Diet, Sulfur Amino Acids, and Healthspan

Tarrytown House Estate & Conference Center
Tarrytown, NY

September 20-22, 2015

Orentreich Foundation for the Advancement of Science, Inc.
To bring together scientists with an interest in diet and healthspan, to exchange knowledge, to generate ideas for future investigations, and to strengthen relationships within this community.
Schedule of Events

Sunday, September 20, 2015

Cocktail Reception
6:00–6:30 pm
Grand Salon, King Mansion

Banquet Dinner
6:30–8:30 pm
Library/Manor, King Mansion

Welcome, David Orentreich, MD
OFAS

Keynote Address, Caleb Finch, PhD
University of Southern California, Davis School of Gerontology
Monday, September 21, 2015

Symposium
8:15 am–5:00 pm
Riverview Room, Atrium

Morning Session, moderator: Jay Zimmerman, OFAS
8:15–8:30 Welcome – Jay Zimmerman
8:30–9:00 Gene Ables, OFAS
9:00–9:30 John Richie, Penn State University
9:30–10:00 Joseph Kemnitz, University of Wisconsin – Madison
10:00–10:15 Break
10:15–10:45 Sean Adams, University of Arkansas for Medical Sciences
10:45–11:15 Robert Koza, Maine Medical Center Research Institute
11:15–11:45 Suresh Tyagi, University of Louisville School of Medicine
11:45–12:15 Jacob Selhub, Tufts University

Lunch
12:15–1:15 pm
Main Dining Room, Biddle Mansion

Afternoon Session, moderator: Arthur Cooper, OFAS
1:15–1:45 James Mitchell, Harvard T.H. Chan School of Public Health
1:45–2:15 Martha Stipanuk, Cornell University
2:15–2:45 Warren Kruger, Fox Chase Cancer Center
2:45–3:00 Break
3:00–3:30 James Mullin, Lankenau Medical Center
3:30–4:00 Jason Locasale, Duke Cancer Institute
4:00–4:30 Arlan Richardson, University of Oklahoma
4:30–5:00 Holly Brown-Borg, University of North Dakota

Group Photo
5:15 pm

BBQ Dinner
6:30–8:30 pm
West Terrace, Biddle Mansion
Tuesday, September 22, 2015

Symposium
8:30 am–12:00 pm
Riverview Room, Atrium

Morning Session, moderator: Mark Horowitz, OFAS
8:30–9:00 Tsang-hai Huang, National Cheng Kung University
9:00–9:30 Rochelle Buffenstein, Calico Labs
9:30–10:00 Maria Figueiredo-Pereira, Hunter College, CUNY
10:00–10:15 Break
10:15–10:45 Vadim Gladyshev, Harvard Medical School
10:45–11:15 George Roth, GeroScience
11:15–12:00 Review – Jay Zimmerman

Lunch
12:00–1:30 pm
Main Dining Room, Biddle Mansion

Symposium Adjourned
Keynote Speaker

Caleb Finch
Davis School of Gerontology, University of Southern California

Caleb Finch, PhD, is ARCO Professor of Gerontology and Biological Sciences at the University of Southern California, with adjunct appointments in the Departments of Anthropology, Molecular Biology, Neurobiology, Psychology, Physiology, and Neurology. His major research interest is the neurobiology of aging and human evolution.

Dr Finch received his undergraduate degree from Yale in 1961 (Biophysics) and PhD from Rockefeller University in 1969 (Biology). His life work is the fundamental biology of human aging, which he began researching in graduate school and has continued since 1972 at USC. Discoveries include a new form of neurotoxicity of amyloid peptides relevant to Alzheimer disease and the role of shared inflammatory pathways in normal and pathological aging processes. Fifteen of his mentored students hold senior positions in universities or pharmaceutical corporations. Finch has received most of the major awards in biomedical gerontology, including the Robert W Kleemeier Award (1985), the Sandoz Premier Prize (1995), and the Irving Wright Award (1999). He was founding Director of the NIA-funded USC Alzheimer Disease Research Center (1984), and continues as it Co-Director and as a co-PI. He also co-founded Acumen Pharmaceuticals, which develops therapeutics for Alzheimer disease. He has written four books, most recently The Biology of Human Longevity: Inflammation and Nutrition in the Evolution of Lifespans (Academic Press, 2007). Recent interests include the paleopathology of human aging and emerging environmental factors in aging, particularly air pollution components from fossil fuels.
Abstracts
Methionine restriction beyond lifespan extension

Gene P Ables, Julie Hens, Sailendra N Nichenametla, David S Orentreich
Orentreich Foundation for the Advancement of Science, Inc, Cold Spring, NY

Dietary methionine restriction (MR) extends lifespan in rodents and several other species. In yeasts, roundworms, Drosophila, and human cells, MR extends lifespan via various intracellular regulatory mechanisms. In rodents, MR induces adiposity resistance, improves hepatic glucose metabolism, preserves cardiac function, and reduces body size, which could affect the onset of age-related diseases. Recent studies have shown that MR affected hormones and enzymes such as Fgf21, Scd1, Ucp1, adiponectin, leptin, CBS, and IGF-1 at the gene and protein levels, potentially altering physiology. The beneficial effects of MR could be explained by increased antioxidant substrates that reduce mitochondrial oxidative stress, as has been shown in the liver, heart, kidney, and brain of rats and pigs. Studies have demonstrated that MR can reduce reactive oxygen species that damage cells and promote cancer progression. Cancer metabolism is hindered by reduced levels of methionine, which are in high demand for protein synthesis. Recent studies demonstrate that either MR or targeting specific genes in the methionine cycle can induce cell apoptosis while decreasing proliferation in several cancer models. The complete mechanism of how MR acts on the cell cycle during cancer has not been completely elucidated, but activation of cell cycle inhibitor p21 may be one mode of action. Epigenetic mechanisms, such as methylation and non-coding RNAs, are also possible downstream effectors of MR, and ongoing studies at OFAS should help to elucidate some of these mechanisms. Cumulative evidence for altered methylation of DNA and histones in the context of natural aging also suggests a role for epigenetics in MR-induced benefits. Despite evidence that changes in dietary methionine can affect epigenetics, it remains to be investigated whether this is a mechanism in MR. The focus of this review is to consolidate research on MR and its involvement in metabolism, cancer, and epigenetics.
Dietary sulfur amino acid restriction in healthy adults

