and treatment of PWS, allowing individuals with PWS to lead more healthy and fulfilling lives. To date, FPWR's competitive grant program has committed more than \$2 million in funds to support a variety of projects relevant to PWS, including genetics of PWS, obesity, model systems, and the evaluation of pharmacological and behavioral interventions.

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## Wednesday, October 17, 2012

The Crowne Plaza Hotel, 4728 Constitution Avenue, Baton Rouge, Louisiana  
Premier 1 Ballroom

3:00 pm – 6:00 pm Registration Packet Pickup, Premier 1 Ballroom Reception Area  
5:30 pm - 8:45 pm Reception, Dinner & Keynote Presentations, Premier 1 Ballroom

Time	Event and Speaker
5:30 pm - 6:30 pm	Reception (open to all conference participants; cash bar)
6:30 pm - 8:45 pm	<b>Dinner and Keynote Presentations</b>
6:30 - 7:30 pm	Dinner (preregistration required)
7:00 - 7:15 pm	Introduction to Meeting - Steven B. Heymsfield, M.D. Executive Director, Pennington Biomedical Research Center
7:15 - 8:00 pm	<b>Keynote Speaker #1 - Randy Seeley, Ph.D.</b> <i>Hypothalamic, Brainstem and Intracellular Nutrient Signals Controlling Food Intake</i>
8:00 - 8:30 pm	<b>Keynote Speaker #2 - Jack A. Yanovski, M.D., Ph.D.</b> <i>Defining Hyperphagia</i>
8:30 - 8:45 pm	Conclusion: Steven B. Heymsfield, M.D.

## Thursday, October 18, 2012

Pennington Biomedical Research Center, 6400 Perkins Road, Baton Rouge, Louisiana 70808  
C. B. Pennington, Jr. Building, Auditorium B/D

8:00 am – 8:30 pm

Time	Event and Speaker
7:00 am - 8:15 am	<b>Shuttle Service to Pennington Conference Site</b> <i>(Every 15 minutes from Crowne Plaza Hotel)</i>
8:00 am – 8:30 am	Registration and Coffee (no breakfast served)
8:30 am – 9:00 am	Welcome and Conference Overview Phillip Brantley, Ph.D., James G. Kane, M.B.A.
9:00 am – 12:15 pm	<b>Session I: Causes of Hyperphagia</b>
9:00 – 9:30 am	<i>Prader-Willi Syndrome – The ‘Window of Opportunity’ PWS as a Unique Vehicle for Research into Hyperphagia</i> Daniel J. Driscoll, M.D., Ph.D.

<b>Time</b>	<b>Event and Speaker</b>
9:30 – 10:15 am	<i>Common Genetic Variants Causing Hyperphagia and Obesity</i> Ruth Loos, Ph.D.
<b>10:15 am – 10:30 am</b>	<b>Break</b>
10:30 – 11:15 am	<i>Novel Genetic Defects Causing Hyperphagia</i> Leslie Baier, Ph.D.
11:15 – 11:45 am	<i>Craniopharyngioma and Hyperphagia</i> Christian L. Roth, M.D.
11:45 – 12:15 pm	<i>SIM1 Gene and Hyperphagia</i> Andrew Zinn, M.D., Ph.D.
<b>12:15 pm – 1:15 pm</b>	<b>Lunch (provided)</b> – Lower Reception area; Auditorium A/C Seating
<b>1:15 pm – 3:15 pm</b>	<b>Session II: Developing Treatments Pros and Cons Panel Facilitated Discussions</b>
1:15 - 2:15 pm	Pros & Cons: Drugs vs. Behavior <i>Best Practice for Treating Hyperphagia will Involve Drugs in addition to Control of the Food Environment and Behavioral Modification</i> Tony Goldstone, M.D., Ph.D., Linda Gourash, M.D., Frank Greenway, M.D.
2:15 - 3:15 pm	Pros & Cons: Bariatric Surgery <i>Bariatric Surgery is an Appropriate Treatment Option for Patients with Genetic or Hypothalamic Obesity</i> Tony Goldstone, M.D., Ph.D., Christian Vaisse, M.D., Ph.D., Ann Scheimann, M.D., M.B.A.
3:15 - 3:45 pm	Pros & Cons – Discussion, including comments by Thomas Inge, M.D., Ph.D, Katherine Manning and Randy Seeley, Ph.D.
<b>3:45 pm – 4:00 pm</b>	<b>Break</b>
<b>4:00 pm – 4:30 pm</b>	<b>Session III:</b>
4:00 – 4:30 pm	<i>How to Run a Clinical Trial for Genetic and Hypothalamic Obesity with Hyperphagia</i> Maïthé Tauber, M.D., Ph.D.
<b>4:30 pm - 6:00 pm</b>	<b>Session IV: Animal and Cell Models of Hyperphagia</b>
4:30 - 5:00 pm	<i>How can Animal Models for Prader-Willi Syndrome help us find Treatments for Hyperphagia?</i> Rachel Wevrick, Ph.D.
5:00 - 5:30 pm	<i>Hyperphagia in Animal Models of Bardet-Biedl Syndrome</i> Val Sheffield, M.D., Ph.D.
5:30 - 6:00 pm	Discussion
<b>6:00 pm - 7:00 pm</b>	<b>Poster Session and Social Hour</b> - Lower Concourse/Lower Reception Area
<b>7:00 pm - 8:30 pm</b>	<b>Dinner and Keynote Presentation</b> – Auditorium A/C
7:00 - 8:00 pm	Dinner
7:30 - 8:15 pm	<b>Keynote Speaker #3: Nicole M. Avena, Ph.D.</b> <i>Addictive Behavior and Hyperphagia</i>
8:15 – 8:30 pm	<b>Wrap Up-</b> Steven B. Heymsfield, M.D.
<b>8:30 - 9:00 pm</b>	<b>Shuttle Service to Crowne Plaza Hotel, Every 15 minutes from PBRC</b>

## Friday, October 19, 2012

Pennington Biomedical Research Center, 6400 Perkins Road, Baton Rouge, Louisiana 70808

C. B. Pennington, Jr. Building, Auditorium B/D

8:00 am - 1:30 pm

Time	Event and Speaker
7:00 am - 8:15 am	<b>Shuttle Service to Pennington Conference Site Every 15 minutes from Crowne Plaza Hotel</b>
8:00 am - 8:30 am	Coffee and Networking (no breakfast served)
8:30 am – 8:45 am	Introductions and Agenda
8:45 am - 9:45 am	<b>Novel Techniques for Investigating Obesity</b>
8:45 - 9:15 am	<i>Novel Genetic and Neuroanatomical Techniques to Dissect Feeding Pathways in Animal Models</i> Joel Elmquist, D.V.M., Ph.D.
9:15 -9:45 am	<i>Using Induced Pluripotent Stem Cells to Investigate Neuronal Phenotypes in Genetic Obesity</i> Rudy Leibel, M.D.
9:45 – 10:30 am	<i>Developmental Epigenetics and Obesity</i> Robert Waterland, Ph.D.
<b>10:30 am – 10:45 am</b>	<b>Break</b>
10:45 am – 12:00 pm	<b>Research Challenges</b> <i>Panel Facilitated Discussion of Research Challenge Questions and Research Agenda</i> Steven Heymsfield, M.D., Tony Goldstone, M.D., Ph.D.
<b>12:00 pm – 1:30 pm</b>	<b>Lunch and Learn:</b> <b>Lunch (provided)</b> – Lower reception area; Auditorium A/C Seating <b>Guided Tour of Pennington Biomedical Research Center</b> – <i>Tours at 12:15, 12:30 and 12:45; departing from Auditorium A/C</i> <b>Social Networking</b>
<b>1:45 pm - 2:00 pm</b>	<b>Shuttles to Crowne Plaza Hotel, Every 15 minutes from PBRC</b>

**The 26th Annual PWSA (USA) Scientific Day  
Conference follows after lunch.**

## **Nutrient Sensing in the CNS**

**Randy J. Seeley, Ph.D.**

*University of Cincinnati, Cincinnati, OH*

Adult mammals do a masterful job of matching caloric intake to caloric expenditure over time. This maintenance of energy balance requires a complex and redundant homeostatic system critically involving a number of systems in the CNS. Unfortunately, over the past decade, there have been dozens of neuropeptide and neurotransmitter systems linked to the control of energy balance that might be involved. One way to begin organizing functional circuits is to identify which of these systems are the direct targets for afferent signals about the status of adipose mass in the periphery. Such "adiposity signals" (like leptin and insulin) have concentrations of receptors in the arcuate nucleus of the hypothalamus.

A key question is why animals when exposed to a high-fat diet gain weight and become resistant to the effects of leptin to reduce food intake. PPARs are nuclear receptors where fatty acids can act as activators. PPARgamma agonists such as rosiglitazone are used as important treatments for diabetes but are associated with weight gain. Our work indicates that the central administration of a single dose of rosiglitazone can produce increased food intake and increased weight gain that persists over several weeks. We have further shown that CNS administration of PPARgamma antagonists can reduce food intake and body weight when animals are maintained on a high-fat diet. In particular, we have observed that while high-fat diets render animals insensitive to the CNS effects of leptin, PPARgamma antagonists can restore normal leptin sensitivity. These data indicate an important role for hypothalamic PPARgamma receptors in the ability of high-fat diets to reduce leptin's ability to reduce food intake.

## Prader-Willi Syndrome: A Unique Vehicle for Research into Obesity and Hyperphagia

**Daniel J. Driscoll, MD, PhD**

*Pediatrics and Genetics, University of Florida College of Medicine, Gainesville, FL*

Prader-Willi syndrome (PWS) is the most frequently diagnosed genetic cause of obesity. It also was the first recognized human disorder related to genomic imprinting. PWS occurs by one of three main mechanisms resulting in the failure of expression of genes located on the paternally inherited chromosome 15: **1)** paternal deletion of the 15q11.2 region; **2)** maternal uniparental disomy of chromosome 15; and **3)** a defect in the imprinting process in 15q11.2 (Cassidy et al., 2012).

