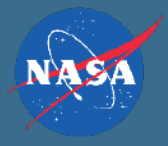
National Aeronautics and Space Administration



NASA AMES SPACE TORPOR WORKSHOP

MOFFETT FIELD, CA

MARCH 12-13, 2018

NASA Ames Office of Chief Scientist

OVERVIEW

NASA AMES SPACE TORPOR WORKSHOP
MOFFETT FIELD, CA

WORKSHOP

Many animal groups have adapted to resource-limited environments through an ability to actively depress metabolism below basal levels, resulting in a metabolic state called torpor. "Synthetic torpor" refers to the induction of torpor in species that do not have the natural ability to do so. Understanding the mechanisms that induce torpor in animals and humans may result in novel approaches for conducting space research, exploration, and emergency response. The workshop aims to investigate the potential of using synthetic torpor for short and long term non-human space research and human space exploration applications by exploring four research areas: natural torpor, synthetic torpor induction, maintenance and recovery methods, and scope of metabolic control in space. The workshop will include keynote and oral presentations, poster sessions, breakout sessions and group discussions, with the primary aim of addressing the scientific relevance and knowledge gaps required to advance synthetic torpor for space research and application.

LOCATION

NASA Research Park, Building 3
Moffett Field, California 94035

POINTS OF CONTACT

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SPONSOR

The Office of the Chief Scientist

NASA Ames Research Center
Moffett Field, California

ORGANIZING COMMITTEE

Dr. Joseph Bielitzki, NASA Kennedy Space Center

Dr. Emery Brown, Massachusetts Institute of Technology

Dr. Hannah Carey, University of Wisconsin-Madison

Dr. Jacob Cohen, NASA Ames Research Center

Dr. Erin Flynn-Evans, NASA Ames Research Center

Dr. Yuri Griko, NASA Ames Research Center

Dr. Craig Heller, Stanford University

Dr. Smith Johnson, NASA Johnson Space Center

NASA AMES SPACE TORPOR WORKSHOP
MOFFETT FIELD, CA

DAY 1
MARCH 12 AGENDA

8:00 AM	Registration and Coffee
8:30 AM	Welcome - *Jacob Cohen*
8:50 AM	**Keynote: Squirrel vs. Bear: Comparing Phenotypes of Mammalian Hibernation** - *Brian Barnes*

Session 1: Dormancy on Earth

9:30 AM	Obligate but Flexible Hibernation in a Clade of Non-Human Primates: The Dwarf Lemurs of Madagascar - *Anne Yoder*
10:00 AM	Torpor in Mice - *Steve Swoap*
10:30 AM	Break
10:45 AM	Sleep, Anesthesia, and Torpor: Distinct Physiologic States - *Keith Ruskin*
11:15 AM	Poster Session and Networking
12:00 PM	Lunch

Session 2: Approaches and Methods to Induce, Maintain, and Recover from Torpor

1:00 PM	Human Thermoregulation - *Craig Heller*
1:30 PM	Incorporating the Gut Microbiome into the Hibernator Metabolic Phenotype - *Hannah Carey*
2:00 PM	Genetic Components Driving the Seasonal Onset of Mammalian Hibernation - *Katharine Grabek*
2:30 PM	Multi-Tissue Chromatin Modification During Hibernation - *Kim Krautkramer*
3:00 PM	Break
3:15 PM	Breakout Session: Challenges and Gaps in our Understanding *Moderator: C. Loren Buck*
4:45 PM	End
6:00 PM	Dinner (Optional)

NASA AMES SPACE TORPOR WORKSHOP
MOFFETT FIELD, CA

DAY 2
MARCH 13 AGENDA

8:00 AM Arrival and Coffee

8:30 AM Welcome - *Jacob Cohen*

Session 2: Approaches and Methods to Induce, Maintain, and Recover from Torpor, Continued

8:50 AM Pharmacological and Nutrition-Based Approaches for Sustained Torpor - *Kelly Drew*

9:30 AM Metabolic Time and Mechanisms Underlying Hibernation - *Sandy Martin*

10:00 AM Suppression of Bone Remodeling Conserves Energy and Bone Mass During Hibernation - *Meghan McGee-Lawrence*

10:30 AM Portable Hibernation-based Solutions for Protection Against Ischemia and Reperfusion Injury in Non-Hibernating Mammals - *Matthew Andrews*

11:00 AM Lunch

12:15 PM **Keynote: Metabolic Stasis and Space Exploration** - *Joseph Bielitzki*

Session 3: Metabolic Manipulation and Metabolic Control in Space

1:00 PM Synthetic Torpor and Metabolic Control Tecnhology: From Laboratory Research to Application in Space Missions - *Yuri Griko*

1:30 PM Dorsal Medial Hypothalamus GABA Neurons that Regulate Torpor: Potential Application to Space Missions - *Hiroshi Yamaguchi*

2:00 PM Thermoregulation, Emergency and Short-Term Human Terrestrial and Space Application - *Jon C. Rittenberger, Smith Johnston*

2:30 PM Applications for Long-Term Human Missions - *John Bradford*

3:00 PM Break

3:15 PM Breakout Session: Space Science Relavance, Approaches, and Knowledge Gaps for Space Research and Application - *Moderator: C. Loren Buck*

4:45 PM Closing Remarks - *Jacob Cohen*

5:15 PM End

LOGISTICS

NASA AMES SPACE TORPOR WORKSHOP MOFFETT FIELD, CA

MEALS

Food will not be provided to workshop attendees. We will provide coffee, tea, and light snacks in the morning.

Lunch:

There are three options for lunch:

1. You can order a to-go order from **Specialty's Café by 9:30 a.m.** on Monday or Tuesday. We will pick it up for you. If you decide to do this you must send a copy of your order (including the items, name it is under, and confirmation number) to jessica.a.partridge@nasa.gov **no later than 9:30 a.m**.

Order instructions:

- Go to https://www.specialtys.com/Menu.aspx
- Click "Pick a café"
- From drop down menu select "Santa Clara County" and set your location to **645 Ellis St. Mountain View, California**
- Select the correct date
- Select 10:30 a.m. for the pick up time

2. You can order from the onsite cafeteria. Given the size of the group you will only have the option to order the special on Monday and Tuesday. **Orders must be placed by 10 a.m**.

Monday Special: Chicken Gyro with an optional side of fries

Tuesday Special: Fish Tacos with an optional side of fries

3. There are several near by restaurants in downtown Mountain View located on Castro Street approximately a 7 minute drive from NASA Ames.

Dinner:

On Monday, March 12th we will have an optional no-host dinner in downtown Mountain View after the workshop. Location is TBD. You are more than welcome to join us.

SPEAKER INFO

Brian Barnes

Director, Institute of Arctic Biology,
University of Alaska Fairbanks

Keynote: "Squirrel vs. Bear: Comparing Phenotypes of Mammalian Hibernation"

Dr. Brian M. Barnes is Director of the Institute of Arctic Biology and Professor of Zoophysiology at the University of Alaska Fairbanks. He also leads the NIH supported Alaska INBRE program that is building state-wide capacity in biomedical and behavioral health research and he is Science Director of the Toolik Field Station in northern Alaska, the flagship U.S. Arctic field station. He received his B.S. in Biology from the University of California, Riverside, Ph.D. in Zoology from the University of Washington, and trained as a post-doctoral scientist in the Departments of Psychology and Zoology at the University of California, Berkeley before moving to Alaska in 1986. Barnes is an environmental physiologist with active research programs in cryobiology, circadian and circannual rhythms, and energetics, especially concerning hibernating mammals.