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Diets restricted in sulfur amino acids (SAA) have been shown in pre-clinical models to have profound beneficial effects, including enhanced lifespan and reductions in a variety of aging-related diseases, disorders, and impairments. These effects may be driven, in part, by changes in key metabolic pathways, resulting in a variety of physiological and cellular changes, including reductions in body weight, adiposity, and oxidative damage. Altogether, these findings suggest that dietary SAA restriction may have clinical implications as a potential anti-aging/disease preventing/healthspan promoting intervention. In order to determine the potential viability of such a strategy in humans, we previously conducted a short-term cross-over controlled feeding study of dietary methionine restriction (MR) in healthy adults. Results demonstrated the overall feasibility of MR feeding in a controlled environment. Further, we observed that MR resulted in changes in a number of blood parameters, including reductions in SAA and lipids and an increase in FGF-21 after 3 weeks; however, no effects were observed for other MR-related markers, including adipokines, IGF-1, and glutathione. Since more recent findings in animal models highlighted the importance of restricting total SAA and not just methionine (Met), we initiated a controlled feeding study of total SAA in healthy adults. The study design consists of two randomized groups (n=10/group) each consisting of three 4-week feeding periods separated by 3-4 week washout periods. Each group started with control diet [30.1 mg/kg/d each of Met and cysteine (Cys)] followed by test diet periods of 70% and 90% Met restriction for one group and 50% and 65% SAA (Met + Cys) restriction for the other. Preliminary results from this study will be presented. Altogether, studies done to date indicate that dietary SAA restriction may represent an important intervention strategy for prevention and treatment, particularly in aging individuals.
Diet, calorie restriction, and aging in rhesus monkeys

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We have been assessing the effects of moderate calorie restriction (CR) on health and lifespan in rhesus macaques since 1989. Beginning when the monkeys were young adults (~10 years of age; median lifespan is ~26 years), all subjects (30 females and 46 males) were fed a purified diet containing 15% protein (lactalbumin), 10% fat (corn oil), and 65% carbohydrate (sucrose, starch, and dextrin), supplemented daily with fresh fruit and vegetables. Control monkeys (C, initially n=38, 3 currently surviving) were given enough food to allow ad libitum access for ~8 hr/day. Restricted monkeys (R, initially n=38, 10 currently surviving) were fed 20-30% less than their individualized baseline intake, subsequently adjusted for changes in intake by C except to safeguard health. Food intake was measured daily, and regular assessments of body mass and composition, metabolic rate and physical activity, and glucose tolerance and insulin sensitivity were made. MRI of the brain was done later in the animals’ lives. Early effects of CR included loss of body weight and body fat, reduced insulin levels and increased insulin sensitivity, and improved lipid profiles. Loss of skeletal muscle occurred during middle age for males, but the decline was slower for R than for C. CR decreased sleeping metabolic rate, but R displayed increased physical activity with lower cost of movement than for C. CR dramatically reduced the incidence of cancer, cardiovascular disease, and type 2 diabetes mellitus. CR also preserved brain cortical and subcortical grey matter volume and attenuated astrogliosis but did not affect amyloid plaque burden or the decline in integrity of the corpus callosum with advancing age. CR increased both healthspan and lifespan in these nonhuman primates.
Intersections between fat metabolism and amino acids

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Fine-tuning the contributions of fat, carbohydrate, and amino acid catabolism toward generation of ATP to power cells is an important aspect of physiological homeostasis. Mitochondrial fuel management involves a balance between types and rates of fuel delivery, ATP demand, and enzyme regulation by metabolites sensitive to redox status (i.e., NADH/NAD+ ratio), reactive oxygen species (ROS) generation, or tricarboxylic acid (TCA) cycle capacity relative to fuel delivery (i.e., acetyl-CoA). Efficiency of mitochondrial oxidation of fuels may be defined as their relative flux toward full combustion vs. partial catabolism, and less efficient mitochondrial oxidation of any fuel leads to accumulation of specific upstream metabolites and derivatives; this contributes to a metabolite “signature” reflected in tissue or blood. An interesting illustration of these concepts is the interplay between mitochondrial fatty acid oxidation (FAO) and amino acid catabolism. The mitochondrial branched-chain ketoacid dehydrogenase complex (BCKDC), for instance, is a primary regulator of BCAA and cysteine oxidative catabolism, and the enzyme is inhibited under conditions of increased FAO. This may explain how essential amino acids are partially “spared” from oxidation during fasting. Higher FAO also drives increased ROS generation, and this may, in theory, alter glutathione generation and cysteine-cystine dynamics. As another example, efficient, complete FAO may be attenuated when anaplerosis (i.e., from metabolism of select amino acids delivering net carbon to the TCA cycle) is limited, as hypothesized in the “anaplerotic stress” model of insulin resistance and type 2 diabetes mellitus. This may present an even greater metabolic challenge since FAO can also drive cataplerosis (loss of net carbon from the TCA cycle). In summary, it is clear that there are several intersections between metabolism of amino acids and fatty acids, and a greater understanding of this cross-talk should provide clues regarding key regulators of metabolic (patho)physiology.
Molecular correlates for the development of adiposity in male C57BL/6J mice after short-term exposure to an obesogenic diet