The obesity in PWS typically begins between 2-4 years of age if the diet is not appropriately managed. Remarkably, as neonates there is an almost complete absence of an appetite drive. The appetite gradually increases in early childhood such that by about 8 years of age the individual with PWS has an insatiable appetite. Through careful longitudinal studies we have been able to discern 7 distinct nutritional phases and sub-phases in PWS (Miller et al., 2011).

The initial nutritional phase, phase 0, occurs *in utero* with decreased birth weight, length and fetal movements. In the first phase the infant is hypotonic and not obese. Sub-phase 1a (median age range = 0-0.75 years) is characterized by poor appetite, feeding, and weight gain. Sub-phase 1b (0.75-2.08 years) occurs when the infant is growing steadily along a growth curve and appears to be growing at a normal rate with an improving appetite.

The second main phase occurs when the weight starts to increase and crosses growth percentile lines. This generally begins between 18-36 months of age. Sub-phase 2a (2.08-4.50 years) is when the child's weight increases such that they cross 1-2 or more growth percentile lines without a significant increase in calories. During this phase the children do not have an increased appetite or increased interest in food. Therefore, these observations indicate that the precipitant for the onset of the early-onset obesity is not a result of hyperphagia, but rather a different etiology. Sub-phase 2b (4.5-8.0 years) occurs when the child has increased their daily calories and has become more overweight/obese if the diet is not appropriately regulated. Individuals in this sub-phase have an abnormally increased appetite and interest in food and typically do some food seeking, but they do not yet have the insatiable appetite and frequent food seeking exhibited in phase 3.

The third phase (8.0 years to adulthood) is the development of an insatiable appetite accompanied by very aggressive food-seeking. This is the classical phase that most people typically associate with PWS, but its onset is actually quite variable in PWS. It may appear as early as 3 years of age or as late as 15 years. In fact, a small minority of individuals with PWS never do go into this phase. The fourth phase occurs in adulthood when an individual who was previously in phase 3 no longer has an insatiable appetite and can feel full. Families and care takers note a significant improvement in appetite and weight control. Most adult individuals with PWS have not yet entered this phase, and may never do so. Longer longitudinal studies are necessary to fully understand this last phase.

For the last 11 years we have been conducting a natural history study of the nutritional phases, first at the University of Florida and then through the auspices of the NIH funded Rare Disease Clinical Research Network. We have been correlating the nutritional phases in PWS with the data we have been accumulating on caloric intake, basal metabolic rates, DEXA body fat measurements and levels of various appetite regulating hormones. Results of these studies will be further discussed.

PWS can serve as an ideal model system to help dissect metabolic and hormonal components in appetite regulation and the development of obesity. The diagnosis is typically made in early infancy due to the hypotonia and failure to thrive prior to the onset of obesity and hyperphagia. There are robust genetic tests to confirm the diagnosis. PWS is a well known condition to geneticists and neurologists who typically are consulted in the neonatal period due to the hypotonia and poor feeding. The existence of well organized and highly motivated PWS support groups nationally and internationally have provided invaluable support to

families, health care providers and researchers. This, combined with a good understanding of the natural history of the various nutritional phases in PWS, should help scientists unravel the mysteries of the early-onset obesity and hyperphagia in PWS. An improved understanding of the factors associated with the various nutritional phases of PWS will not only benefit the treatment and management of PWS, but also should provide valuable insights into obesity in the general population.

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*Selected References:*

Cassidy SB, Schwartz S, Miller JL and Driscoll DJ: Prader-Willi Syndrome. *Genet Med* 14:10-26, 2012

Miller JL, Lynn CH, Driscoll DC, Goldstone AP, Gold JA, Kimonis V, Dykens E, Butler MG, Shuster JJ and Driscoll DJ: Nutritional Phases in Prader-Willi Syndrome, *Am J Med Genet A*, 155:1040-1049, 2011.

## Common Genetic Variants Causing Hyperphagia and Obesity

Ruth J.F. Loos, PhD

Mount Sinai School of Medicine, New York, NY

Large-scale genome-wide associations studies (GWAS) have so far identified more than 55 loci associated with obesity-susceptibility traits, including BMI, WHR, body fat%, and extreme and early-onset obesity. In ongoing analyses by the GIANT (Genetic Investigation of Anthropometric Traits) consortium, which combined the data of up to 340,000 individuals from 125 genetic association studies, the number of loci associated with BMI and WHR is set to more than triple. Although these loci explain only a fraction of the overall variation in obesity-susceptibility, they may harbor genes that are involved in pathways relevant to obesity. As the genome-wide association approach is hypothesis-generating, the role of most of these loci and of the genes they harbor in relation to obesity risk remains to be elucidated. While the ongoing large-scale effort by the GIANT consortium is starting to reveal several loci that harbor genes in pathways that have so far been less apparent, i.e. in glucose and insulin homeostasis, mitochondrial processes, lipid metabolism, and the immune system, the previous observation that many BMI loci contain genes that have a potential neuronal role continues to be consistently confirmed. This begs the question whether any of these loci increase the risk of obesity through increasing food intake or through influencing related behaviors and sensations, such as increasing the feeling of hunger, reducing satiation, amongst others. Studying the association between the obesity-susceptibility loci in relation to such markers of food intake in epidemiological studies is however a challenging undertaking for several reasons. First, most obesity-susceptibility loci have been identified through meta-analyses including data from 30,000 to upto 340,000 individuals. As such, to examine associations between the obesity-susceptibility loci with food intake traits, the study sample size will need to be of a similar large-scale magnitude to provide sufficient statistical power to either confirm or refute the hypotheses. Second, food intake and related behaviors or sensations are often inaccurately measured, using questionnaire data, in particular in large-scale studies. Furthermore, self-reported data is subjective and often biased by individuals' BMI or obesity status. These difficulties in assessing the food intake related makers will again affect the statistical power to observe associations. Third, our earlier question assumes that increased food intake is indeed associated with increased BMI. However, this association is often weak in epidemiological settings, often because of the inaccurate and biased self-reported data. As a consequence of these methodological challenges, no convincing associations have so far been reported between any of the obesity-susceptibility loci and markers of food intake. Nevertheless, there is evidence from animal and human case studies that some of the loci harbor genes that affect food intake. For example, some loci harbor genes (*MC4R*, *BDNF* and *POMC*) in which mutations lead to monogenic obesity through hyperphagia. For other loci (*SH2B1*, *NPC1*), animal models have shown that deficiency of the derived protein affects weight gain through influencing energy intake. These observations had already been made before the GWAS discoveries, but studies focusing on the newly identified loci and their role in food intake are emerging, with the *FTO* gene being studied the most.

While GWAS and subsequent epidemiological studies are limited in their ability to follow-up on traits that are inaccurately measured (such as food intake, but also physical activity, etc), they are able to examine the association of the obesity-susceptibility genes with metabolic traits and diseases to gain insights in the pathways in which they may be involved. By integrating data across metabolic traits, it has become apparent that some obesity-susceptibly loci increase risk of various traits and diseases through diverse pathways. A few BMI-increasing loci show even significant association with decreased metabolic risk. Such loci might be particularly informative when trying to identify the pathways in which they are involved. Another approach towards understanding the genetic basis of obesity is by studying traits that intermediate in the causal pathways. Preliminary results of a GWAS of circulating leptin levels, showing that besides *LEP* also other loci affect leptin levels, some of which show intriguing associations with related metabolic traits.

## Novel Genetic Defects Causing Hyperphagia

**Leslie Baier, PhD**

*NIH/NIDDK/PECRB; Diabetes Molecular Genetics Section, Phoenix, AZ*

Studies in monozygotic twins have provided compelling evidence that body mass index (BMI) is a highly heritable trait. The high rates of obesity in populations from developed and developing countries have led to the assumption that common variation in the human genome underlies this common disease. However, analysis of more than 1 million common variants using techniques such as genome-wide association studies (GWASs) have not identified a single variant that has a large effect size on BMI across multiple ethnic groups. Instead, dozens of common variants have been identified that are significantly and reproducibly associated with BMI in studies which include thousands of subjects such as the GIANT consortium, but each variant individually has only a minor impact on BMI. This has led many investigators to reconsider the assumption that common variation must underlie common disease, and potential roles for rare and/or ethnic specific variants are being explored.

Much of our current knowledge of rare variants affecting hyperphagia in humans originated in rodent studies. In particular, the discovery of the hormone leptin and its downstream signaling pathway led to the identification of specific causative variants that underlie rare monogenic forms of childhood obesity. Following the systemic release of leptin and its subsequent interaction with the leptin receptor on the surface of neurons of the arcuate nucleus region of the hypothalamus, the downstream signals that regulate satiety and energy homeostasis are then propagated via proopiomelanocortin (POMC), cocaine-and-amphetamine-related transcript (CART), and the melanocortin system which includes the melanocortin 4 receptor (MC4R). These genes involved in regulating hunger and satiety have been directly sequenced in cohorts of extremely obese children, primarily in the laboratories of Stephen O'Rahilly and Sadaf Farooqi. Candidate gene studies have determined that functional mutation within the leptin gene (LEP) itself is exceedingly rare; in contrast, loss of function mutations in the gene that encodes the leptin receptor (LEPR) have been found in 3% of probands with severe early-onset obesity in a study that included consanguineous families. Null mutations in POMC lead to obesity, but heterozygous mutations in POMC, including loss of function mutations in the post-translationally modified products alpha and beta melanocyte stimulating hormone (MSH) are not consistently associated with severe childhood obesity. Dozens of different, rare missense variants in the single exon of MC4R have been identified, the majority of which are consistent with a dominant inheritance of monogenic obesity. Missense variants in MC4R occur in nearly 6% of patients with severe, early onset obesity, making heterozygous, loss of function mutations in MC4R the most common cause of monogenic obesity in humans.

Similar to the leptin/MC4R pathway, the brain-derived neurotrophic factor (BDNF) and its tyrosine kinase receptor (TrkB) were also initially studied in mouse models. Both genes are expressed in hypothalamic nuclei and their protein products were found to have a role in satiety and locomotor activity. BDNF homozygosity in mice is lethal, but heterozygous mice with reduced BDNF expression exhibit abnormal eating behavior leading to an obese phenotype. Similarly, TrkB hypomorphic mice, which express full-length TrkB at about 25% of normal levels, display excessive feeding behavior. Rare de novo mutations in the BDNF and TrkB have been observed in humans who exhibit hyperphagia and severe obesity, and more recently, a common Val66Met polymorphism in BDNF has been associated with BMI in human populations.