Abstract:
This talk contrasts the natural history, seasonal timing, thermoregulation, and energetics of two classic mammalian hibernators, the arctic ground squirrel and the American black bear. Both species begin hibernation in anticipation of winter by fattening and increasing variability of body temperatures, but once torpor begins, the 1 kg ground squirrel decreases core body temperatures (Tb) to -3 degrees Celsius whereas Tb of the 100 kg black bear averages 34 degrees C. This difference is related to body mass and thermal conductance. Minimum metabolism in hibernating ground squirrels reaches 2% of basal rates and 25% of basal rates in bears; both species show have Tb independent mechanisms of metabolic suppression. Ground squirrels return to normal levels of Tb each 3 weeks when they sleep for less than one day; bears spend up to 80% of hibernation in sleep, from which they can arouse quickly. Neither species display circadian rhythms during hibernation. In both, metabolic fuel use is reprogrammed to use fat and both show stasis in mass of muscle and bone despite near complete disuse. Component phenotypes of hibernation, especially in bears, offer attractive applications for extending deep space travel in astronauts, if they can be reverse engineered into people. We need to understand the molecular and genetic bases of mammalian hibernation first.

SPEAKER INFO

Anne Yoder

Braxton Craven Professor of Biology, Duke University

"Obligate but Flexible Hibernation in a Clade of Non-Human Primates: The Dwarf Lemurs of Madagascar"

Anne D. Yoder is the Braxton Craven Professor of Evolutionary Biology at Duke University and also the Director of the Duke Lemur Center. She received her BA from UNC-Chapel Hill and her Ph.D. from Duke. After a postdoctoral appointment at Harvard, an assistant professorship at Northwestern, and an associate professorship at Yale, she finally returned to her North Carolina roots. She joined the Duke faculty in June of 2005 and assumed the Directorship of the Duke Lemur Center in January of 2006.

Her research focuses on the biological diversity of Madagascar, especially its iconic lemurs. She employs integrative evolutionary genetics and genomics to investigate the historical patterns and processes that characterize, generate and maintain species diversity in the highly endangered Malagasy system. She has maintained a decades-long fascination with the hibernation phenotype expressed by dwarf lemurs, culminating in a multidisciplinary collaboration that is examining the ecology, behavior, gene regulation, and fundamental physiological patterns associated with the hibernation phenotype.

Abstract:
Dwarf lemurs are small-bodied nocturnal primates that are endemic to the island of Madagascar. Though there are presently only four recognized genera of dwarf lemurs, they occur in virtually habitat in Madagascar, from the hot and dry deciduous forests of the southwest to the cold and wet rainforests of the eastern escarpment. Despite the broad array of habitats and ecologies that they occupy, dwarf lemurs share one striking characteristic that is unique within the primate order: they are obligate hibernators.

Anne Yoder will present the results gathered over the past decade of study by an interdisciplinary team comprised of sleep specialists, behavioral ecologists, genomicists, and physiologists. This team of investigators has found that though hibernation occurs in all dwarf lemurs, the mode of hibernation can differ depending upon environment, ranging from passive response to ambient temperatures in hot environments to protected heterothermy in cold environments. Moreover, the disparate approaches of captive environmental manipulations and transcriptome characterization imply that the hibernation phenotype in dwarf lemurs may result from the "rescue" of ancestral traits that characterized the earliest mammals.

SPEAKER INFO

Steve Swoap

Professor of Biology, Williams College

"Torpor in Mice"

Steve Swoap received his PhD in Physiology and Biophysics in the lab of Dr. Kenneth Baldwin at University of California, Irvine. He then trained in molecular cardiology in Dr. Sandy Williams' lab at the University of Texas, Southwestern Medical Center in Dallas. Steve became an assistant professor of Biology at Williams College in 1996 and moved through the ranks to be a full professor as of 2007. Steve served as the chair of the department for 5 years and chair of the Biochemistry program for 1 year. Steve has received several grants from NIH and NSF to fund his research. He regularly publishes with his undergraduates on the physiological consequences of caloric restriction in the mouse.

Abstract:
In response to an acute negative energy balance, mice can enter into a torpid state. Torpor is a controlled reduction in metabolic rate to levels well below basal metabolic rate. This results in a fall in core body temperature to a few degrees above ambient temperature, with a minimum temperature around 17°C in the mouse. In addition, heart rate, blood pressure, peripheral blood flow, and ventilation plummet during a bout of torpor. The mechanisms that drive a mouse into torpor are only beginning to be elucidated. Central action of adenosine appears to be important for torpor induction. Similarly, low circulating levels of blood glucose and leptin are required for engagement of torpor in the mouse. One region of the hypothalamus within the brain, namely the arcuate nucleus, is responsive to both leptin and glucose. Optogenetic stimulation of this area in the presence of food induces consumptive behavior, while stimulating in the absence of food results in deeper and longer torpor bouts. This suggests this region of the brain participates in homeostatic control of energy balance.

SPEAKER INFO

Keith Ruskin

Professor of Anesthesia and Critical Care,
University of Chicago

"Sleep, Anesthesia, and Torpor: Distinct Physiologic States"

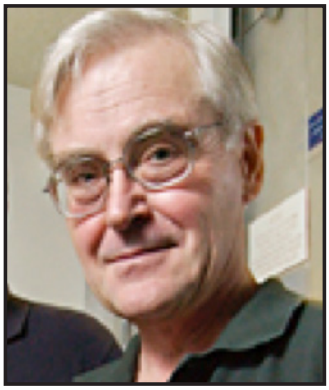
Keith Ruskin is a Professor of Anesthesia and Critical Care and Director of Neurosurgical Anesthesia at the University of Chicago. Keith attended medical school at the University of Miami School of Medicine and completed his residency at New York University Medical Center. Before moving to Chicago, he was Professor of Anesthesiology and Neurosurgery at Yale University.

Keith's major academic interests include human performance and aerospace medicine, and his career has focused on teaching these disciplines to practicing physicians. Keith has given talks on safety, human performance, and aerospace physiology. He has given lectures on safety, human performance, and aerospace physiology to undergraduate, graduate, and medical students at the University of Chicago and as a visiting professor at other medical schools. Keith is working with NASA psychologists to develop a fatigue risk management program for anesthesiologists who must work overnight shifts. He currently teaches an undergraduate course on anesthetic mechanisms and pain physiology, and is developing a course on human performance in extreme environments.

Keith is Chair of the Aerospace Medical Association's Aerospace Human Performance Committee and is also a member of the American Society of Anesthesiologists' Committee on Patient Safety and Patient Safety Editorial Board. Keith has had a lifelong interest in aviation and currently holds a Commercial Pilot certificate with Airplane Single-Engine Land and Sea, Multi-Engine Land, and Instrument Airplane ratings. He holds a SIC type rating for the DC-3.