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Heterogeneity in high fat diet (HFD)-induced obesity within a population of inbred mice has been shown to be associated with changes of gene expression in adipose tissue. A gene with a large degree of variation among mice, mesoderm specific transcript (Mest), has also been shown to be highly inducible after short-term exposure to dietary fat, and its expression in adipose tissue prior to HFD-feeding is predictive of individual susceptibility to the development of obesity. To gain insight on the relationship of Mest with phenotypic changes in body composition within a population of inbred mice after a short exposure to dietary fat, 96 individually housed 8-week-old C57BL/6J mice were fed a diet containing 58% kcal fat for a period of only 2 weeks. Measurements of Mest mRNA after the dietary regimen in visceral epididymal (EPI) and subcutaneous inguinal (ING) fat shows a range of 12-fold and 90-fold respectively and was highly and positively associated with changes in fat mass. Surprisingly, there was only a slight association of adipose Mest expression with food intake normalized to either bodyweight or lean mass as measured via NMR. In addition, adipose Mest expression coincides (ING; R=0.91; EPI; R=0.62) with the expression of transcription factor Kruppel-like factor 14 (KLF14), an imprinted gene that is thought to play a major role in the regulation of gene expression in adipose tissue. Other genes shown to be predictive for the development of adiposity (Bmp3, Sfrp5, and Nkd1) identified in previous studies were also highly associated with variation in fat mass as expected, whereas Pparg2 showed no association with any indices of fat mass accumulation. Our data suggest that KLF14 transcriptional activity may at least partially mediate adipose tissue Mest to promote fat mass accumulation in mice following exposure to an obesogenic diet.
Mitochondrial division/mitophagy inhibitor (Mdivi) ameliorates pressure overload-induced heart failure

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We have previously reported the role of anti-angiogenic factors in inducing the transition from compensatory cardiac hypertrophy to heart failure and the significance of MMP-9 and TIMP-3 in promoting this process during pressure overload hemodynamic stress. Several studies reported the evidence of cardiac autophagy, involving removal of cellular organelles like mitochondria (mitophagy), peroxisomes, etc., in the pathogenesis of heart failure. However, little is known regarding the therapeutic role of mitochondrial division inhibitor (Mdivi) in pressure overload induced heart failure. We hypothesize that treatment with Mdivi inhibits abnormal mitophagy in a pressure overload heart and thus ameliorates heart failure condition. To verify this, ascending aortic banding was done in wild type mice to create pressure overload-induced heart failure; mice were then treated with Mdivi and compared with vehicle treated controls. Results: Expression of MMP-2, vascular endothelial growth factor, CD31, was increased, while expression of anti-angiogenic factors like endostatin and angiostatin, along with MMP-9 and TIMP-3, was reduced in Mdivi treated AB 8-week-old mice compared to vehicle treated controls. Expression of mitophagy markers like LC3 and p62 was decreased in Mdivi treated mice compared to controls. Cardiac functional status assessed by echocardiography showed improvement, and there was also a decrease in the deposition of fibrosis in Mdivi treated mice compared to controls. The above results suggest that Mdivi inhibits the abnormal cardiac mitophagy response during sustained pressure overload stress and propose the novel therapeutic role of Mdivi in ameliorating heart failure.
The atherogenic effect of methionine

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The popularity of the homocysteine theory of arteriosclerosis can be traced to the study by Wilken and Wilken in 1976 showing that the concentrations of homocysteine-cysteine mixed disulfide after a methionine (Met) load were higher in patients with CVD than in healthy controls. What was typical of this and the subsequent studies showing associations between homocysteine and a variety of diseases (CAD, stroke, cognitive impairment, etc.) was that the differences in homocysteine concentrations were small, unlike the high concentrations seen among those with the rare congenital vitamin B12 or cystathionine-β-synthase deficiencies. What fueled this area further are the many studies with cell culture, animals, and humans showing adverse effects of “high homocysteine”, which was introduced either as a bolus at high non-physiological concentrations or as a Met load that resulted in higher plasma homocysteine and at the same time there was a decrease of flow mediated brachial artery after stimulation, higher oxidative stress, increased coagulation, and circulating adhesion molecule levels and others. These studies neglected the possibility that Met load is also associated with increased plasma Met. To address this question, we fed APOE-4-deficient mice with experimental diets designed to achieve three conditions: (i) high Met intake with normal blood homocysteine; (ii) high Met intake with B vitamin deficiency and hyperhomocysteinemia; and (iii) normal Met intake with B vitamin deficiency and hyperhomocysteinemia. Mice fed Met-rich diets had significant atheromatous pathology in the aortic arch, even with normal plasma homocysteine levels. Mice fed B vitamin-deficient diets developed severe hyperhomocysteinemia without any increase in vascular pathology. Our findings suggest that moderate increases in Met intake are atherogenic in susceptible mice while high plasma homocysteine is not. We propose that it was the high Met that was responsible for the adverse effects after the Met load.
Dietary sulfur amino acid control of endogenous hydrogen sulfide production