In addition to performing candidate gene analysis to identify rare variation in extreme case samples, recent investigations have included genome-wide detection of large, rare deletions in extreme cases. One of these studies has uncovered overlapping deletions on chromosome 16p11.2. The various deletions encompassed several genes but all included SH2B1, which is involved in leptin and insulin signaling. Deletion carriers are hyperphagic and severely insulin resistance, even after accounting for their degree of body fatness.

While studies in children with extreme obesity have proven successful in identifying rare variants for hyperphagia, not all "novel" variants are necessarily rare across all populations. Allele frequency varies considerably among different ethnic groups, and many minority groups, who were not included in the large GWAS meta-analyses for obesity performed to date, have very high rates of this disease. The Pima Indians of Arizona are an interesting population in that they have one of the world's highest prevalence rates of obesity, and have minimal European admixture, suggesting that they may have some "novel" (i.e. - non-Caucasian)

genetic contributors to this disease. For example the protein coded by HCRTR2 is a G-protein coupled receptor that binds the hypothalamic neuropeptides orexin A and orexin B and is involved in regulating feeding behavior. A variant with a risk allele frequency of 0.48 in HCRTR2 is associated with BMI in Pima Indians, but this variant has a frequency of 0.04 in Africans and is monomorphic (for the non-risk allele) in Caucasians. Alternatively, similar genes may be contributing to hyperphagia in different ethnic groups, but the inherited causal variant may differ. For example, common non-coding variation in both the SIM-1 and LEPR loci are reproducibly associated with BMI in Native Americans, whereas in Caucasians rarer coding variants and/or large chromosomal deletions or rearrangements have been associated with obesity.

Even within a genetically similar population, different causal variants within a single gene can exist. For example, sequencing of MC4R in a population-based study of 7900 Pima Indians from a single community detected 10 different missense variants, four of which have not been previously reported in other ethnic groups. A total of 237 of the 7900 Pima Indians carried a missense MC4R variant (population-based frequency of 3%) as compared to a frequency of 1 in 1000 carriers in the general UK population (population-based frequency of 0.1%). These distinct rare causal variants in close genetic proximity can confound large GWAS analyses. To complicate associations in this region even further, many populations also have common variation near the MC4R locus that is associated with BMI. Pima Indians have common variation near the 5'UTR of MC4R that is associated with BMI, where the risk allele frequency is 0.47 in Pima Indians and 0.12 in Caucasians. This variation is distinct from the common variation near the MC4R locus previously reported by the GIANT study; Pima Indians are essentially monomorphic for the non-risk allele of the variant associated with BMI in Caucasians.

Obesity, in particular childhood obesity, is perhaps our largest public health concern and many resources are being devoted to identifying the heritable basis for this disease. Excellent studies have shown the importance of rare variants in the early development of this disease, but unfortunately the most common cause of extreme childhood obesity is haploinsufficiency of the MC4R gene. The complexity of the signaling of the melanocortin system, including effects on the cardiovascular system, make it a difficult target for drugs without substantial risk for side effects. Among the other well-studied obesity genes, BDNF and POMC both code for ligands and are therefore not traditional drug targets. Many of the gene products along this pathway are also difficult to manipulate because they are expressed in the CNS.

Therefore, future research must include identifying new pathways that are more accessible for therapy.

Genetic research in obesity, similar to genetic research for other polygenic complex diseases, is moving towards whole genome sequencing as a more thorough, hypothesis-free investigation. As Next Generation sequencing costs are decreasing, it will become more feasible to sequence the large numbers of subjects required for identifying genes for polygenic diseases. Sequencing of whole genomes will also allow better detection of variation that is more complex than the simple polymorphisms which were analyzed by GWASs. It is estimated that 8% of individuals have a large (>500 kb) deletion or duplication that occurs at an allele frequency of <0.05%. Copy-number variants (CNVs) are also important in that they have been subjected to sudden, rapid, and often adaptive, evolution in human populations.

Epigenetics is also an emerging field in the genetics of polygenic disease. Technology that allows large-scale exploration of epigenetic factors such as DNA methylation, histone modification, RNA processing, and microRNA expression is becoming available. However, it must be remembered that the most important outcome of understanding the genetic heritability of a disease such as obesity is using this information for prevention or treatment. Given our current understanding of the genetic basis for common, polygenic obesity, this may be a daunting task.

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## Craniopharyngioma and Hyperphagia

**Christian L. Roth, MD**

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One of the most recalcitrant examples of obesity is hypothalamic obesity (HO) in patients with hypothalamic lesions and tumors such as craniopharyngioma (CP). CP is an embryological tumor located in the hypothalamic and/or pituitary region, frequently causing not only hypopituitarism, but also leading to damage of medial hypothalamic nuclei due to the tumor and its treatment by surgery and irradiation. HO syndrome in CP patients is characterized by fatigue, decreased physical activity, uncontrolled appetite, and morbid obesity, and is associated with hyperinsulinemia and leptin resistance.

After surgery, hyperphagia and obesity occur on average in about 50% of all CP patients, although study results vary from 6% to 91%. Risk factors for developing obesity in CP patients include: large hypothalamic lesions and tumors that reach the floor of the third ventricle and the area beyond mammillary bodies; hydrocephalus; aggressive resection; and hypothalamic irradiation. In our own clinical series, patients with morbid obesity had lesions affecting several medial hypothalamic nuclei such as hypothalamic arcuate (ARC), ventromedial (VMN) and dorsomedial (DMN) nuclei (Roth, *Front Endocrinol* 2011). In particular VMN damage can lead to disinhibition of the vagal tone, resulting in excess stimulation of pancreatic  $\beta$ -cells, hyperinsulinemia, and obesity. Alternatively, sympathetic nervous output might be reduced, leading to decreased physical activity. Several previous studies including our own data show that the secretion of satiety regulating peptides, such as ghrelin and peptide YY, may be altered in CP patients. Thus, using functional magnetic resonance imaging (fMRI) -a powerful tool for observing the human brain's *in vivo* responses to stimuli- we assessed pre- and post-meal responses to visual food cues in brain regions of interest in CP patients. Following the test meal, BMI matched controls showed suppression of activation by food cues while CP patients showed trends towards higher activation. These data support the hypothesis that perception of food cues may be altered in CP patients with HO, especially after food intake.

Mechanisms leading to the profoundly disturbed energy homeostasis are complex. To further elucidate underlying mechanisms, our group created a combined medial hypothalamic lesion (CMHL) rat model in which the ARC, VMN and DMN are destroyed bilaterally to mimic the metabolic effects of CP. This model is characterized by excessive weight gain, increased body adiposity and food intake. Moreover, similar to that of CP patients, plasma alpha-melanocyte stimulating hormone (MSH) levels are reduced, ambulatory activity levels are lowered and the degree of hyperleptinemia and hyperinsulinemia is inappropriate for the degree of obesity (Roth et al. *Pediatr Res* 2011).

There is an urgent need to find an efficacious treatment for HO. Recently, we used the CMHL rat model to test the efficacy of three pharmaceutical agents that act downstream of the mediobasal hypothalamus to reduce food intake and body weight. These agents include the melanocortin 3/4 receptor agonist MTII, the glucagon-like peptide (GLP)-1 agonist exenatide and the psychomotor stimulant methylphenidate. Peripheral administration of MTII reduced food intake and body weight relative to sham-vehicle-treated controls ( $p < 0.05$ ). Indirect calorimetry established that the effect of MTII was due to both a reduction in food intake, as well as an increase in energy expenditure. Similar to MTII, both sham-lesioned and CMHL rats exhibited significant reductions in both food intake (lesion -20.8%, control -13.7%) and body weight when treated with exenatide relative to saline-controls. Finally, using a crossover design study, we found that treatment with methylphenidate in both sham and CHML rats caused a significant decrease in food intake (CMHL -23%,  $p = 0.008$ ; control -20%,  $p = 0.002$ ) and body weight compared to saline-treated controls.

In summary, the CMHL model most accurately mimics the complex metabolic abnormalities observed in obese CP patients and provides a foundation for testing pharmacological approaches to treat obesity in children with hypothalamic dysfunction. Follow-up studies are required to further elucidate the effects of these three potential candidates for the treatment of HO.

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## SIM1 Gene and Hyperphagia

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Energy homeostasis is tightly regulated genetically. A large number of loci with modest effects, e.g., *FTO*, contribute to the heritability of body mass index (BMI) and related phenotypes, and mutations of a small number of genes have been found to cause monogenic obesity. Most of the Mendelian obesity genes were first identified in mouse models, with human mutations subsequently detected from directed screening of individuals with severe and/or familial obesity. For some of these genes, e.g., *MC4R*, mutations with major effects on protein function cause monogenic obesity, whereas subtle variation contributes to BMI as a complex trait. Both modest-effect and especially Mendelian obesity genes have highlighted the role of the central nervous system and hypothalamic leptin-melanocortin signaling pathways in energy homeostasis (1).

*SIM1* encodes a member of the bHLH-PAS family of transcription factors expressed in the developing and adult hypothalamus. Homozygous *Sim1* knockout mice, which die perinatally, lack the paraventricular nucleus of the hypothalamus (PVN), a major site of *Mc4r* action in feeding regulation. Heterozygous mutation of *SIM1* was first associated with hyperphagia in a girl with severe, early onset obesity and normal energy expenditure. Subsequent studies showed that heterozygous *Sim1* knockout mice showed hyperphagia with normal energy expenditure, exacerbated by high fat diet, and decreased PVN oxytocin and vasopressin expression. PVN oxytocin neurons projecting to the hindbrain have been previously implicated in satiety in response to *Mc4r* signaling and dietary fat, and intracerebroventricular oxytocin partially rescued the hyperphagia of *Sim1* heterozygotes. Consistent with these data, a recent study showed that acute inhibition of oxytocin-expressing *Sim1* PVN neurons in mice increases food intake, whereas activation of these neurons inhibits feeding. Classical lesioning of the PVN resulted in hyperphagia, and *Sim1* heterozygous mice were initially proposed to be hyperphagic on the basis of reduced number of PVN neurons. However, we did not observe a reduced number of PVN neurons in *Sim1* heterozygotes. In addition, *Sim1* expression in adult PVN neurons suggested that it has post-developmental, physiologic functions. Consistent with this hypothesis, transgenic overexpression of *Sim1* ameliorated high fat diet-induced hyperphagia without altering PVN morphology.