Abstract:
Normal sleep, anesthesia, and torpor are distinct states that affect brain activity, metabolic rate, and other physiologic functions. Sleep progresses through four stages from light sleep to deep sleep and back. Rapid eye movement (REM) sleep is characterized by theta and alpha rhythms on EEG, rapid eye movements, and muscle atonia. Sleep is known to affect thermoregulation, with non-REM sleep producing decreases in core temperature and metabolic rate. Most anesthetic agents, including potent volatile anesthetics and intravenous agents such as propofol bind to gamma-aminobutyric acid (GABA) receptors in the central nervous system. These drugs are currently thought to act through subcortical centers involved in the control of sleep-wake states. They also hypothalamus. Dexmedetomidine and ketamine appear to act on some of the same neuronal circuits as propofol, but target alpha-2 adrenergic and N-methyl-D-aspartate receptors. Mammalian torpor involves specific, CNS-mediated changes in thermoregulation and metabolic rate. The ability to display torpor exists in species that rely upon energy conservation to survive in extreme climates (e.g., bears). Although torpor does not naturally occur in humans, one interesting case report describes a patient with repeated circadian-regulated episodes of hypothermia that produced a torpor-like state for several hours. This report, along with other studies of the mechanism of thermoregulation, suggest that it may be possible to exploit neuronal circuits responsible for thermoregulation in order to reduce energy expenditure and produce synthetic torpor.

SPEAKER INFO



Craig Heller

Lorry I. Lokey/Business WIre Professor

"Human Thermoregulation"

H. Craig Heller received his PhD degree from Yale University in 1970. After a postdoctoral fellowship at The Scripps Institution of Oceanography, he joined Stanford University in 1972. Dr. Heller was named the Lorry I. Lokey/ Business Wire Professor of Biological Science and Human Biology in 1993; he is also Professor of Psychiatry and Behavioral Sciences (by courtesy). Dr. Heller served as Associate Dean of Research from 1994 to 1997 and chairman of Biological Sciences from 1997 to 2002. His research focuses on the neurobiology of sleep, biological rhythms, and thermoregulation. In addition, he has a long record of research on mammalian hibernation and the roles of sleep and circadian control systems in that phenomenon. Current work in this laboratory includes research on the roles of sleep and circadian rhythms in performance and learning and memory. The lab is working towards clinical trials of a pharmacotherapy that would mitigate the learning disability of Down Syndrome. Extensions of this work are being initiated with mouse models of Alzheimer's Disease. Another area of research in the Heller laboratory is the regulation of body temperature in humans. A technology for rapid and non-invasive management of body temperature was developed in the laboratory and numerous applications of this technology ranging from therapeutics, to industrial medicine, to athletic performance enhancement are being developed.

Abstract:
The classic view of the mammalian thermoregulatory system includes a hypothalamic thermostatic mechanism that uses hypothalamic temperature as the major negative feedback signal and uses skin temperatures as feedforward signals that alter the hypothalamic temperature set points for effector responses. This system in humans regulates body temperature in the approximate range of 36.5 to 37.5°C. In mammalian torpor the hypothalamic temperature set points are adjusted to lower levels resulting in a lowering of body temperature and a consequent decrease in metabolic rate. Thermoregulatory responses can be blocked pharmacologically, but can human hypometabolism be achieved non-pharmacologically? We have established that the major human effectors for loss of heat consist of vascular structures in the glabrous skin. We can use those limited body surfaces to extract heat from the body, but regulatory responses shut them down if core temperature falls. Since most of the body surface is a good thermal sensor, but not a good heat exchanger, we ask whether a feedforward signal of warm trunk temperature can be used to facilitate heat extraction from the glabrous skin and thereby achieve a small degree of hypometabolism. Should pharmacological methods be used to suppress metabolism, could heat extraction from the glabrous skin be used to achieve efficient lowering of body core temperature?

SPEAKER INFO

Hannah Carey

Professor of Comparative Biosciences,
University of Wisconsin School of Veterinary Medicine

"Incorporating the Gut Microbiome into the Hibernator Metabolic Phenotype"

Hannah V. Carey, PhD, is a Professor in the Department of Comparative Biosciences at the University of Wisconsin School of Veterinary Medicine. She received her PhD in Zoology from the University of California, Davis studying foraging and nutritional ecology of marmots, and completed postdoctoral training in intestinal transport physiology at the University of Nevada School of Medicine and the Ohio State University College of Medicine. Dr. Carey's research program investigates natural adaptations to extreme changes in physiology and nutrition in hibernating mammals, and their potential applications to biomedicine. Her specific focus is on responses of the gastrointestinal tract and liver, and the gut microbiome to the feeding-fasting cycles that accompany hibernation in ground squirrels. Dr. Carey's research has been funded by the National Institutes of Health, the National Science Foundation, the US Army Research Office and the Defense Advanced Research Projects Agency. She has served on committees and in leadership roles in the American Gastroenterological Association and the American Physiological Society (APS). She served on the governing council of APS, and was APS President from 2007-2008. Dr. Carey is the North American Editor of the Journal of Comparative Physiology B, and is currently the Vice President for Science Policy of the Federation of American Societies for Experimental Biology. Dr. Carey served as a Program Director at the National Science Foundation, Division of Integrative Organismal Systems from 2010-2011. She is the Director of the UW-Madison Biotron Laboratory, a campus facility that provides controlled environment space for plant, animal and material research and testing.

Abstract:
Fasting during the hibernation season can affect organ function throughout the body, but has particularly strong effects on the gastrointestinal tract. These include increased intestinal permeability, mucosal atrophy, oxidative stress and multiple changes in the intestinal immune system. These effects are also evident in nonhibernating species after prolonged fasting or total parenteral nutrition. The altered dietary landscape during hibernation not only affects the host animal but also eliminates key metabolic resources for gut bacteria, including complex plant polysaccharides and other fermentable substrates that escape absorption in the small intestine. As the hibernation season progresses, bacterial numbers and microbiota diversity fall. The relative abundance of bacteria that prefer complex plant glycans is reduced, whereas those species that can utilize host-derived substrates (e.g., mucin glycans) for their metabolic needs increase. It is now clear that metabolic activity of the gut microbiome can have widespread effects on host biology and health. Our ongoing studies suggest that hibernation leads to mutualistic protective responses, possibly driven by altered levels of bacterial metabolites that affect host signaling pathways, that preserve homeostasis in the gut ecosystem. Understanding how feeding/fasting cycles in hibernators affect crosstalk between animal hosts and their microbial symbionts may lead to new approaches to reduce adverse effects of disturbances in the host-microbe relationship in non-hibernators, such as dietary change, prolonged fasting, total parenteral nutrition or radiation injury.