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Hydrogen sulfide (H$_2$S) is a gas easily identified by its distinctive odor, and although toxic at high concentrations, it has recently gained recognition for its numerous beneficial health effects. Many experiments documenting such benefits, ranging from extended longevity in lower organisms to protection from ischemic injury in mammals, are based on exposure to exogenous sources of H$_2$S. However, there is a growing appreciation for the importance of endogenously produced H$_2$S in a variety of health outcomes. H$_2$S is generated by enzymes of the evolutionarily conserved transsulfuration pathway (TSP), including cystathionine-$\beta$-synthase (CBS) and cystathionine-$\gamma$-lyase (CGL), responsible for the biosynthesis of cysteine from methionine. We recently linked functional benefits of dietary restriction (DR), i.e., reduced food intake without malnutrition, on stress resistance and longevity in model organisms to increased TSP activity and endogenous H$_2$S production. DR includes various regimens aimed at either reducing overall calorie intake (calorie restriction, intermittent/every-other-day fasting) or reducing particular nutrients such as protein or sulfur amino acids, methionine and cysteine (methionine restriction), with overlapping functional benefits on stress resistance, metabolic fitness, and lifespan. We found that multiple DR regimens increased CGL expression and H$_2$S production, and that this was blocked by selective re-addition of dietary cysteine with a concomitant loss of DR benefits. We will discuss the small but growing body of literature linking the TSP to the functional benefits of DR in part through the production of endogenous H$_2$S, with an emphasis on regulation of the TSP and H$_2$S production by diet and molecular mechanisms of beneficial H$_2$S action.
Blocking metabolism of cysteine to cysteinesulfinate: Consequences of taurine depletion and hydrogen sulfide overproduction

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Cysteine homeostasis is dependent on the regulation of cysteine dioxygenase (CDO) in response to sulfur amino acid intake. Knockout of the murine Cdo1 gene results in elevated cysteine levels, severe impairment in ability to synthesize taurine, and an increased catabolism of cysteine to hydrogen sulfide (H\textsubscript{2}S). In an effort to distinguish whether the Cdo1-null mouse phenotype is due to taurine depletion or to excess levels of cysteine and its greater catabolism via desulfhydration, mice were fed either a basal or taurine-supplemented semi-purified diet. The lack of taurine was associated with a lack of taurine conjugation of bile acids, a dramatic increase in the total and unconjugated hepatic bile acid pools, and an increase in betaine and other molecules that serve as organic osmolytes. We identified cysteinesulfinic acid decarboxylase, betaine:homocysteine methyltransferase (BHMT), organic solute and steroid transporter subunit beta, and cholesterol 7\alpha-hydroxylase as proteins whose hepatic expression is strongly regulated in response to taurine depletion in the Cdo1-null mouse. Taurine supplementation of Cdo1-null mice restored hepatic levels of these proteins to wild-type levels, whereas taurine supplementation had no effect on abundance of these proteins in wild-type mice. The observation of a strong effect of taurine on BHMT expression suggests that BHMT downregulation may allow betaine to play a greater role as a cellular osmolyte. Parameters that were altered in Cdo1-null mice but were not corrected by taurine supplementation include elevated tissue and urine thiosulfate levels, which are indicative of excess flux of cysteine through desulfhydration pathways. In addition, low serum leptin levels, high serum insulin levels, elevated serum triglyceride levels, elevated hepatic levels of long-chain acyl-carnitines, and elevated hepatic levels of stearoyl-CoA desaturase 1 and acetyl-CoA carboxylase were observed, indicative of alterations in hepatic lipid metabolism. More work is needed to understand the cause of these changes in hepatic lipid metabolism.
The effect of dietary modulation of sulfur amino acids on cystathionine beta synthase deficient mice

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Cystathionine-β-synthase (CBS) is a key enzyme in the methionine and cysteine metabolic pathway. It catalyzes the irreversible conversion of homocysteine to cystathionine, which is subsequently converted to cysteine. Thus, CBS acts as a metabolic “gate keeper”, regulating the flow of fixed sulfur to the cysteine metabolic pathway. Mutations in the CBS gene cause clinical CBS deficiency, a disease characterized by elevated plasma total homocysteine (tHcy) and methionine and reduced plasma cysteine. The treatment goal of CBS-deficient patients is to normalize the metabolic values of these three metabolites using a combination of vitamin therapy and dietary manipulation. In order to better understand the effectiveness of nutritional treatment strategies, we have performed a series of long-term dietary manipulation studies using our previously developed Tg-1278T Cbs-/- mouse model of CBS deficiency. These mice have undetectable levels of CBS activity, extremely elevated levels of plasma tHcy, modestly elevated plasma methionine, and low plasma cysteine. They exhibit several easily discernible phenotypes, including osteoporosis, loss of fat mass, reduced lifespan, and facial alopecia. In these mice, we have tested three different dietary manipulations: 1) supplementation with N-acetylcysteine; 2) restriction of dietary methionine; and 3) supplementation with betaine. We found that methionine restriction is the most effective approach at reversing Cbs-/- phenotypes, although some beneficial effect is also observed with betaine supplementation. Our studies suggest that dietary methionine restriction is the most effective treatment for CBS deficiency, and that elevated tHcy is the key pathogenic factor.
Improvement of epithelial barrier function by methionine restriction

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The singular importance of epithelial barrier function in both systemic physiology and prevention of inflammation induced us to examine the possible effects of methionine restriction (MR) on epithelial tight junction (TJ) structure and permeability. We used two very different but well described epithelial models, the LLC-PK1 renal epithelial cell line and rat distal colon. In LLC-PK1 epithelia, MR did not affect cell growth or differentiation. However, the TJ proteins claudin-3 and claudin-7 were significantly decreased in abundance, whereas claudin-4 and claudin-5 were markedly increased in abundance. The functional result of these structural changes was improved epithelial barrier function, measured as increased transepithelial electrical resistance (Rt) and decreased transepithelial (paracellular) diffusion of 14C-D-mannitol (Jm). In our animal model study, rats were maintained on a MR diet (0.17% L-methionine [w/w] vs. the normal 0.86%) for 28 days prior to removal of their distal colon. Animals on the MR diet showed small but significant reductions in the plasma and (intracellular) colonocyte levels of methionine. Colon mucosal sheets from rats on the MR diet showed increased Rt with simultaneous decrease in Jm, both indicating improved colon epithelial barrier function in MR. Western blot analyses and RT-PCR showed an increase in claudin-3 and a change in the post-translational modification of occludin, data reinforcing a paracellular barrier alteration. Improvement of epithelial barrier function at the level of the TJ may be a general benefit of MR.
Dynamics of histone methylation mediated by the status of methionine metabolism