Furthermore, viral-mediated overexpression of *Sim1* in adult mice reduced food intake, whereas inhibition of *Sim1* expression increased feeding. Finally, conditional postnatal knockout of *Sim1* caused hyperphagia, with no loss of PVN neurons or gross changes to their hindbrain projections. These lines of evidence strongly supported a physiologic role for *Sim1* in regulation of food intake (2).

In order to inactivate *Sim1* in adult mice with fully formed, mature hypothalamic circuits, we generated a tamoxifen-inducible *Sim1* knockout mouse. Using this system, we confirmed that *Sim1* inactivation increased food intake and weight gain without affecting gross PVN neuron survival. Induced *Sim1* knockout also caused increased water intake, probably via decreased vasopressin expression (central diabetes insipidus).

*Sim1* and its as yet unidentified transcriptional targets are thus potential targets for treating hyperphagia. Unlike other genes such as *MC4R* that modulate both food intake and autonomic nervous system activity, *SIM1* appears to selectively or preferentially regulate feeding. CHIP-Seq experiments are in progress to determine *Sim1* genomic binding sites in cultured cells; the inducible *Sim1* knockout mice will be useful for validating *Sim1* PVN target genes *in vivo*.

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## **Hyperphagia and Related Behavior in Prader-Willi Syndrome**

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Those confronted with the day-to-day challenges of behavior management for PWS require an accurate understanding of the characteristically persistent, extraordinary and often dangerous behaviors of persons with PWS. Because of the complexity of the disorder, some reductionist thinking is needed to organize caregivers' moment-to-moment responses but wholly incorrect paradigms lead to mismanagement. Existing neuroscience and behavioral phenomenology of PWS inform our understanding of PWS hyperphagia presented in an automotive analogy (Car Model) for parents, teachers and professional carers.

PWS is characterized by the body's inability to adapt to homeostatic dysregulation (global feedback failure). Failure to suck and feed in the neonatal period is an early indicator of faulty drives (lack of hunger, the first and most important organizing drive in life) and leads to failure to thrive. Scheduled feeding of prescribed calories leads to survival with subsequent growth. Weight gain precedes the increase in calories, and an increased interest in food becomes apparent around the same time that the first tantrum occurs. Both of these behaviors indicate the timely development of the reward drive, which is a manifestation of orbitofrontal maturation. From this point on, hyperphagia leads to weight gain through impaired satiety mechanisms and food becomes the major organizer of thought and behavior. It is also apparent that the abnormal appetitive drive (reward drive) and failed satiety mechanisms involve more than just food; collections of preferred items and over use of all commodities, telephone and internet use, grooming and tobacco products ensue, requiring external controls for management just as with food. Personality traits, such as excessive, repetitive questioning and perseverative behaviors, also lack a typical response to habituation and satiety and require external cues and environmental interventions for management. These behaviors are apparent by age 10 years.

Controlled food access is an essential management tool for weight regulation in PWS. But controlling food access does not manage the preoccupation with food or food-related behaviors in PWS. Behavioral disturbance in PWS (impulsive tantrum or shut down) is related to disappointment (emotional response) when the outcome of a situation (cognitive prediction/idea) is discrepant from expectations (contextual conditioning via learning and memory). In the macrosphere of economics, food security pertains to the knowledge of where the source of nourishment will originate across the day. It can be applied to population studies of obesity because typical individuals will eat more of available calories (compensation) when balanced meals (needing) and preferred sources (wanting) are not present. For the person with PWS, psychological food security manages food preoccupation and behavior. Managing expectations by knowing what is available to eat (the menu and amount), when it will be served (the schedule), and controlling access and supervision (no chance of getting more) leads to psychological contentment (satisfaction). FOOD SECURITY, summarized in the mantra, "NO DOUBT, NO HOPE, NO DISAPPOINTMENT" provides the necessary feedback to override failed satiety mechanisms. Because disappointment is avoided, behavioral control is better maintained and intake and behavior can be managed in concert. When food ceases to be the major organizer of thought and behavior in persons with PWS, individuals have greater freedom to use their brain for other developmentally appropriate tasks, such as learning, socializing and engaging in creative processes.

## Treatment Will Involve Drugs in addition to Control of the Food Environment and Behavioral Modification

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Hypothalamic obesity is caused by bilateral damage to the ventromedial hypothalamus and results in obesity that is usually resistant to diet, exercise and behavior modification. Hypothalamic obesity releases the vagus nerve from inhibitory influences and the increased vagal traffic increases insulin output, reduces blood sugar and results in hyperphagia. The hypothalamic damage also reduces sympathetic tone, metabolic rate and increases food intake. Since most obesity medications act in the hypothalamus, they have limited use in treating hypothalamic obesity.

Dextroamphetamine has been used to treat hypothalamic obesity by increasing sympathetic tone. Five subjects were given 12.5-20mg/d for 24 months. During the treatment period they gained 0.4 kg/mo compared to the 10 months prior to treatment when they gained 2kg/mo ( $p=0.009$ ). On dextroamphetamine, the subjects had improved attention, behavior and were more active physically (1).

Octreotide has been used to treat hypothalamic obesity by reducing the exaggerated insulin response. Eight children with hypothalamic obesity who were gaining 1kg/mo for six months were treated with octreotide for 6 months. Their peak insulin response to an oral glucose tolerance test (OGTT) dropped from  $281 \pm 47 \mu\text{U/mL}$  to  $114 \pm 35 \mu\text{U/mL}$  ( $p=0.04$ ) and their weight decreased by 0.8kg/month ( $p=0.04$ ). In a randomized placebo-controlled trial 18 children with hypothalamic obesity were treated with 5-15  $\mu\text{g/kg/d}$  of octreotide or placebo subcutaneously for 6 months. The octreotide group gained  $1.6 \pm 0.6 \text{ kg}$  compared to  $9.1 \pm 1.7 \text{ kg}$  in the control group ( $p<0.001$ ) and the peak insulin during an OGTT was less in the octreotide group ( $135 \pm 39$  vs.  $324 \pm 65 \mu\text{U/mL}$ ) (2).

Triiodothyronine at hyperthyroid levels caused weight loss due to its actions outside the brain to increase metabolic rate (3). Caffeine and ephedrine also caused a 10% weight loss in 3 subjects with hypothalamic obesity (4). This suggests that drugs acting on peripheral targets to decrease insulin levels and increase metabolic rate might have promise in the treatment of hypothalamic obesity.

Beloranib is a candidate obesity drug being developed by Zafgen. Beloranib is an inhibitor of methionine aminopeptidase-2 (MetAP2) which works in the periphery to reduce fatty acid synthesis, reduce insulin levels and food intake while increasing fat mobilization, fatty acid oxidation and energy expenditure based on comparisons similar to pair feeding. MetAP-2 inhibition is thought to work by reducing activity of ERK1/2, decreasing insulin levels and inflammation while increasing FGF21 and fat oxidation. Ob/ob mice have a leptin deficiency on a C57 black 6 (C57B6) background. Beloranib treatment returns body weight in ob/ob mice to the weight of the wild-type C57B6 mice. In a human phase 1b trial in which beloranib was given at a dose of  $0.9\text{mg/M}^2$  intravenously twice weekly, obese human females lost 1 kg/wk over the 4-week trial and the drug was well tolerated.

Since beloranib acts peripherally to decrease insulin levels, fatty acid synthesis and increase energy expenditure, it was hypothesized that it would effectively treat hypothalamic obesity. Hypothalamic obesity was created using gold thioglucose (GTG) in mice. Forty-eight days after the GTG treatment, the control group treated with saline gained 20% of their body weight while the mice treated with GTG increased their food intake and gained 50% of their body weight. A pilot study was then conducted in which 8 GTG treated mice were treated with vehicle and 10 were treated with beloranib  $0.1\text{mg/kg/d}$  subcutaneously for 10 days. Body weight in the beloranib treated group fell by 1%/day from baseline in the 10 days and food intake returned to the level of the non-GTG treated controls. The vehicle treated group gained 3% of their body weight.

Thus, hypothalamic obesity with its impaired sympathetic tone, increased insulin secretion and hyperphagia represents a challenge to treatment with modification of the food environment, behavioral modification or medication. Although prior attempts at treating the hyperphagia of hypothalamic obesity have been met with limited success, beloranib, a candidate obesity drug acting outside the brain to lower insulin levels and increase energy expenditure, has shown promise of successful weight loss and reduced food intake in a pilot

trial in hypothalamic obesity in GTG mice. If further studies with beloranib in hypothalamic obesity confirm and extend the results of the pilot study, beloranib may represent a potential medication to accompany modification of the food environment and behavioral modification in the treatment of hypothalamic obesity.

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## How to Run a Clinical Trial for Genetic and Hypothalamic Obesity with Hyperphagia

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The issue of how to run a clinical trial for genetic and hypothalamic obesity with hyperphagia is crucial. The example of Prader-Willi syndrome gives some useful indications.

First the age of the study population is important as there are different nutritional phases with age with the paradigm of PWS. The possible interactions with psychotropic medications often taken by these persons need to be investigated.

From an ethical point of view, we think that it is not possible to stop the strict control to food access which is mandatory for these persons. Even for a clinical trial, the evaluation of eating behavior and food intake when persons are exposed to food ad libitum is not recommended.

As eating behavior is part of the “general” behavior troubles a complete evaluation is needed including food intake, eating behavior and general behavior. The evaluation of the effect of the study drug includes calorie intake, food preferences, adapted questionnaires of food intake and eating behavior (to age and disease if available i.e. the PWS hyperphagia questionnaire). Visual analogic scales for hungry and satiety are helpful. Specific tool tools can be developed to assess food related emotion. Foraging, craving , storage behaviors have to be noted.

Whether the study is performed ambulatory at family home or group homes or in patients admitted in dedicated centers or hospitals is also important. We have built a home-made grid for persons with PWS to routinely /daily evaluate behavior when patients are admitted in our dedicated center, including the key features of PWS. These grids are filled by the careers and score by our team psychologist.