SPEAKER INFO

Katharine Grabek

Postdoctoral Scholar, Stanford University School of Medicine

"Genetic Components Driving the Seasonal Onset of Mammalian Hibernation"

Katharine Grabek is a postdoctoral scholar in the Department of Biomedical Data Science at Stanford University, where she is mentored by Dr. Carlos Bustamante. She completed her Ph.D. in 2014 in Human Medical Genetics at the University of Colorado, Anschutz Medical Campus, under the mentorship of Dr. Sandy Martin. She is especially interested in understanding the evolutionary and genetic mechanisms that underlie mammalian hibernation. Her research has focused on utilizing proteomic, transcriptomic and genomic approaches to link the 13-lined ground squirrel's genome to phenome. More specifically, her dissertation research identified proteins and transcripts differentially expressed in the 13-lined ground squirrel's heart and brown adipose tissue, respectively. For her postdoctoral research, she has worked on improving the contiguity of 13-lined ground squirrel's genome assembly. She has also worked on estimating the heritability of, and identifying genetic variants significantly associated with, the seasonal onset of hibernation. Prior to her Ph.D., Katharine received her B.S. in biotechnology in 2006 and M.S. in biology in 2008 at Plymouth State University. When not doing research, Katharine enjoys hiking, skiing and spending time with her family.

Abstract:
When housed in an animal facility, 13-lined ground squirrels exhibit individual variation in the timing of hibernation onset. This timing is not explained by environmental or biological factors, such as body mass and sex. Following the hypothesis that underlying genetic components instead drive hibernation onset, a modified ddRAD sequencing protocol was used to characterize genetic variation in 153 13-lined ground squirrels. Combining this with datalogger records, high heritability (61-100%, n=72) was estimated for the seasonal onset of hibernation. After applying a genome-wide scan with 46,996 variants, 2 independent loci were significantly associated with the timing of hibernation onset (α=0.1, $p<7.14x10-6$). An additional 12 loci were suggestively significant ($p\leq2.13x10-4$) for association with the phenotype. These associated variants were located near genes related to hibernation physiology, including those that control food intake, heart rate and insulin signaling. Finally, using existing transcriptome datasets, an expression quantitative trait loci (eQTL) analysis identified significant transcript abundance associations ($q<0.1$) for 8/14 variants. These results highlight the power of applying a genetic mapping strategy to hibernation and present new insight into the genetics driving its seasonal onset.

SPEAKER INFO

Kimberly Krautkramer

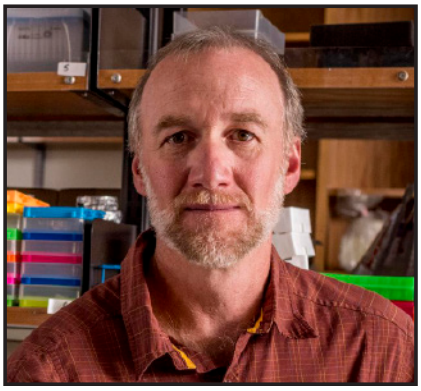
Medical Scientist Training Program (MD-PhD) Fellow,
Wisconsin Institute for Discovery and the University of
Wisconsin School of Medicine and Public Health

"Multi-Tissue Chromatin Modification During Hibernation"

Kimberly Krautkramer received her PhD at the University of Wisconsin-Madison, and is currently completing the final year of her MD training there as well. Her research focuses on regulation of the epigenome, and ultimately gene expression programs, by environmental factors, including diet and nutrient availability, and has pioneered work linking the gut microbiota to these processes. Within this framework, she works very closely with the Dr. Hannah Carey laboratory and Dr. Rashpal Dhillon to understand epigenetic control throughout the mammalian hibernation cycle and how the gut microbiota may play a role in this process.

Abstract:
Hibernation is characterized by a dramatic regulation of metabolic rate during torpor-arousal cycles, which affects levels of circulating metabolites. This, in turn, has the potential to induce dynamic alterations in histone acetylation and methylation. Eukaryotic histone-modifying enzymes are known to be sensitive to levels of both host and gut microbial small molecule metabolites. The fundamental unit of chromatin is the nucleosome, which is comprised of a core of histone proteins wrapped by genomic DNA. Histones are subject to a multitude of post-translational modifications (PTMs) which dictate how accessible genomic DNA is to processes such as transcription and replication. Using LC-MS/MS, we have examined global histone PTM states in thirteen lined ground squirrel tissues throughout the hibernation cycle. Our data reveal differential chromatin signatures that are both unique to each tissue examined and also to each phase of hibernation. We have linked these changes to the availability of both host and gut microbial metabolite availability, which undergo measurable seasonal changes, and have identified candidate histone-modifying enzymes that are regulated in response to these changes. Collectively, our results suggest that the robust metabolic and nutritional shifts associated with hibernation drive changes in chromatin state and may provide key insight into the molecular drivers of mammalian torpor.

SPEAKER INFO



C. Loren Buck

Professor of Biology and Associate Director,
Center for Bioengineering Innovation,
Northern Arizona University

Dr. C. Loren Buck received a PhD in Biology from the University of Alaska Fairbanks in 1998. He is currently Professor of Biological Sciences and Associate Director of the Center for Bioengineering Innovation at Northern Arizona University. Dr. Buck is an environmental physiologist broadly interested in adaptations and responses of animals to extreme and changing environments. His research employs both laboratory and field approaches and a wide variety of techniques spanning from genomes to phenomes to populations. His research has long focused on various aspects of hibernation including metabolic suppression, biological timing and the influence of gut microbiota on physiology. In addition, the Buck laboratory is investigating mechanisms of pathologies related to toxicant exposure among indigenous peoples resident to arctic Alaska, Arizona and Australia. A critical component of these ecotoxicology projects is use of a community-based participatory research approach. The Buck laboratory is currently funded by the National Science Foundation, the National Institutes of Health and private foundations.

SPEAKER INFO

Kelly Drew

Professor of Chemistry and Biochemistry,
Institute of Arctic Biology, University of Alaska Fairbanks

"Pharmacological and Nutrition-Based Approaches for Sustained Torpor"

Dr. Drew received a BS in psychology from the University of Alaska Fairbanks and PhD in Neuropharmacology from Albany Medical College, Albany, NY, and was a postdoctoral fellow in Neuropharmacology at the Karolinska Institute, Stockholm, Sweden. She has studied aspects of hibernation related to mechanisms of and protection from brain injury at the University of Alaska Fairbanks since 1990 where she is now a Professor in the Department of Chemistry and Biochemistry and the Institute of Arctic Biology. Currently her laboratory focuses on developing A1 adenosine receptor agonists for targeted temperature management and seizure prophylaxis after cardiac arrest, stroke, and spinal cord injury.

Abstract:
Pharmacological and Nutrition-Based Approaches for Sustained Torpor will provide a brief overview of pharmacological approaches to inducing torpor with focus on A1 adenosine receptor agonists. Nutritional-based approaches to promote thermolytic effects of A1 adenosine receptor agonists, and mitigate side-effects of prolonged hypothermia in non-hibernating mammals will also be discussed.

SPEAKER INFO

Sandy Martin

Professor of Cell and Developmental Biology,
University of Colorado School of Medicine

"Metabolic Time and Mechanisms Underlying Hibernation"

Sandy developed an early fascination with manned space flight, in no small part a consequence of growing up in Albuquerque, NM, during the cold war space race between the US and the USSR. The three air force bases in town, plus Sandia Laboratories and Lovelace Clinic all played key roles in the early space program and the excitement for launches was palpable. In those days astronauts were pilots and it was a tough road for a girl to become a pilot, but science offered an alternative route.