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S-adenosylmethionine (SAM) and S-adenosylhomocysteine (SAH) link metabolism to methylation status. However, it is unknown whether fluctuations in SAM and SAH can be sensed to alter the kinetics of key histone methylation marks such as H3K4me3. We provide evidence that methionine metabolism is sufficient to directly determine the levels of histone methylation through its ability to modulate SAM and SAH. This dynamic interaction occurred rapidly, and methionine insufficiency leading to a depletion of H3K4me3 could be fully recovered upon restoration of methionine levels. Modulation of methionine in diet led to changes in both metabolism and histone methylation in liver. In humans, methionine variability in fasting serum was found to be commensurate with concentrations needed for these dynamics and could be explained in part by diet. Together these findings demonstrate that flux through methionine metabolism and the sensing of methionine availability may be configured to allow for direct communication to the chromatin state in cells.
The role of DNA methylation in the anti-aging mechanism of dietary restriction

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Research conducted over the past 60 years has shown that dietary restriction (DR) extends the mean and maximum lifespan of a wide variety of organisms. In addition, DR has been shown to delay the onset and progression of most age-related diseases as well as improve most physiological processes that decline with age. Therefore, DR is believed to retard aging and has become the gold standard by which other manipulations that increase lifespan are compared. An important facet of DR that has been largely overlooked by the research community is that DR can have early effects that create a cellular memory, which persists even when DR is discontinued. Therefore, DR could be increasing lifespan and retarding aging through a novel mechanism that involves a molecular signal(s) that arises shortly after the implementation of DR and has an impact on the animal over its lifespan, even if DR is discontinued. The most likely molecular process by which DR could increase lifespan and retard aging after being discontinued would be through an epigenetic mechanism, specifically DNA methylation. We are currently generating the first data on the effect of DR on DNA methylation using a novel next generation sequencing approach that detects cytosine methylation (5mC) in CpG islands, shores, and shelves, as well as gene promoters and intragenic regions in the hypothalamus genome, because the hypothalamus is a major nutrient sensor that integrates and coordinates various signals (e.g., nutrient sensing, satiety, and changes in adiposity).
Impact of dietary methionine on aging: Dependence on growth hormone status

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Growth hormone (GH) plays a major role in aging and longevity in mammals. A lack of GH signaling (either GH deficiency or GH resistance) results in extended healthspans and lifespans in mice. Stress resistance is also greater when somatotropic signaling is low. In contrast, high plasma GH levels have been shown to accelerate aging-related dysfunction, decrease stress resistance, and shorten lifespan. Altering dietary methionine has also been shown to affect survival in rodents. Our studies show that methionine restriction extends lifespan in mice with normal or high levels of GH but not in mice that are GH deficient or GH resistant. These data indicate that intact GH signaling is necessary to discriminate variations of this amino acid emanating from the diet. Metabolomic data support this hypothesis, showing that the lack of GH signaling may buffer the changes in various metabolic pathways normally impacted by changing dietary methionine levels. Thus, reduced somatotropic signaling may reprogram metabolism by shifting resources away from growth and proliferation and more towards stress resistance and cytoprotection.
Dietary restrictions, bone density, and bone quality

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Caloric restriction (CR), protein restriction (PR), or specific amino-acid (e.g., methionine restriction, MR) as different dietary restrictions have been well-proven regarding their comprehensive benefits in metabolism and health. Based on bone densitometric measurements, dietary restrictions caused weight loss accompanied by reduced areal bone mineral density (aBMD), bone mass, and/or bone size, which are considered harmful to bone health. However, in the wake of improvements in bone densitometric instruments (e.g., high resolution X-ray tomography), dietary restrictions were verified to cause reductions in bone mass/size rather than volumetric bone mineral density (vBMD). Furthermore, according to the concept of bone quality, bone health consists of diverse indices rather than simply being represented by densitometric measurements. Indeed, there is evidence showing that moderate dietary restrictions do not impair intrinsic bone material properties in spite of the reduced whole bone strength due to absolute smaller bone size. In the present review, we integrated reports from traditional densitometric measurements, metabolic status assays (e.g., energy metabolism, oxidative stresses, and inflammatory responses), and biomaterial analyses, and provided a revised concept regarding the effects of CR, PR, and MR on the skeleton.
Maintenance of glutathione redox status in the naked mole-rat heart under conditions of high oxidative stress

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Unlike all other mammals studied to date, not only can the naked mole-rat (NMR) achieve an extraordinary lifespan, but it is also able to maintain cardiovascular function for at least 75% of this extraordinary longevity. Oxidative stress is largely implicated in both the age-associated decline in cardiovascular function already evident in middle age and in cardiovascular disease. Therefore, we sought to test the hypothesis that resistance to oxidative stress allows the NMR to well maintain cardiovascular function. We treated NMRs and mice with a large bolus of doxorubicin (DOX; 20 mg/kg), a potent cardiac oxidative stressor. Echocardiography showed that 7 days after DOX treatment mice had a significant 25% decline in cardiac contractility, whereas NMRs maintained heart function. We found that DOX caused an increase in reduced glutathione (GSH) levels in NMR hearts, but no change in those of mice. Oxidized glutathione levels (GSSG) were conversely maintained in NMR hearts, but increased in hearts of mice. As a result, the GSH:GSSG ratio declined in mice but was maintained in NMRs with DOX, indicating a preservation of redox status in NMR hearts. Furthermore, DOX caused no change in glutathione S-transferase (GST) activity in mouse hearts but induced a significant increase in GST activity in the hearts of NMRs. Taken together, these data indicate that the NMR heart has a robust glutathione antioxidant capacity to stave off the damaging effects of oxidative stress allowing for the maintenance of cardiac function, and this likely plays a large role in the species’ trait of healthy cardiovascular aging.
Prostaglandin J2: A potential target for halting inflammation-induced neurodegeneration