From a pathophysiological point of view, in addition to these clinical evaluations, blood samples are generally performed, before and after the start of therapy, fasting and post meals. Blood sample difficulties and/or limitations particularly for persons with obesity and/or, assays difficulties are challenging questions. In addition what is the signification of a plasma value for neuropeptides or hormones?

It is now undoubtedly interesting to combine brain imaging and particularly functional studies such as PET scan or fMRI in various conditions at rest or after various stimulations. Here the point is how many brain imaging can be made from an ethical point of view besides the radiation risk?

Finally the dose and modalities of administration of treatment have to be discussed given the fact that persons with PWS are often very sensitive to psychotropic treatments and may require lower doses than other patients. Escalating doses studies may then be necessary.

Moreover, rare diseases add another line of complexity to design studies with enough statistic power.

## How can Animal Models for Prader-Willi Syndrome Help us Find Treatments for Hyperphagia?

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### Overview:

Eating disorders that cause unhealthy increases or decreases in body weight are a rising cause of morbidity, mortality and health care costs worldwide. Four percent of North Americans are estimated to suffer from some type of serious eating disorder and about 36% are obese. The etiology of disordered eating encompasses environmental, sociological and genetic components. Moreover, inadequate perinatal nutrition can program epigenetic changes that predispose the individual to obesity and diabetes in adult life<sup>5,6</sup>. While the heritability of body mass index (a surrogate marker for obesity) in adults is estimated at 40-70%, genetic factors contribute to over 80% of the variation in children and adolescents. Mutations in specific genes cause about 5-10% of cases of childhood-onset obesity, and these genes have revealed important pathways that regulate energy balance. Many obesity susceptibility genes act in the central nervous system, and interact with each other and with an environment that provides easy access to cheap, calorically-dense, highly palatable food.

Prader-Willi syndrome (PWS) is a rare disorder that illustrates the importance of genetics in regulation of body weight. Constant hunger and obsession with food are cardinal findings in PWS: life-threatening obesity is inevitable if the environment is not strictly controlled. Affected individuals also face intellectual disability, excessive daytime sleepiness and low sex hormone levels. Not only do people with PWS consume very large amounts of food if permitted, but their food perceptions, satiety responses, and emotional reactions to food are highly aberrant. PWS can cause indiscriminate eating, such as eating pet food or spoiled food, and stealing or hoarding food. Most caregivers need to lock up food to prevent binge eating, which can lead to stomach rupture, gastric necrosis, and death. Functional brain imaging studies in PWS reveal over-activation of reward circuits and decreased activity in cortical inhibitory circuits in response to eating or just pictures of food. This suggests an underlying imbalance in the cognitive control of food motivation, food consumption, and satiety. Similar circuits are altered in women with bulimia, suggesting that the pathways disrupted in PWS may overlap with those important in other eating disorders. While brain imaging identifies abnormal circuits, it provides no information about cause and effect or about the biochemical pathways involved. Despite decades of research and the identification of genes inactivated in PWS, the molecular pathogenesis of compulsive eating in PWS remains poorly understood. Although PWS occurs in only 1 in 15,000 people, solving the puzzle of this very severe genetic eating disorder will provide a new molecular entry point into more common complex and heterogeneous eating disorders.

### Models:

At least six PWS candidate genes have been identified and three of these genes (*SNORD116*, *MAGEL2* and *NECDIN*) produce aberrant phenotypes when the orthologous genes are disrupted in mice. Deletion of the entire cluster of PWS candidate genes causes high rates of lethality shortly after birth, limiting the usefulness of this mouse model. Mice lacking only *Snord116* have abnormal feeding behaviour, mice lacking only *Magel2* have increased fat mass and decreased voluntary activity, and mice lacking *Necdin* have increased fat mass when fed a high fat diet. Elucidating the intricate neural circuits that interact with peripheral organs to maintain appropriate food intake and body weight may provide new opportunities to develop effective therapies for people with PWS and others with rare or common eating disorders.

### Research Needs:

Inactivation of one (or more) PWS candidate genes causes excessive eating and binge eating in people with PWS. At least one of the PWS genes participates in a neural pathway that modulates reward-based eating behavior. However, few rigorous studies of feeding behaviour and of the neural pathways important in feeding have been performed in PWS model mice. Studies of PWS genes in model organisms will provide novel insight into the neural pathways that are critical to the pathogenesis of severe eating disorders.

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## Hyperphagia in Mouse Models of Bardet-Biedl Syndrome

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An effective approach to the molecular dissection of complex diseases is to investigate Mendelian disorders that have phenotypic overlap with complex disease. An outstanding example of such a disorder and a major focus of our laboratory is the heterogeneous autosomal recessive Bardet-Biedl syndrome (BBS). Primary diagnostic features of BBS are obesity, retinal degeneration, polydactyly, hypogonadism, renal anomalies, and cognitive impairment. In addition, BBS patients have an increased incidence of diabetes and hypertension. Mutation carriers of BBS are predisposed to hypertension, diabetes mellitus and obesity suggesting that the biological systems in which BBS genes play a role can contribute to non-syndromic disorders. Our work, along with the work of others, has led to the identification of multiple genes that independently cause this disorder, as well as the identification of two protein complexes<sup>1,2,3</sup>. We and others have now shown that there are at least sixteen BBS genes. We have also created animal models of BBS<sup>4-8</sup>. My laboratory has developed zebrafish gene-knockdown models of the known BBS genes<sup>4</sup>, and mouse knockout or knockin models for seven (*Bbs1*, *Bbs2*, *Bbs3*, *Bbs4*, *Bbs6*, *Bbs7*, *Bbs8* and *Bbs11*)<sup>5-8</sup>. The development of animal models in our laboratory has been pursued for five primary reasons: (1) To understand the molecular and cellular pathophysiology; (2) to confirm the disease-causing role of specific genes; (3) to identify phenotypes associated with specific genetic mutations; (4) to explore genetic interactions; and (5) to pursue treatments for the disease.

An initial clue suggesting a function for BBS proteins and the pathophysiology of BBS came from mouse models indicating that BBS genes/proteins play a role in cilia function. The spermatozoa of BBS mouse models do not form flagella<sup>5-8</sup>. Furthermore, data from us and others show conservation of BBS genes in ciliated organisms, but not in non-ciliated organisms. These findings indicated that BBS genes play a role in cilia formation, maintenance, and/or function. My collaborators and I have shown that seven of known BBS proteins (BBS1, BBS2, BBS4, BBS5, BBS7, BBS8 and BBS9) form a stable complex (known as the BBSome) that transiently associates with PCM-1, a core component of centriolar satellites<sup>2</sup>. This function of the BBSome is linked to the Rab8 nucleotide exchange factor, Rabin8, which localizes to the basal body and contacts the BBSome through BBS1. This interaction facilitates GTP loading of Rab8. Rab8<sup>GTP</sup> targets vesicles to the cilium to promote ciliary membrane elongation.

Mouse studies have greatly contributed to our understanding of obesity in BBS. BBS knockout mice have hyperphagia, decreased activity, and increased circulating levels of leptin<sup>9-10</sup>. Our studies show that BBS knockout mice are leptin resistant with respect to metabolic responses. In addition, we have demonstrated hypertension in some BBS knockout mice. The hypertension results from increased renal sympathetic nerve activity associated with high circulating leptin levels. Collectively, these studies show that BBS mice have a novel mechanism of obesity and hypertension resulting from selective leptin resistance. These models are proving useful in the development of novel treatments<sup>11</sup>.

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## Addictive Behavior and Hyperphagia

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The increase in the prevalence of obesity, along with the convenient availability of highly-palatable, calorically-dense foods, has led some to suggest that hedonic hyperphagia may be a cause of increased body weight. It is well known that overeating of palatable food can have powerful effects on brain reward systems, however, it is debated whether excessive intake of palatable food can produce signs of dependence such as those seen in response to drugs of abuse. In an effort to better understand this concept, several studies have been conducted using laboratory animal models to assess whether overeating of palatable foods can produce behaviors and changes in reward-related brain systems that are similar to those seen with some drugs of abuse. In the case of binge consumption of 10% sucrose, observed behaviors include tolerance, signs of opiate-like withdrawal, enhanced motivation to obtain sucrose, and a heightened sensitivity to, or consumption of, drugs of abuse. Accompanying brain changes include alterations in dopaminergic, cholinergic and opioid systems in the nucleus accumbens, which are similar to the effects seen in response to some drugs of abuse. While rats bingeing on sucrose show these behavioral and neurochemical signs of addiction, they maintain a normal body weight. However, studies addressing overconsumption of palatable foods have been extended to compare the effects of overeating a variety of nutrients and palatable foods in addition to sucrose. Findings produced by these studies show that when rats overeat fat-rich diets they can gain excess body weight, but different behavioral signs of addiction are seen. Recently, clinical studies have used psychometrics and brain imaging techniques to study overeating within clinical populations. The results of these studies also suggest that aspects of drug-like dependence can be observed in response to excessive intake of palatable foods in some individuals. Collectively, these findings show aberrant behaviors and brain changes that can develop when rats or humans excessively eat palatable foods, and suggest differences in aspects of addiction that emerge when body weight and the type of palatable food are considered.

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## **Investigating Autonomic Regulatory Networks Controlling Energy Balance and Glucose Homeostasis**

**Joel K. Elmquist, DVM, PhD**

*Division of Hypothalamic Research, Departments of Internal Medicine and Pharmacology  
University of Texas Southwestern Medical Center, Dallas, TX*

The brain plays a critical role in regulating food intake, body weight and blood glucose levels. Dysfunction of this central regulation results in obesity and type II diabetes. Therefore, to understand the causes and to develop treatments for obesity and diabetes, it is first necessary to unravel the brain pathways regulating coordinated energy homeostasis. Metabolic cues and neurotransmitters act on key collection of neurons both within and outside the hypothalamus to regulate food intake and body weight and glucose homeostasis. However, the inherent complexity of these CNS circuits has made it extremely difficult to definitively identify the key neurons that are required to maintain glucose homeostasis and energy balance. Over the past several years the ability to manipulate gene expression in a neuron-specific fashion has become feasible. We will describe some our recent findings using mouse models that allow neuron-specific manipulation of genes regulating energy balance and glucose homeostasis. It is our hope that these studies have provided insights into the mechanisms through which the nervous system regulates food intake, body weight and blood glucose levels.