Sandy earned her undergraduate degree in human biology at Stanford and had the good fortune to be introduced to basic research working with Dale Kaiser on Myxococcus xanthus. As a PhD student in Biochemistry at UC Berkeley her thesis research with Allan Wilson examined silencing of the delta globin gene in Old World Monkeys. Finally, she was part of the team that discovered that LINE-1 is an active retrotransposon while doing postdoctoral work with Clyde Hutchison and Marshall Edgell at UNC. After a brief stint in biotech, Sandy returned to academia, developing her lab working on the genetics and biochemistry of LINE1 retrotransposition and began work on hibernators at the University of Colorado School of Medicine.

Abstract:
The long-term goal of Sandy's work is to elucidate the molecular foundations that underlie the extreme physiology of hibernating mammals with the hope of translating critical aspects of their remarkable phenotype to humans. If many phylogenetically interspersed species can safely and reversibly lower their metabolic rate to a few percent of resting, and allow their body temperature to drop to near freezing, why can't we? Engineering a reversible metabolic depression in humans that is based on natural hibernation would be a huge boon for the treatment of cardiac arrest, stroke and trauma, routine surgery and manned space missions. The immediate goal of her ongoing work is to exploit the natural rhythms of hibernation, which depend on metabolic time, to define the relevant biochemical mechanisms. This talk will highlight three arguments: first, mimicking natural hibernation holds more promise for safe, reversible metabolic depression in humans than elaborating current medical practice; second, why we should expect studies of natural hibernation to lead to discoveries that translate to the engineering of metabolic depression in humans; and third, why the field has not yet achieved the depth of knowledge needed engineer human hibernation, and what is needed to make the crucial discoveries.

SPEAKER INFO

Meghan McGee-Lawrence

Assistant Professor, Department of Cellular Biology and Anatomy
Medical College of Georgia, Augusta University

"Suppression of Bone Remodeling Conserves Energy and Bone Mass During Hibernation"

Meghan McGee-Lawrence studied Biomedical Engineering under Dr. Seth Donahue at Michigan Technological University, receiving her PhD in 2009. Meghan's doctoral research focused on understanding the effects of hibernation on bone mass and bone remodeling in several different hibernating species including bears, 13-lined ground squirrels, and marmots. After graduating, Meghan completed postdoctoral training in molecular and cell biology under Dr. Jennifer Westendorf at the Mayo Clinic, with a primary focus on epigenetic and transcriptional regulation of bone formation. Meghan began her independent career in the Department of Cellular Biology and Anatomy at the Medical College of Georgia (Augusta University) in 2014. Her current research interests include bone (osteocyte) mechanobiology during exercise and disuse, epigenetic changes in mesenchymal stem cells that contribute to bone loss and fatty infiltration of the skeleton with aging, and the role of the skeleton in whole body metabolism and insulin sensitivity. Her research program is funded by the National Institute on Aging, the National Science Foundation, and the American Diabetes Association.

Abstract:
Reduced weight-bearing activity (disuse) typically leads to bone loss because bone formation and bone resorption become unbalanced, leading to a net decline in the amount of bone being formed relative to the amount being resorbed. Hibernation is a natural model of musculoskeletal disuse because hibernating animals greatly reduce weight-bearing, physical activity for up to 6 months annually. While these animals would be expected to lose bone during this period of inactivity, hibernating species like bears preserve bone structure and strength by maintaining balanced bone remodeling activity. While bone formation and resorption activity remain balanced, bone remodeling in general is greatly reduced during hibernation, consistent with the goal of conserving energy during long periods of food scarcity. It is likely that hibernators have evolved sophisticated physiological processes to prevent hypercalcemia and conserve energy that simultaneously maintain skeletal integrity. Investigating the roles of neural and hormonal control of bone metabolism in hibernating animals could give valuable insight into translating the mechanisms that prevent disuse-induced bone loss in hibernators into novel therapies for preventing disuse-induced bone loss during long-term spaceflight.

SPEAKER INFO

Matthew T. Andrews

Professor of Biochemistry and Biophysics and Executive Associate Dean, College of Science, Oregon State University

"Portable Hibernation-Based Solutions for Protection Against Ischemia and Reperfusion Injury in Non-Hibernating Mammals"

Matt Andrews is Professor of Biochemistry and Biophysics and Executive Associate Dean in the College of Science at Oregon State University. His career as a faculty member and P.I. began in the Department of Genetics at North Carolina State University where he was an Assistant and Associate Professor from 1987 to 2000. In 2000 he moved to the Department of Biology at the University of Minnesota Duluth where he served as Department Head, Director of Graduate Studies, Founding Director of the Bio-Translational Research Center, and McKnight Presidential Professor. In 2016 he moved to Oregon State to join the Department of Biochemistry and Biophysics, and gain additional administrative, personnel and budgetary experience as Associate Dean. His research program is centered on the genes and small molecules that regulate mammalian hibernation. His findings include hibernation strategies that can be applied to human health such as a novel therapy for ischemia and reperfusion injury. Andrews has been funded by NIH, DARPA, U.S. Army Research Office, and the U.S. Army Medical Research and Materiel Command.

Abstract:
A small-volume (1 ml/kg) fluid based on metabolic adaptations in hibernating mammals has been developed to avoid damage associated with ischemia and reperfusion injury that can occur during entry, maintenance, and arousal from torpor. This fluid is composed of the D-stereoisomer of β-hydroxybutyrate (D-BHB) and melatonin. During hibernation D-BHB is a circulating 4-carbon fuel source that crosses the blood brain barrier and is catabolized in the heart and brain without generating lactic acid. Melatonin is a potent antioxidant that naturally peaks in the blood during arousal from torpor, and decreases shock-induced oxidative stress through its inherent antioxidant action and receptor-mediated effects. This formulation has been shown to improve survival in non-hibernating mammals such as rat and pig models of hemorrhagic shock, and has received approval in a Pre-IND Meeting with the FDA (PIND 130671, July 8, 2016). A freeze-dried formulation with a short reconstitution time has recently been developed to increase portability and long-term storage.

SPEAKER INFO

Joseph Bielitzki

Consultant and Science Advisor
Chief Veterinarian, NASA

Keynote: "Metabolic Stasis and Space Exploration"

Currently serves as the Chief Veterinarian for NASA. He also works as science and technology consultant for a international food manufacturer working on problems in nutrition, agronomy, and supply chain issues. He previously served as a program manager for DARPA managing a large set of life sciences programs, including biowarfare defense, metabolic control, immune function and tissue engineering. Prior to that he worked in a variety of academic institutions providing laboratory animal care. He is a recognized authority on animal care regulation and ethical issues surrounding animal use. He works with his wife on a variety of great ape conservation issues in central Africa and supports a variety of youth basketball programs in eastern DRC.