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We are addressing how prostaglandins, which are bioactive products of inflammation, contribute to neurodegenerative disorders including Alzheimer’s (AD) and Parkinson’s (PD) diseases. Prostaglandins are produced from arachidonic acid via cyclooxygenases, which are enzymes that play a major role in inflammation. Epidemiological studies show that chronic treatment with low levels of cyclooxygenase inhibitors (i.e., NSAIDs) lowers the risk of developing AD and PD. So far, NSAIDs are the only approved clinical drugs that prevent or delay the onset of these disorders. Unfortunately, inhibiting cyclooxygenases with NSAIDs blocks the synthesis of downstream neuroprotective as well as neurotoxic prostaglandins, thus producing adverse side effects. New therapeutic strategies that neutralize the effects of specific neurotoxic prostaglandins downstream from cyclooxygenases could have a great impact on treating these devastating neurodegenerative disorders with fewer negative side effects.

We chose to focus our studies on prostaglandin J2 (PGJ2) because it is by far the most neurotoxic when compared to prostaglandins A1, D2, and E2. Unlike other prostaglandins, PGJ2 and its metabolites have a cyclopentenone ring with reactive α,β-unsaturated carbonyl groups. These carbonyl groups form covalent Michael adducts with free thiols present in specific cysteine residues within proteins. Electrophiles, such as PGJ2, that bind to key protein cysteine(s) are regarded as playing an important role in determining whether neurons will live or die.

I will discuss our in vitro and in vivo studies showing that PGJ2 induces pathological processes relevant to neurodegenerative disorders. Furthermore, we found that increasing intracellular cAMP with the lipophilic peptide PACAP27 counteracts some of the detrimental effects induced by PGJ2. In conclusion, there is a need for new approaches that target neurotoxic prostaglandins such as PGJ2 downstream of cyclooxygenases. These approaches hold great promise for treating neurodegenerative disorders by preventing inflammation-induced neurodegeneration without affecting the beneficial effects of neuroprotective prostaglandins.
Understanding control of lifespan through comparative genomics and methionine status

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Understanding the mechanisms that control lifespan is among the most challenging biological problems. Many complex human diseases are associated with aging, which is both the most significant risk factor and the process that drives the development of these diseases. The aging process can be regulated during evolution. For instance, mammals are characterized by >100-fold difference in lifespan, which can both increase and decrease during evolution. We employ this diversity in mammalian lifespan and the associated life-history traits to shed light on mechanisms that regulate species lifespan. For this, we utilize methods of comparative genomics to examine genomes of short- and long-lived species and carry out analysis of lifespan across a panel of mammals. We sequenced the genomes of several mammals of exceptional lifespan, including mole-rats and microbats, and identified genes that may contribute to their longevity. We also carried out analyses of gene expression and metabolites across a large panel of mammals. These studies point to both lineage-specific and common adaptations to longevity involving various pathways. One pathway that emerges as relevant to the control of lifespan is methionine availability. Indeed, reduced methionine intake (MR) can extend lifespan in rodents by mimicking dietary restriction, but whether this regimen represents a general strategy for regulating aging has been controversial. We found that MR can extend lifespan of both fruit flies and yeast, but this effect was dependent on the status of other amino acids. Under certain conditions, MR mimicked the effect of dietary restriction and was associated with decreased reproduction, whereas under other conditions, it was ineffective, and the regulation of lifespan was uncoupled from reproduction. These studies provide insights into the roles of methionine in aging and suggest a strategy for lifespan extension by MR. It is our hope that a better understanding of molecular mechanisms of mammalian lifespan control will lead to a better understanding of human diseases of aging.
Manipulation of healthspan and function by dietary restriction mimetics

George S Roth
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After nearly a century of rigorous investigation and testing, dietary caloric restriction (CR) remains the most robust and reproducible method for slowing aging and maintaining health, function, and vitality. This intervention has been applied to species across the evolutionary spectrum, but for a number of reasons, practical applicability to humans has been questioned. To overcome these issues, we initiated the field of CR mimetics in 1998 and have observed its development into a full-fledged “anti-aging” industry at the present time. Basically, strategies which enable individuals to obtain the biological benefits of CR, without reducing actual food intake, can be considered CR mimetics, whether functional, pharmaceutical, nutraceutical, or other. Some of the best known candidates include resveratrol and related agents, the antidiabetic drug metformin, and rapamycin and other mTOR regulators. While the mechanisms of action vary, these and essentially all CR mimetic candidates work through at least some of the same pathways as actual CR.

However, we believe the most efficient strategy for mimicking CR is to act as close to the initial energy processing events as possible and have, therefore, focused on glycolytic inhibition. Proof of principle was initially obtained with 2-deoxyglucose, which exerted a number a similar metabolic sequellae to full CR, although this compound exhibited a narrow efficacy/toxicity range. The second generation of glycolytic-inhibiting CR mimetics was therefore spearheaded with mannoheptulose, a seven-carbon sugar derived primarily from unripe avocados, that inhibits hexokinase without apparent side effects. CR-like benefits include better insulin/glucoregulatory control, maintenance of youthful body composition, increased strength and agility, immune and stress/inflammation protection, weight control, and improved health/longevity.