Supported by: NIH R01DK53301, NIH RL1DK081185, and NIH P01DK088761.

## Using Induced Pluripotent Stem Cells to Investigate Neuronal Phenotypes in Genetic Obesity

**Liheng Wang, Lisa Cole, Dieter Egli, Rudolph Leibel**

*Columbia University & New York Stem Cell Foundation, New York, NY*

Hypothalamic, brainstem and other neurons act centrally to regulate energy homeostasis in response to circulating and neural signals. These cells are not directly accessible in human subjects. We are seeking to generate such cells *in vitro* using stem cell-based approaches. We have selected “monogenic” forms of human obesity in which to test the feasibility of such an approach.

Prader-Willi syndrome (PWS) is caused by a loss of a paternally expressed, imprinted region on chromosome 15q. Bardet-Biedl (BBS), Joubert (JBST) and Alstrom (ALMS) syndromes are caused by mutations of a specific group of proteins that are components of the primary cilium. The primary cilium on neurons “convenes” important signal receptors including Smo, Sstr3, ACIII, Lepr and Mchr1. Specifically how BBS/JBST/PWS mutations affect the function of hypothalamic neurons is not well understood.

To investigate the neurobiology of obesity in BBS and PWS, we have established *in vitro* models by reprogramming skin fibroblasts from BBS/PWS patients into induced pluripotent stem cells (iPSCs) and further differentiating these cells into neurons by dual SMADs inhibition. iPSCs derived from unaffected healthy subjects are used as controls in these study. We have found that the maternal imprinting is preserved in PWS iPSCs and iPSC-derived neurons (in collaboration with Daniel J. Driscoll, UF).

Neurogenesis was unaffected in BBS iPSC-derived neurons. However, BBS10 mutant neurons possessed longer cilia than control iPSC-derived neurons. The JBST lines which carry a hypomorphic mutation in *RPGRIP1L* showed defective ciliogenesis manifest as fewer, shorter cilia based on ACIII and ARL13B staining. The BBS neurons displayed relative insulin resistance (decreased p-AKT levels in response to insulin). We also observed impaired leptin signaling in RFP-LEPR overexpressing BBS fibroblasts compared with control fibroblasts. Lentivirus-mediated expression of the wildtype BBS transgene rescued leptin signaling in BBS mutant fibroblasts.

## Developmental Epigenetics and Obesity

**Robert A. Waterland, PhD**

*USDA/ARS Children's Nutrition Research Center, Baylor College of Medicine, Houston, TX*

Epigenetics describes the study of mitotically heritable and stable alterations in gene expression potential that are not caused by changes in DNA sequence (1). Animal models and the human neurodevelopmental disorder Prader-Willi syndrome demonstrate that epigenetic dysregulation can cause obesity. The extent to which epigenetic mechanisms contribute to the worldwide obesity epidemic, however, remains unclear.

Understanding the epigenetic contribution to human disease is substantially more complex than studying genetic pathogenesis. A major reason is the inherent tissue-specificity of epigenetic regulation. Unlike in genetic studies of obesity, in which an individual's genotype can be assessed from peripheral blood or buccal DNA, such easily obtainable samples will in most cases not be indicative of epigenetic variation in tissues of primary importance to body weight regulation. Elucidating epigenetic mechanisms in human obesity is further complicated by multiple interactions among environment, genetics, epigenetics, and obesity. Effects of environment, moreover, must be considered in a developmental perspective; developmental periods when epigenetic mechanisms are undergoing establishment or maturation constitute critical windows when environment can affect these processes, with lifelong consequences (2).

For these reasons, we have been developing mouse models in which to study early environmental influences on developmental epigenetics and obesity. The agouti viable yellow ( $A^{vy}$ ) mouse provides an excellent model in which to study effects of maternal obesity on the offspring.  $A^{vy}/a$  mice are spontaneously hyperphagic and become extremely obese as adults, but remain fertile. Using this model, we recently showed that maternal obesity promotes obesity in her offspring, and that this transgenerational amplification of obesity is prevented by a pro-methylation dietary supplement (3). We have now replicated and expanded these studies; I will present data refining the earlier report.

Given its central role in regulating food intake and energy expenditure (4), the hypothalamus is an obvious tissue in which to explore a potential epigenetic basis for induced alterations in body weight regulation. Our current hypothesis is that maternal obesity alters the intrauterine environment, affecting developmental epigenetics of hypothalamic body weight regulation in the fetus, leading to permanent changes in food intake and/or energy expenditure. The hypothalamus is comprised of distinct regions, or 'nuclei', with specialized functions, gene expression patterns (4) and epigenetic regulation (5). Additionally, the nervous system includes diverse cell types; the simplest classification distinguishes neurons and glia, which are epigenetically distinct (6; 7). To better understand how maternal obesity causes persistent changes in regulation of body weight and body composition, it will be necessary to characterize epigenetic effects within specific nuclei and cell types of the hypothalamus. Moreover, since fetal life is a critical period for not only epigenetic but also neuroanatomic development, studying these processes in an integrated fashion will likely be necessary to gain a clear understanding of how maternal obesity affects the establishment of hypothalamic body weight regulation. I will summarize our progress toward achieving these goals.

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**Nicole Avena, PhD**

**Assistant Professor**

*University of Florida College of Medicine, Gainesville, FL*

Dr. Nicole Avena is a research neuroscientist and studies intersects that may exist among nutrition, diet and addiction. She received a Ph.D. in Neuroscience and Psychology from Princeton University in 2006, followed by a postdoctoral fellowship in molecular biology at The Rockefeller University in New York City. She is presently Assistant Research Professor at University of Florida, Department of Psychiatry, and also holds an appointment as Visiting Research Associate at Princeton University. Her research achievements have been honored by several prestigious groups, including the New York Academy of Sciences, the American Psychological Association, the National Institute on Drug Abuse. She has published over 50 scholarly journal articles, an edited book (*Animal Models of Eating Disorders*, Springer-Humana Press), and several reviews/commentaries. She is also passionate about translating science for the public, and maintains a blog for *Psychology Today*.



**Leslie J Baier, PhD**

**Department Head**

*Diabetes Molecular Genetics Section Phoenix Epidemiology and Clinical Research Branch, NIDDK, National Institutes of Health, Phoenix, AZ*

**Research Statement:**

The escalating rates of obesity and type 2 diabetes are primarily attributed to changes in the environment, coupled with changes in lifestyle. However, in most developed countries, food is now plentiful and lifestyle is generally sedentary, but not all people become obese, and furthermore, most obese people do not develop type 2 diabetes. Multiple studies have shown that heritable factors underlie a significant portion of the variation in risk for obesity and type 2 diabetes, and it is generally believed that expression of this genetic susceptibility is influenced by environmental variables. The Pima Indians of Arizona have the highest reported prevalence of type 2 diabetes of any population in the world. They are also a very obese population. The goal of my lab is to identify and characterize susceptibility genes for type 2 diabetes and obesity among this Native American population.

Our recent genetic studies have utilized genome-wide approaches to identify potential susceptibility loci for type 2 diabetes and obesity. We have completed two genome-wide association studies (GWASs) that utilized a 100,000 SNP and a 1 million SNP platform to identify common variants associated with type 2 diabetes, obesity, or pre-diabetes/pre-obesity traits in Pima Indians. A few variants associated with these diseases in GWASs from other ethnic groups showed similar associations in Pima Indians, however, several strong and reproducible associations were identified that were not reported in other GWASs, suggesting ethnic specific heterogeneity in risk factors for these common diseases. Follow-up fine mapping and functional studies for several of these new susceptibility variants is ongoing. We are also pursuing the hypothesis that multiple rare variants may underlie a proportion of the variance of these common diseases. Whole exome sequence data are available on 180 Pima Indians, and whole genome sequencing is currently completed on 35 Pima Indians while 200 additional Pima genomes are anticipated in the coming months. We also have genome-wide expression data (1M exons) from human skeletal muscle and adipose biopsies from more than 200 non-diabetic Pima Indians who had been characterized for metabolic traits related to diabetes and obesity. These data are being used to identify expression profiles that may predict the onset of diabetes. Expression data are also being merged with GWAS genotypic data and whole genome sequence data to identify cis and trans acting factors that may contribute to these polygenic diseases



**Daniel J. Driscoll, MD, PhD**

**Professor of Pediatrics and Genetics**

*John T. and Winifred M. Hayward Professor of Genetics Research  
University of Florida College of Medicine, Gainesville, FL*

Dr. Driscoll has been conducting clinical and laboratory research on Prader-Willi syndrome since the late 1980's. He has been a major contributor to the understanding of the genetics of Prader-Willi syndrome (PWS) and genomic imprinting in the PWS region as well as to the elucidation of the natural history of PWS. He is widely published on PWS and a major spokesperson on PWS in the US and internationally. He is the principal investigator for the Prader-Willi syndrome component of an NIH funded 11 year national Rare Disease Center grant. In 2006 he was elected to the prestigious Society of Scholars at the Johns Hopkins University based on his seminal research contributions to the field of genetics. He has received board certification in Pediatrics; Clinical Genetics; Molecular Genetics; and Cytogenetics. He is a member of the Board of Directors and Chair of the Clinical Advisory Board for the Prader-Willi Syndrome Association (PWSA) USA. In addition, he is a member of the Medical and Scientific Advisory Board of the International Prader-Willi Syndrome Organization (IPWSO).



**Joel Elmquist, DVM, PhD**

**Maclin Family Professorship in Medical Science, in Honor of Dr. Roy A. Brinkley  
Carl H. Westcott Distinguished Chair in Medical Research  
Internal Medicine, Psychiatry, Pharmacology  
*UT Southwestern Medical Center, Dallas, TX***

**Research Interests**

Body Weight Homeostasis  
Central Autonomic Control  
Diabetes and Glucose Homeostasis  
Neurobiology and Neuroanatomy of the Hypothalamus

The Elmquist lab focuses on the functional neuroanatomy of the mammalian hypothalamus. Working mainly on the regulation of body weight homeostasis, food intake and control of the autonomic nervous system, their current projects involve investigating the central mechanisms underlying the actions of leptin, melanocortins, orexin, glucagon-like peptide 1, and serotonin.