Abstract:
The controlled reduction of metabolism during space flight has any number of benefits. The most obvious is the reduced burden on limited resources, such as food, water, oxygen, and environmental life support systems. Metabolic stasis provides a control mechanism for dealing with any number of emergency situations; severe hemorrhage, ischemic injuries, radiation exposure, loss of critical environmental control to name few. The limiting factor in each condition is an adequate supply of oxygen at the cellular level, more specifically the ability of oxygen to remove the accumulated electrons and reactive oxygen species produced during oxidative phosphorylation. As an input/output system, metabolic control either reduces electron production or facilitates electron removal or buffering. Animal models provide a number of naturally occurring systems that provide survival during limited caloric availability, hostile environmental conditions, and hypoxic events; all of which need additional consideration for developing reversible, torpor like states in non-hibernating species.

SPEAKER INFO

Yuri Griko

Senior Research Scientist, NASA Space Biosciences Research Branch, NASA Ames Research Center

"Synthetic Torpor and Metabolic Control Technology: From Laboratory Research to Application in Space Missions"

Dr. Yuri Griko is a Senior Research Scientist at NASA. His laboratory of Countermeasures Development at NASA Ames Research Center works on the technology assessment and application of the metabolic control strategy for spaceflight applications.

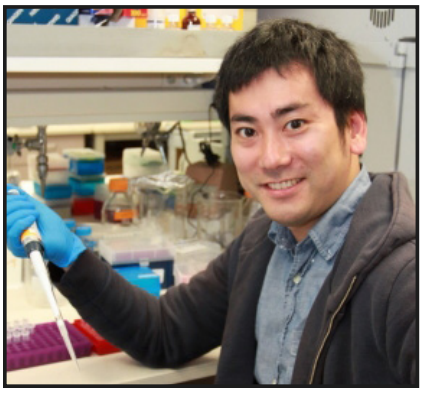
Yuri Griko received his Ph.D. degree in Biophysics and Biochemistry from Moscow Institute of Physics and Technology in 1987. Since 1981, he has worked as a Senior Scientist and acting Director of Laboratory in the Institute of Protein Research (Russia). Previously, he held different positions in the Department of Chemistry at Cambridge University (UK), the Department of Biology at Johns Hopkins University, the position of Director of Research at Biolinx Inc., and the position of a Director of Biophysics at Clearant Inc.

Dr. Griko's professional experience combines scientific expertise and research program management in the following areas: protein-based drug design, pharmaceutical product characterization, radiation countermeasure development, biophysics, protein and genetic engineering.

His current work primarily focus on the development of biomedical countermeasures against potential medical conditions induced by the spaceflight environment. Within the scope of the Countermeasure Development project, his lab team tests the hypothesis that metabolic suppression induced in animals will profoundly reduce their sensitivity to the damaging effect of radiation and microgravity, as well as other kinds of stresses caused by exposure to the space environment.

Abstract:
As human presence in space will likely extend throughout the solar system, up-mass and power constraints will become of paramount importance in considering logistics of transporting experimental animals and humans into space. Life support costs will be a significant part of the mission payload. One solution may be to take advantage of the emerging science of metabolic control, which allows the metabolism of animals to be reversibly reduced to a minimal level for a period of time. In the hypometabolic stasis animals are capable of tolerating the environmental extremes exhibited in spaceflight, including altered gravity, exposure to space radiation, chemically reactive planetary environments, and temperature extremes. Integration of a "metabolic control technology" within deep space mission architecture will solve many problems associated with long-duration space missions, such as payload cost reduction, space flight duration logistics, and demonstrate the potential application of this technology for human astronauts. In this report, Dr. Griko will present results of recent studies at NASA Ames Research Center and discuss the importance of utilizing metabolic control technology with particular attention given to the spaceflight experiments beyond low Earth orbit (LEO).

SPEAKER INFO



Hiroshi Yamaguchi

Postdoctoral Fellow, Luis de Lecea Laboratory,
Department of Psychiatry and Behavioral Sciences,
Stanford University

"Dorsal Medial Hypothalamus GABA Neurons That Regulate Torpor: Potential Application to Space Missions"

Dr. Hiroshi Yamaguchi earned his Ph.D. in molecular cell biology from Osaka University in Japan under the supervision of Dr. Shigekazu Nagata. His thesis work was focusing on the molecular mechanism of the engulfment of dying cells and its immunosuppressive effects. Through this work, Dr. Yamaguchi had learned the techniques in molecular biology, cell biology and biochemistry including the design of plasmid DNA, gene transduction using viral vectors and quantification of small molecules.

Dr. Yamaguchi joined the Luis de Lecea lab at Stanford as a postdoctoral fellow in 2015 and has established CRISPR/Cas9-mediated cell type-specific gene editing system in adult mouse brain by taking advantage of his expertise in molecular biology. Dr. Yamaguchi is investigating the neuronal mechanism of torpor using viral tracing, optogenetic, chemogenetic tools and CRISPR/Cas9 technologies.

Abstract:
Torpor is characterized by an active depression in metabolic rate below the basal level. Mice exposed to cold temperature coupled with caloric restriction go into torpor within 12 hours of being withheld food. Despite it is expected that the technologies which can control metabolism could offer benefit when transporting experimental animals aboard spacecraft on long-duration missions, the neuronal mechanism of controlling torpor and metabolism has not been fully understood. In this study, we identify the vesicular GABA transporter Vgat-positive neurons in the dorsomedial hypothalamus are activated before, during and after torpor. We show that the suppression of DMH Vgat-positive neurons blocks the induction of torpor. The anterograde tracing of DMH Vgat-positive neurons reveals that DMH Vgat-positive neurons strongly project to the preoptic area which is known to be involved in the regulation of animal's body temperature. Taken together, these results reveal the brain circuit that can control mouse torpor.

SPEAKER INFO

Jon C. Rittenberger

Associate Professor of Emergency Medicine, Occupational Therapy and Clinical and Translational Science, University of Pittsburgh

"Thermoregulation, Emergency and Short-Term Human Terrestrial and Space Application"

Jon Rittenberger received his Medical Doctorate from the University of Pittsburgh in 2002 and completed his Emergency Medicine residency in 2005. He was recruited to remain as the Resuscitation Outcomes Consortium Fellow between 2005-2007 and earned his Master of Science in Clinical Research. Dr. Rittenberger was selected for a KL2 scholarship through the Clinical and Translational Science Institute at the University of Pittsburgh (2007-2011) and has received funding from the National Institutes of Health, American Heart Association and several philanthropic foundations. Dr. Rittenberger was a founding member of the Post Cardiac Arrest Service at the University of Pittsburgh and has cared for over 2500 patients resuscitated from cardiac arrest over the last 12 years. He is a board-certified Emergency Physician and serves as the Director of the Applied Physiology Laboratory at the University of Pittsburgh. Drawing on his clinical experience, Dr. Rittenberger's lab manipulates temperature in healthy individuals with the goal of safely decreasing metabolism for both clinical care and space travel.

Abstract:
Metabolic manipulation is commonly used in the clinical setting for patients with critical illness. By inducing a synthetic torpor, oxygen consumption, CO_2 production, nutrient need and waste production can be decreased. We will discuss the following examples and explore how synthetic torpor may be used. 1) Apollo 13, 2) STS-107 Columbia, 3) Future scenarios for Orion with the possibility of remaining in a space suit for 4 days. Dr. Rittenberger will present how metabolic manipulation is used in clinical medicine along with potential applications for long-duration synthetic torpor in Astronauts.