While the entire field continues to evolve rapidly, the current status will be reviewed with particular focus on recent developments, most practical relevance and applicability for potential consumers, and new strategies for the future.
Speaker Biographies

**Gene Ables** received his degree of Doctor of Veterinary Medicine from the University of the Philippines and then obtained his PhD from Hokkaido University (Japan). His post-doctoral research in Preventive Medicine and Nutrition at Columbia University focused on liver lipid metabolism. In 2006, he was appointed Associate Research Scientist at the Columbia University Medical Center. Dr. Ables joined OFAS in April 2011 as a Senior Scientist. His project focus on the effects of methionine restriction (MR) in the heart, bones, kidneys, and adipose tissue. He also aims to identify the roles of FGF21 and CBS in MR mice. Recently appointed Associate Science Director, he leads investigations of the methionine-restricted diet’s effects on metabolism, cancer, and epigenetics.

**Sean Adams** is Professor and Chief, Developmental Nutrition Section in the Department of Pediatrics at University of Arkansas for Medical Sciences, and is the Director of the Arkansas Children’s Nutrition Center. He received his Bachelor’s degree in Biology from California State University, Fresno, followed by a Master’s in Marine Sciences from UC Santa Cruz. He completed his PhD in Nutritional Sciences at the University of Illinois at Urbana-Champaign. After his postdoctoral training at the University of Barcelona and UT Southwestern Medical School, Dr. Adams was a research scientist in biopharma for over 7 years. Before coming to Little Rock, he was an Associate Adjunct Professor in Nutrition at UC Davis and led the Obesity and Metabolism Research Unit of the USDA–Agricultural Research Service Western Human Nutrition Center in Davis, CA. His research aims to prevent metabolic disorders such as diabetes, determine how specific foods and physical activity modify disease risk, and identify molecular biomarkers reflective of a healthy or disordered metabolism.

**Holly Brown-Borg** received BS and MS degrees from the University of Nebraska-Lincoln and a PhD in physiology from North Carolina State University. She completed postdoctoral fellowships as an ARS Research Associate at the USDA Research Center in Nebraska and as a Research Associate in the Department of Physiology at Southern Illinois University School of Medicine. Dr. Brown-Borg moved through the ranks to Professor in the Department of Pharmacology, Physiology, and Therapeutics at the University of North Dakota School of Medicine and Health Sciences. She is a Past-President of the American Aging Association and a Fellow of the Gerontological Society of America. She has organized several scientific meetings including AGE, GSA (Biological Sciences), and Biology of Aging Gordon Research Conference. She currently organizes the biennial International Symposium on Neurobiology and Neuroendocrinology of Aging held in Bregenz, Austria. Her research interests focus on the role of the endocrine system in aging and lifespan as it relates to metabolism, stress resistance, mitochondrial function, and DNA methylation.
Rochelle (Shelley) Buffenstein recently joined Calico, a research and development company specifically focused on understanding the biology of aging and the factors that control lifespan. Prior to that position she was a Professor at the Sam and Anne Barshop Institute for Aging and Longevity Studies at UTHSCSA. She is a comparative biologist who pioneered the use of the naked mole-rat as a model of exceptional bio-gerontological interest. Her research strives to determine the molecular mechanisms used in nature to modulate both species lifespan and healthspan. Using a multidisciplinary mechanistic approach, she specifically examines why some mammals, such as mice, age extremely rapidly, exhibiting pronounced declines in all aspects of their biology, and how other species, such as naked mole-rats, bats, and whales can maintain physiological function and disease-free good health for a larger proportion of their long lifespans. Elucidating these mechanisms may lead to therapeutic targets to retard the aging process and delay the onset of age-associated disability and diseases such as cardiovascular disease, cancer, diabetes, and Alzheimer’s disease.

Maria E. Figueiredo-Pereira is originally from Portugal and received her PhD in Biology from New York University in 1985. She then spent two years as a post-doctoral fellow at the Population Council/Rockefeller University (NYC) in the lab of Dr. Mario Ascoli where she studied the role of PKA in steroidogenesis. In 1987 she moved to Mount Sinai Medical School (MSSM) in NYC as a post-doctoral fellow in Dr. Sherwin Wilk's lab in the Department of Pharmacology. She headed her own lab at MSSM from 1990-97. Her studies focused on characterizing the biochemical properties of the 20S proteasome and its inhibitors. In 1998, Dr. Figueiredo-Pereira joined the Department of Biological Sciences at Hunter College, City University of New York, as an Associate Professor and became a tenured Full Professor in 2007. Dr. Figueiredo-Pereira has been working/publishing in the field of neural dysfunction since 1994. Her lab has conducted more than 25 years of studies on the ubiquitin/proteasome pathway and other proteolytic systems, and her research has garnered financial support from both the NIH and the Michael J. Fox Foundation. Her expertise is on neuroinflammation and on the ubiquitin/proteasome pathway, its regulation by cAMP, and its role in neurodegeneration. She is currently investigating how impairment of the ubiquitin/proteasome pathway and its regulatory mechanisms lead to neurodegeneration involved in disorders such as Alzheimer’s and Parkinson’s diseases and amyotrophic lateral sclerosis.

Vadim Gladyshev attended Moscow State University (Russia), receiving his BS/MS degree in 1988 and PhD degree in 1992. This was followed by postdoc training at NIH and a faculty position at University of Nebraska. Since 2009, he has been a Professor of Medicine and Director of the Center for Redox Medicine at Brigham and Women’s Hospital, Harvard Medical School, and an Associate Member of the Broad Institute. Dr. Gladyshev has been working in the areas of selenium and redox biology as applied to aging and cancer.
He has a long-term interest in the understanding of aging, functions of trace elements, and mechanisms of redox control involving methionine and cysteine. Dr. Gladyshev was elected as an AAAS fellow and is a recipient of the NIH Director’s Pioneer Award.