**Linda M. Gourash, MD**  
*The Pittsburgh Partnership*

Dr. Gourash is a Developmental and Behavioral Pediatrician. She received her medical degree from Georgetown University Medical School in Washington D.C., and completed her pediatric and subspecialty training at the Children's Hospital of Pittsburgh in 1980 before serving on the full time faculty of the University of Pittsburgh School of Medicine until 1991 in the Departments of Pediatrics and Psychiatry.

As the Medical Director of the Prader-Willi and Behavioral Disorders Program of the Children's Institute of Pittsburgh she worked for more than 5 years almost exclusively with children and adults with Prader-Willi Syndrome and related disorders who were referred for inpatient crisis intervention for medical and behavioral problems from throughout the USA and Canada. Dr. Gourash has served on the Board of Directors of the Prader-Willi Syndrome Association of the USA. She is currently providing clinical consultation for the International Prader-Willi Syndrome Organization and the PWSA-USA. She provides consultation and educational programs throughout the US and internationally through Pittsburgh Partnership, Specialists in PWS. Dr. Gourash is featured in a DVD produced by the PWSA and IPWSO who recorded her presentations for more widespread distribution. Dr. Gourash has a private practice in Developmental and Behavioral Pediatrics in Pittsburgh, PA.



**Frank Greenway, MD**

**Professor & Outpatient Clinic Director**

*Pharmacology Based Clinical Trials, Pennington Biomedical Research Center, Louisiana State University System, Baton Rouge, LA*

Dr. Greenway is Professor and Chief of the Outpatient Clinic, Out-Patient Clinic Unit, Clinical Trials Recruiting, and Pharmacology-based Clinical Trials at Pennington Biomedical Research Center.

He received his M.D. from the University of California, Los Angeles, CA, in 1970. Dr. Greenway's area of interest is obesity treatment including diets, herbal supplements, obesity surgery and obesity drug development. He is part of the Divisions of Obesity and Functional Foods.



**Steven B. Heymsfield, MD**

**Executive Director**

*Pennington Biomedical Research Center, Louisiana State University System, Baton Rouge, LA*

Steven B. Heymsfield, M.D. is the Executive Director of Pennington Biomedical Research Center of the Louisiana State University System and he holds the George A. Bray, Jr. Chair in Nutrition. Previously he was the Global Director of Scientific Affairs for the obesity franchise at Merck & Co. where he oversaw scientific aspects of the Company's obesity drug development program. Dr. Heymsfield received a degree in medicine from Mount Sinai School of Medicine, and he completed his internship and residency at Emory University, continuing on to become a Fellow in Medicine prior to his Columbia University appointment as Professor of Medicine and Deputy Director, New York Obesity Research Center, in 1986.

Dr. Heymsfield has published more than 450 peer-reviewed papers covering topics such as obesity, anorexia nervosa, bulimia nervosa, malnutrition, pregnancy, body composition, and caloric expenditure. His contributions to the study of human nutrition led to the TOPS Award from NAASO, the Rhoads Award of the American Society of Parenteral and Enteral Nutrition, and the Forbes Memorial Award Lecture, International Society of Body Composition Research. He was honored for his role in the FDA ban on ephedra, receiving the 2004 NYC Mayor's Award for Science and Technology. Dr. Heymsfield was elected Fellow of the American Society for Nutrition in 2009 and Fellow of the American Society of Parental and Enteral Nutrition in 2012.

In addition to his strong interest in biological method development, Dr. Heymsfield maintains an active clinical research program, extending his earlier research at Columbia University. Dr. Heymsfield is past President of the American Society of Clinical Nutrition and of the American Society of Parenteral and Enteral Nutrition.



**Rudolph Leibel, MD**

**Christopher J. Murphy Memorial Professor of Diabetes Research**  
**Professor of Pediatrics and Medicine**  
**Director, Division of Molecular Genetics**  
**Co-Director, Naomi Berrie Diabetes Center**  
*Columbia University, New York, NY*

**Research Interests and Specialties:**

Obesity

Type 2 diabetes

Stem Cell biology in analysis of human disease.

Dr. Leibel has worked in obesity research for over 25 years. His research has related to adipose tissue biochemistry and cellular physiology, the molecular genetics of control of body weight in rodents and humans, the bioenergetics of body weight regulation in humans and the role of leptin in these processes, and the molecular genetics of type 2 diabetes. He and his associates conduct studies in both rodents and humans, and have recently undertaken collaborative experiments designed to create disease-related cells and tissues from human embryonal stem cells. He is a member of the Institute of Medicine of the National Academy of Sciences, and has recently served as a member of the Federal Advisory Council for NIDDK and as an Associate Editor of the Journal of Clinical Investigation.



## **Ruth Loos, PhD**

### **Professor and Program Director**

*Genetics of Obesity and Related Metabolic Traits Program, Charles R. Bronfman Institute for Personalized Medicine*

*Department of Preventive Medicine, Mount Sinai School of Medicine, New York, NY*

### **Research Interests**

Dr. Loos primary research interests focuses on the identification of genes and genetic loci contributing to the risk of obesity and related metabolic traits. She has been involved in gene-discovery since 2005, when 'genome-wide association' was introduced and has since actively contributed to many consortia that use this approach to identify genetic loci for a large number of metabolic traits. Increasingly, her gene-discovery work also focuses on the identification of low-frequency variants through the implementation exome-chip genotyping and sequencing projects, not only in individuals of white European descent, but also in those of African and Hispanic decent.

Ruth is a member of steering committee of the GIANT (Genetic Investigation of ANTropometric Traits) consortium, led by Professor Joel Hirschhorn and is actively involved in the many working groups. Ruth has set up GWAS consortia for body fat percentage, for leptin levels, and also for resting heart rate. Furthermore, she has been involved in the GWAS consortia for blood pressure (ICBP), lipids (GLGC), glucose and insulin (MAGIC), and type 2 diabetes (DIAGRAM), amongst others.

Besides gene-discovery, Ruth uses epidemiological methods to follow-up on established loci with the aim to elucidate the pathways through which they increase risk of metabolic disease. Furthermore, her work also assesses the public health implications of the established loci by examining their predictive value and their interaction with lifestyle factors such as diet and physical activity.

### **Previous positions**

Ruth obtained her PhD at the University of Leuven (Belgium) in 2001, after which she was a postdoctoral fellow at the Pennington Biomedical Research Center in Baton Rouge (LA, USA) in Dr Claude Bouchard's Human Genetics laboratory. There, her research mainly concerned the identification of genetic variants for energy expenditure and fat oxidation through linkage and association studies. In July 2005, she joined the MRC Epidemiology Unit of the Institute of Metabolic Science in Cambridge (England) to become Group Leader of the Genetic Aetiology of Obesity Programme. She also lectured at Department of Genetics of the University of Cambridge. Ruth joined the Mount Sinai School of Medicine in New York in December 2011, and remains an honorary member of the MRC Epidemiology Unit in Cambridge.



**Christian Roth, MD**

**Associate Professor**

*Seattle Children's Hospital, Center for Integrative Brain Research (CIBR), Seattle, WA*

**Clinical Interests**

Clinical Interests: Children with endocrine disorders and diabetes mellitus. Research Interests: Obesity studies, including appetite-regulating peptides, factors of the metabolic syndrome, hypothalamic obesity and genetic and environmental factors involved in the onset of puberty.

**Research Description**

My research is focused on childhood obesity, diabetes and puberty. It includes metabolic factors in body weight regulation and hypothalamic control of feeding circuits, food reward, genes involved in childhood obesity and diabetes, as well as post-craniopharyngioma obesity. At CIBR, we are studying the neural aspects of eating and endocrine disorders in an effort to better understand childhood obesity and its treatment. We are using a variety of methods, including animal models (brain lesion, dietary, and genetic), endocrine studies, functional brain imaging (fMRI), and investigations of the eating-related neural and behavioral consequences of damage to specific brain structures that occurs in patients with brain tumors such as craniopharyngioma. We are studying metabolic factors and brain responses to obesity intervention. In collaboration with researchers at the University of Washington, the Roth lab is testing a new theory that the brain does not appropriately suppress appetite after a meal in obese children through the use of fMRI. Based on the results, future studies will refine treatment procedures, developing and testing alternate strategies for obesity treatment in children.



**Ann Scheimann, MD, MBA**

**Associate Professor of Pediatrics**

Division of Pediatric Gastroenterology and Nutrition  
*Johns Hopkins School of Medicine, Baltimore, MD*  
Adjunct Faculty, Department of Pediatrics  
*Baylor College of Medicine, Houston, TX*

Dr. Scheimann received her doctorate of medicine at the University of Cincinnati School of Medicine and completed her pediatric residency and pediatric gastroenterology and nutrition fellowship at Baylor College of Medicine/Texas Children's Hospital. She was full time faculty within the Division of Pediatric Gastroenterology and Nutrition at Baylor College of Medicine until 2000 when she moved to join the full-time faculty within the Department of Pediatrics/Division of Pediatric Gastroenterology at Johns Hopkins School of Medicine but remained adjunct faculty at Baylor College of Medicine directing the Prader-willi Syndrome Clinic at Texas Children's Hospital. Dr. Scheimann completed a Masters in Health Sciences Management at Johns Hopkins School of Business in 2005.

Dr. Scheimann's focus of research interest has been in nutrition and obesity with special areas of interest in Prader-willi Syndrome and nonalcoholic fatty liver disease. She has authored or co-authored to date more than 40 peer-reviewed publications in addition to book chapters, and meeting presentations.



**Randy Seeley, PhD**

Donald C. Harrison Endowed Professor, Pathology & Lab Med  
Director, Cincinnati Diabetes and Obesity Center  
*University of Cincinnati*

**Research Summary**

Dr. Seeley's work has focused on the actions of various peripheral hormones in the CNS that serve to regulate food intake, body weight and the regulation of circulating fuels. In particular, he has focused upon the numerous hypothalamic and G.I. peptides and their associated receptors that influence both energy intake as well as peripheral metabolic processes.