SPEAKER INFO

Smith L. Johnston

Medical Officer and Flight Surgeon,
NASA Johnson Space Center

"Thermoregulation, Emergency and Short-Term Human Terrestrial and Space Application"

Smith Johnston, from Woodstock, Georgia, received a Bachelor of Science in biology in 1976 and a Doctor of Medicine in 1981 from Emory University in Atlanta, Georgia. From 1984 to 1990, Dr. Johnston completed residencies in Internal and Aerospace Medicine from Wright State University, as well as a Master's of Science in Aerospace and Preventive Medicine. Dr. Johnston is a member of the Clinical Faculty, at the University of Texas Medical Branch, Dept. of Preventive, Occupational and Environmental Medicine in Galveston, Texas. Dr. Johnston has spent most of his career as a Medical Officer and Flight Surgeon for NASA Medical Operations Branch at the NASA Johnson Space Center in Houston, Texas. Over the past 25 years he has supported the medical care of the active Astronaut Corps, their families, and the retired Astronauts. He has been the lead physician for the International Space Station (ISS) Emergency Medical System and Crew Return Vehicle development and has supported two Expedition ISS missions and over 25 Shuttle missions. Over the last five years he has served as the Medical Director of NASA-JSC Aerospace and Occupational Medicine Clinics, and is presently the lead of NASA's Astronaut Medical Selection and Retention Standards, and the Fatigue Management and Human Health, Performance, and Longevity Programs. Dr. Johnston is Board Certified in Aerospace Medicine from the American Board of Preventive Medicine and a Fellow of the Aerospace Medical Association. Dr. Johnston's expertise centers on taking the innovations discovered from the US and International Space Programs to benefit, not only the lives of the Astronauts and Cosmonauts, but also his Earth-bound patients.

Abstract:
Metabolic manipulation is commonly used in the clinical setting for patients with critical illness. By inducing a synthetic torpor, oxygen consumption, CO_2 production, nutrient need and waste production can be decreased. We will discuss the following examples and explore how synthetic torpor may be used. 1) Apollo 13, 2) STS-107 Columbia, 3) Future scenarios for Orion with the possibility of remaining in a space suit for 4 days. Dr. Rittenberger will present how metabolic manipulation is used in clinical medicine along with potential applications for long-duration synthetic torpor in Astronauts.

SPEAKER INFO

John E. Bradford

President and COO, SpaceWorks Enterprises

"Applications for Long-Term Human Missions"

John E. Bradford is President and COO of SpaceWorks Enterprises in Atlanta. SpaceWorks is an aerospace engineering design and analysis firm focusing on next-generation space systems, future technologies, and emerging space markets.

Dr. Bradford has over 20 years of experience in the aerospace sector. He has served as Program Manager for numerous government-sponsored activities with NASA, the Air Force, DARPA, and commercial space industry. He has a wide variety of technical interests and expertise that spans human space exploration, advanced space launch, and hypersonic flight systems. His most notable work in support of human space exploration is in the area of human stasis, or torpor.

He received his Doctorate and Master's Degree in Aerospace Engineering from Georgia Tech. He also holds a Bachelor of Science degree in Aerospace Engineering from North Carolina State University. He is a Senior Member of AIAA, a NASA Academy (NAAA) alumnus, on the Steering Committee for NASA's annual RASC-AL student design competition, and a NASA NIAC Fellow. Dr. Bradford is a native of California and resides in Atlanta, Georgia with his wife and two children.

SpaceWorks Enterprises, under a research grant with NASA's STMD, has been advancing the idea and technology to place astronauts in a medically induced hypothermic state during the transit phases of deep-space missions. Microgravity, exposure to solar and galactic radiation, and long-term social isolation all present difficult medical challenges for the design of deep-space missions. As the human body is not naturally adapted and designed for survival in the space environment, the ability to render the crew inactive with suppressed metabolic activity offers multiple mission-level advantages from both an engineering and medical perspective.

Abstract:
The SpaceWorks team has been quantifying the system-level effects for this technology on deep-space exploration, with an emphasis on Mars missions. Studies have shown the design of the in-space habitat can be significantly impacted, with reduced volume, mass, and power requirements. These benefits result in smaller propulsive stages and/or shorter mission transit times, a reduced number of Earth-to-Orbit heavy lift launches, and improved radiation shielding.

A summary of the results obtained for a nearer-term exploration class Mars mission, as well as potential impact on future settlement class missions, will be discussed and presented.

Advancing Torpor Inducing Transfer for Human Stasis to Mars

Presented by: Dr. John E. Bradford, SpaceWorks Enterprises

Through a research grant from NASA's NIAC program, SpaceWorks and its team members have been evaluating the advantages and implementation approaches for sustaining crew members in long-duration, hypothermic stasis during the transit phases of deep space missions. The study team members consist of researchers from the Mayo Clinic, University of Alaska - Fairbanks, and a former Space Shuttle astronaut/ISS Commander. For the effort, both the medical and engineering aspects of the technology are being evaluated in the context of human exploration missions to Mars in the 2030 timeframe.

Urea-Nitrogen Salvage and Ureolytic Microbes in the Arctic Ground Squirrel Gut

Presented by: Dr. Khrys Duddleston, University of Alaska – Anchorage

Urea-nitrogen salvage (UNS) occurs when urea-nitrogen liberated by ureolytic microbes in the gut is utilized by the host in biosynthetic processes. UNS is long proposed as a mechanism by which protein is conserved during hibernation. The goal of this project is to determine the degree to which the arctic ground squirrel (AGS), an obligate seasonal hibernator, relies upon UNS to meet its nitrogen needs, and to characterize the ureolytic component of the gut microbiota. At pre-selected time points across the annual cycle of hibernation and summer activity, AGS were injected with 15N/13C-labeled urea and the release of 13CO2 in breath and incorporation of 15N in tissues determined. Breath collected from summer active and hibernating squirrels was enriched in 13CO2 indicating ureolytic activity in the gut. Tissues collected from summer active and hibernating squirrels were enriched in 15N, more so during hibernation, confirming the reliance upon UNS to meet nitrogen demand during hibernation. Cecal samples were collected to enumerate ureolytic bacteria in the gut and characterize the functional diversity of ureolytic component of the gut microbiota using 16S rRNA gene surveys, and metagenomics and metatranscriptomics analysis, which are ongoing.

Adapting Synthetic Torpor to Spaceflight Scenarios: Seldom-Discussed Challenges

Presented by: Dr. Matthew D. Regan, University of Wisconsin – Madison

Synthetic torpor—a state of reversible metabolic depression that is artificially induced in animals that are unable to naturally enter torpor—offers tremendous potential benefits to human spaceflight. There are a small number of technologies that are currently capable of placing mammalian model species (mice, rats) in synthetic torpor. The challenges of adapting these technologies to humans have been discussed in the literature, but the challenges of adapting them to spaceflight scenarios—specifically the spaceflight mission and the spacecraft environment—are seldom discussed. In this poster, we discuss some of these challenges, including (among other things) whether synthetic torpor will confer the same space-related protective benefits on animals as natural torpor, how synthetic torpor may affect crewmember cognition, and what demands existing synthetic torpor technologies may place on spacecraft capacities. For each challenge, we propose a potential ground-based experiment to better understand it, and ultimately, better understand how existing synthetic torpor technologies may (or may not) be adapted to spaceflight scenarios.

Role of Mitochondrial Protein Acetylation During Torpor

Presented by: Dr. Rush Dhillon, University of Wisconsin – Madison

Torpor is characterized by a dramatic change in metabolism that can modify the acetyl landscape of cellular proteins. Mitochondrial protein lysine N-e-acetylation has been implicated as a major regulatory mechanism for modulating protein function. Here, the role of mitochondrial acetylation was investigated in summer 13-lined ground squirrels and in torpid squirrels during hibernation. Additionally, these acetylation patterns were compared to metabolically-depressed naked mole rats under hypoxia, as well as a dysfunctional hyperacetylation model of aging mice. Torpor is characterized by a dramatic change in metabolism that can modify the acetyl landscape of cellular proteins. Mitochondrial protein lysine N-e-acetylation has been implicated as a major regulatory mechanism for modulating protein function. Here, the role of mitochondrial acetylation was investigated in summer 13-lined ground squirrels and in torpid squirrels during hibernation. Additionally, these acetylation patterns were compared to metabolically-depressed naked mole rats under hypoxia, as well as a dysfunctional hyperacetylation model of aging mice. Over 600 proteins were identified using an in-house mass spectrometry method to directly quantify the stoichiometry of site-specific acetylation of the mitochondrial proteome, revealing an acetyl stoichiometry from <1% to >99%. Torpor in ground squirrels was associated with a significantly greater number of high-stoichiometry proteins relative to their summer counterparts. Similar hyper-acetyl patterns in the aged models reveal permanent dysfunction to the electron transport chain that is apparently reversible in ground squirrels. Together, these findings suggest and important regulatory role for acylmodifications during programmed metabolic depression.

Development of New Capabilities for Rodent Research for Long-Duration Missions on the International Space Station

Presented by: Dr. Ruth Globus, NASA Ames

For the suppression of metabolism to be applied successfully to space exploration, development and testing in model organisms such as rodents will be needed. Rodent models are important for advancing biomedical research both on Earth and in space, and thus over the last 58 years, several national space agencies have developed various specialized flight hardware to accommodate mice or rats. Furthermore, the National Research Council's Decadal survey (2011) emphasized the importance of expanding NASA's life sciences research to perform long-duration rodent experiments on the International Space Station (ISS). To accomplish this objective, new flight hardware, operations, and science capabilities were pioneered and developed at NASA Ames Research Center (ARC) to enhance science return from both commercial (CASIS) and government-sponsored rodent research. We modified and customized hardware, procedures, and operations for mission-specific requirements to accommodate both on-orbit dissections and live animal return (LAR). On-orbit sample recovery avoids the complications associated with reentry and recovery on Earth. Starting with launch on a SpaceX Dragon capsule of the validation mission in 2014, the Rodent Research (RR) team successfully performed seven long-duration missions on the International Space Station (ISS). Five missions were performed with female mice while two missions were completed with male mice; all mice were group-housed. Additionally, to accommodate the mice during rest, we developed Huts as a form of enrichment; huts were carefully designed for adult mice complying with animal welfare requirements

as well as engineering and operational constraints. With LAR, mice were returned after long duration habitation on the ISS in a Dragon capsule on three separate missions to date. The mice were delivered to principal investigator's laboratories after re-entry for either for live measurements or analysis of freshly euthanized and dissected animals. In addition, with collaboration of commercial, academic, and government entities, the RR team enabled researchers to study the effects of the space environment on the musculoskeletal and neurological systems of mice as model organisms of human health and disease, particularly in areas of muscle atrophy, bone loss, and bone healing from fractures data from these flight experiments contribute to the science community via both primary investigations and banked samples which can be shared in publicly available data repositories such as GeneLab. Following each flight, numerous tissues and thousands of samples wereharvested and distributed from the Space Life and Physical Sciences Program to Principal Investigators (PIs) through the Ames Life Science Data Archive (ALSDA) and Space Biology's Biospecimen Sharing Program. Recent improvements in flight hardware, and the experience gained working with both researchers and ISS crew members, have expanded NASA's capabilities for conducting long-duration rodent research on the ISS. In conclusion, the Rodent Research project enables study of both spaceflight effects on animal physiology and pharmaceutical countermeasures; perhaps in the future, this system may prove useful for testing novel interventions for deep space travel, such as suppression of metabolism.

Studying Hibernation in a Dish -- iPSCs from a Hibernator Provide a Platform for Investigating Cold Adaptation and Its Potential Medical Applications

Presented by: Dr. Wei Li, NIH

The strategies adopted by many hibernators to suppress metabolism while evading cold- and other stress-induced cellular damage have enormous potential for medical applications. The development of the first iPSC line from a mammalian hibernator (13-lined ground squirrel, Ictidomys tridecemlineatus) provides a versatile platform for studying unique cold-adaptive features of different cell and tissue types in vitro. By comparing ground squirrel and human iPSC-derived neurons, the authors identified mitochondrial and lysosomal pathways as being critical for microtubule stability in the cold. Manipulating these pathways significantly enhanced microtubule cold-stability in human iPSC-neurons and preserved the structure and function of the rat retina after cold-exposure. The same treatments also protected the structure of cold-stored mouse kidneys, demonstrating the potential for prolonging the shelf-life of organ transplants. Prospectively, ground squirrel iPSCs can be a valuable tool for exploring cellular mechanisms of metabolic adaptation and stress responses in hibernators, and for facilitating the translation of hibernation research to medical applications.

Toward Torpor Mechanisms: Genome and Gene Expression in the Meadow Jumping Mouse

Presented by: Dr. William J. Israelsen, University of Texas Southwestern

Hibernating mammals provide a natural example of torpor, a state of depressed metabolism with many potential applications. The meadow jumping mouse (Zapus hudsonius) is a small North American rodent that hibernates in response to shortened day length. These animals can thus be induced to hibernate in a laboratory setting and to enter torpor when fasted. Assembly of the meadow jumping mouse genome allows comparative analysis with other hibernating and non-

hibernating species and provides the ability to study gene expression during torpor. To understand the cell-autonomous response to cold, meadow jumping mouse cells were exposed to temperatures typical of active (37°C) and hibernating (6°C) animals and subjected to mRNA sequencing. Expression changes were found in genes involved in growth signaling, transcription, and the circadian clock, among others. These results provide a baseline for understanding the relative contribution of cold temperature to the changes in gene expression observed during torpor in hibernating mammals. Interestingly, the observed changes are not analogous to the cold shock response of unicellular organisms and suggest that hibernating mammals may not employ a unique cell-based response to cold temperature when compared to non-hibernators.

The NASA Ames Office of Chief Scientist would like to thank everyone who made this workshop possible:

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Facilitators: Desi Bridges and Jessica Partridge

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Participants and Attendees

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