**Maïthé Tauber, MD**

**Pediatrician and Professor of Pediatrics**

**Coordinator of the French Reference Centre for Prader-Willi Syndrome**

**Head, Endocrinology, Obesity, Bone Diseases, Genetics and Medical Gynecology**

**President, Regional Network for Pediatric Obesity**

**President, National Association for the Networks for Pediatric Obesity**

*Hôpital des Enfants and Paul Sabatier Université, Toulouse, France*

**Specialty**

Pediatric endocrinology

**Research Interests**

25 years of experience in the care of PWS children with particular emphasis on early diagnosis , endocrine issues, treatment of co morbidities, multidisciplinary care, new treatments for PWS.

Research on obesity particularly in prevention, organization of the regional network for pediatric obesity, epidemiological studies and genetics studies in collaboration.



**Christian Vaisse, MD, PhD**

**Associate Professor**

*University of California School of Medicine, San Francisco, CA*

**Academic Titles:**

Vera M. Long Endowed Chair in Diabetes Research

Professor of Medicine

Diabetes Center and Department of Medicine

University of California San Francisco

**Research Interests and Specialties:**

Obesity

Human Genetics

Central Regulation of Energy Homeostasis

Dr. Vaisse research focuses on identifying genetic defects implicated in the onset and progression of multi-factorial metabolic diseases such as obesity and type 2 diabetes. His research combines human genetic approaches with molecular biology, biochemistry and animal studies. His work focuses in particular on the hypothalamic effectors of leptin.



**Robert A. Waterland, Ph.D.**

**Associate Professor**

*Baylor College of Medicine, Departments of Pediatrics and Molecular & Human Genetics  
USDA/ARS Children's Nutrition Research Center, Houston, TX*

Dr. Robert Waterland is an Associate Professor at Baylor College of Medicine, and is based in the USDA/ARS Children's Nutrition Research Center in Houston, Texas. He holds faculty appointments in the Department of Pediatrics / Nutrition and the Department of Molecular & Human Genetics.

He received his B.S. in Physics from Virginia Polytechnic Institute and State University, and worked for several years at the University of Pennsylvania, first with Britton Chance (biochemistry/biophysics), then with Albert Stunkard (clinical obesity research). After earning his Ph.D. in Human Nutrition from Cornell University (with Cutberto Garza), he conducted postdoctoral research in developmental genetics with Randy Jirtle at Duke University.

Dr. Waterland's research focuses on understanding how nutrition during critical periods of prenatal and early postnatal development affects gene expression, metabolism, and chronic disease susceptibility in adulthood. His laboratory studies both mouse models and humans to elucidate the mechanisms by which early nutrition and other environmental influences affect the establishment and maintenance of epigenetic mechanisms. He is a member of the American Society for Nutrition and the American Society of Human Genetics, and serves on the council of the International Society for Developmental Origins of Health and Disease and the board of directors of the Epigenetics Society.



**Rachel Wevrick, PhD**

**Professor**

*Academic Lead, Research Education, Women and Children's Health Research Institute*

*Member, Centre for Neuroscience, University of Alberta, Alberta, Canada*

*Member, Alberta Diabetes Institute*

Rachel Wevrick, Ph.D. is a Professor of Medical Genetics at the University of Alberta. Her research focuses on the genetic basis of developmental delay and obesity in children. Prader-Willi syndrome is a sporadic chromosomal disorder that causes neonatal hypotonia, developmental delay, childhood-onset obesity with disordered eating, and abnormalities of sleep and respiration. Dr. Wevrick co-discovered many of the genes inactivated in Prader-Willi syndrome, including *Necdin*, *MAGEL2*, and *IPW*. The Wevrick research group is currently studying the roles of PWS genes in the normal development of the nervous, muscular, and endocrine systems. The mouse homologs of three PWS candidate genes, namely *Magel2*, *necdin*, and *Snord116* have important roles in growth and differentiation. The Wevrick laboratory is evaluating the normal roles of these genes and the effect of their loss in mouse models of Prader-Willi syndrome.



**Jack Yanovski, MD, PhD**

**Chief**

*Section on Growth and Obesity, PDEGEN, NIH, National Institute of Child Health, Bethesda, MD*

Jack Yanovski is Chief of the Section on Growth and Obesity, in the Program in Developmental Endocrinology and Genetics of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, one of the National Institutes of Health in Bethesda, Maryland. He obtained his medical degree at the University of Pennsylvania, where he was also awarded a PhD in Physiological Psychology. Dr. Yanovski completed residency training in Pediatrics at the Children's Hospital of Philadelphia and fellowship training in Pediatric Endocrinology at the National Institutes of Health. In response to the growing problem of pediatric obesity in the United States, Dr. Yanovski founded the NIH's Unit on Growth and Obesity. Dr. Yanovski has carried out a series of clinical studies related to the evaluation and treatment of overweight and obesity in children and adults, as well as laboratory investigations of molecular etiologies for obesity. Dr. Yanovski has authored or co-authored over 200 published manuscripts and has served as a standing member of the NSCF, NIH Study Section, and as Chair of The Obesity Society's annual Scientific Meeting. Among other awards, he has twice received the Public Health Service's Outstanding Service Medal for his studies on obesity.



**Andrew Zinn, MD, PhD**

**Professor**

*Eugene McDermott Center for Human Growth & Development and Department of Internal Medicine*

*University of Texas Southwestern Medical School, Dallas, TX*

**Research Interests**

Sex chromosome abnormalities

Birth defects

Genetic obesity

**Current Research**

Our lab is studying the genetics of obesity, in particular, the molecular mechanisms that regulate appetite. We focus on SIM1, a hypothalamic transcription factor gene mutated in a girl with severe, early onset hyperphagic obesity. We identified neuroendocrine pathways regulating feeding behavior that are perturbed in a mouse Sim1 knockout model that recapitulates the girl's hyperphagic obesity phenotype. We are presently using conditional knockout mice to dissect Sim1's temporal and spatial actions. We are also seeking to identify Sim1 transcriptional target genes in CNS neurons relevant to appetite regulation.

## 2012 HYPERPHAGIA and 26<sup>th</sup> Annual PWSA CONFERENCE SPEAKERS

### **Nicole Avena, PhD**

Assistant Professor  
University of Florida College of Medicine  
Department of Psychiatry  
PO Box 100256  
Gainesville, FL 32610-0256  
Topic: *Keynote: Addictive behavior and hyperphagia*  
Phone: 352-294-4935  
Email: navena@ufl.edu

### **Leslie Baier, PhD**

Department Head, NIH  
Diabetes Molecular Genetics Section, PECRB, NIDDK  
445 North 5<sup>th</sup> Street, Ste. #210  
Phoenix, AZ 85004  
Topic: Novel Genetic Defects Causing Hyperphagia  
Phone: 602-440-6570  
Email: lbaier@mail.nih.gov

### **George Bray, MD**

Professor, Clinical Research  
Pennington Biomedical Research Center  
6400 Perkins Road  
Baton Rouge, LA 70808  
Topic: *Keynote Speaker: 26<sup>th</sup> PWSA Scientific Conference “*  
Phone: 225-763-3140  
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### **Daniel Driscoll, MD, PhD**

Professor, Department of Pediatrics  
University of Florida College of Medicine  
Molecular Genetics and Microbiology  
1600 SW Archer Road  
Gainesville, FL 32610-0296  
Topic: *Prader-Willi Syndrome – The ‘Window of Opportunity’  
PWS as a Unique Vehicle for Research into Hyperphagia*  
Phone: 352-294-5050  
Email: driscdj@peds.ufl.edu

### **Joel Elmquist, DVM, PhD**

Professor  
UT Southwestern Medical Center  
Maclin Family Professorship in Medical Science  
5323 Harry Hines Blvd.  
Dallas, TX 75390  
Topic: *Novel genetic and neuroanatomical techniques to dissect feeding pathways in animal models*  
Phone: 214-648-2911  
Email: joel.elmquist@utsouthwestern.edu

**Tony Goldstone, MD, PhD**

Senior Clinician Scientist and Consultant Endocrinologist  
Hammersmith Hospital at Imperial College London  
Metabolic and Molecular Imaging Group, MRC Clinical Sciences Center  
South Kensington Campus  
London, SW7 2AZ United Kingdom

Topic: *Pros & Cons 1: Drugs vs. Behavior Intro; Pros & Cons 2: Bariatric Surgery Intro; and Panel facilitated discussion of research challenge questions and research agenda*

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Topic: *Cons: Best practice for treating hyperphagia will involve drugs in addition to control of the food environment and behavioral modification*

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Topic: *Pros: Best practice for treating hyperphagia will involve drugs in addition to control of the food environment and behavioral modification and Panel Discussions of research agenda*

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Topic: *Using induced pluripotent stem cells to investigate neuronal phenotypes in genetic obesity*

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**Ruth Loos, PhD**

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Topic: *Common genetic variants causing hyperphagia and obesity*

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Topic: *Craniopharyngioma and hyperphagia*

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Topic: *Cons: Bariatric surgery is an appropriate treatment option for patients with genetic or hypothalamic obesity*

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**Randy Seeley, PhD**

Donald C. Harrison Endowed Professor

University of Cincinnati

Director, UC/CCHMC Center of Excellence in Obesity and Diabetes

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Keynote: *Hypothalamic, brainstem and intracellular nutrient signals controlling food intake*

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**Val Sheffield, MD, PhD**

Professor of Pediatrics

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Pediatrics and Medical Genetics

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Topic: *Hyperphagia in animal models of Bardet-Biedl Syndrome*

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**Maïthé Tauber, MD, PhD**

Professor

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Topic: *How to run a clinical trial for genetic and hypothalamic obesity with hyperphagia*

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Topic: *Pros: Bariatric surgery is an appropriate treatment option for patients with genetic or hypothalamic obesity*

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**Robert Waterland, MD, PhD**

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Topic: *Developmental epigenetics and human disease*

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**Rachel Wevrick, PhD**

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Department of Medical Genetics

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Topic: *How can animal models for Prader-Willi Syndrome help us find treatments for hyperphagia?*

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**Jack Yanovski, MD, PhD**

Chief, Section on Growth and Obesity, PDEGEN

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Topic: *Defining Hyperphagia*

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Topic: *SIM1 gene and hyperphagia*

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