**Tsang-hai Huang** completed his PhD in exercise science from National Taiwan Normal University in 2001. He then pursued a postdoctoral fellowship in bone biology with an emphasis on the effects of ultrasound in bone cells at National Taiwan University Hospital (2001-2). As a visiting postdoctoral fellow in Jack Lewis’s Lab at the University of Minnesota (2002-3), he studied the methodology of material properties of cartilage using a nano-indentation system. He has been on the faculty of National Cheng Kung University (Taiwan) since 2003; there, he has organized a laboratory with expertise in animal studies looking at the effects of endurance exercise and nutritional interventions on bone health. Preliminary findings of his recent studies suggest that smaller bones resulting from dietary restrictions (e.g., caloric and methionine) and endurance exercise is likely a structural shift of bone size without compromised bone material properties. He has recently begun considering the evaluation of bone health from an anthropology-like viewpoint. Putting his research ideas into his own life, Dr. Huang is an amateur triathlete and a lover of the vegetarian diet.

**Joseph Kemnitz** received both undergraduate and doctoral degrees from the University of Wisconsin. He is now professor of Cell and Regenerative Biology in the School of Medicine and Public Health at the University of Wisconsin-Madison. He is director emeritus of the Wisconsin National Primate Research Center and former director for translational technologies and resources in the Institute for Clinical and Translational Research. His research has focused on nutritional issues across the lifespan in nonhuman primates. For more than 25 years, he has been studying the effects of moderate caloric restriction on healthspan and lifespan of rhesus macaques.

**Robert Koza** obtained his PhD in Biochemistry at the University of New Hampshire (1989) where he studied the role of polyamines in cellular growth and proliferation under the mentorship of the late Dr. Edward J. Herbst. During postdoctoral studies at the Wistar Institute (Philadelphia) and the Lankenau Medical Research Center (Wynnewood, PA) with Dr. Thomas O’Brien, he was involved in investigating the role for polyamines in the development and progression of epidermal carcinogenesis. In 1994, Dr. Koza joined Dr. Leslie P. Kozak at The Jackson Laboratory as a Research Associate and subsequently moved with Dr. Kozak’s laboratory to the Pennington Biomedical Research Center (PBRC; Louisiana State University System) as an Instructor in 1998. During this time, Dr. Koza’s research focused on metabolic mechanisms of energy expenditure and Ucp1 thermogenesis, and he was involved in establishing and directing the Genomics Core Research Facility at PBRC. In 2002, as an Assistant Professor at PBRC, Dr. Koza developed a research program
to study mechanisms associated with non-genetic variation of metabolic disease and is currently funded for these studies by the NIH/NIDDK. Dr. Koza has served on several NIH review panels and is a member of the Cellular Aspects of Diabetes and Obesity Study Section at the NIH/NIDDK. Dr. Koza joined the Maine Medical Center Research Institute (Scarborough, ME) as a Faculty Scientist in 2013 and continues as an adjunct associate professor at PBRC.

**Warren Kruger** graduated magna cum laude from Cornell University, received his PhD in Biochemistry from the University of California, and was a Postdoctoral Fellow in the Department of Genetics at Stanford University. He is currently a full professor in the Cancer Biology program at Fox Chase Cancer Center, where he has been since 1995. He has published more than 70 peer-reviewed papers, been an invited speaker at numerous international conferences, and has obtained research grants from a wide variety of sources, including the NIH, Department of Defense, American Cancer Society, and American Heart Association. His lab focuses on the study of sulfur amino acid metabolism and its relationship to human health and disease.

**Jason Locasale** is an Assistant Professor in the Division of Nutritional Sciences at Cornell University. He graduated summa cum laude from Rutgers University with a dual degree in Chemistry and Physics. He received his PhD in Biological Engineering from the Massachusetts Institute of Technology. He then studied cancer metabolism at Harvard Medical School where he worked as an American Cancer Society postdoctoral fellow and later as an Instructor on the faculty. Dr. Locasale's research focuses on understanding metabolism in cell growth, cancer pathogenesis, and therapeutic intervention. He has defined the mechanistic principles that lead to the Warburg Effect—the observation that tumor cells process glucose through fermentation even when oxygen is abundant for respiration—and is now investigating its downstream consequences on cellular physiology, translating this knowledge to develop biomarkers of agents that affect glucose metabolism in cancer. His work on utilizing glucose-metabolizing cancer cells has led him to study the interplay between metabolism, signal transduction, and epigenetics. At the core of this effort lies the utilization of computational modeling and mass spectrometry-based metabolomics. Dr. Locasale is a recipient of the NIH Pathway to Independence Award, International Life Sciences Future Leader Award, and the Benjamin Trump Award for Excellence in Cancer Research from the Aspen Cancer Society, and was nominated as a visiting professor at the Epply Institute for Cancer Research. He has co-authored numerous textbooks and patents.

**James Mitchell** graduated from the University of Virginia in 1993. After this, he worked on DNA replication in yeast as a technician in Dr. Bruce Stillman's lab at Cold Spring Harbor Laboratory. He then moved to California to do his graduate studies at the University of California, Berkeley, where he worked on human telomerase ribonucleoprotein structure
and function in the lab of Dr. Kathleen Collins. There, he helped to identify the aplastic anemia syndrome dyskeratosis congenita as the first recognized telomere maintenance disorder, or telomeropathy. Dr. Mitchell completed his postdoctoral studies in Rotterdam (the Netherlands) in Prof. Jan Hoeijmakers’ lab, where he worked on premature aging in a DNA repair-deficient mouse model of the segmental progeria Cockayne syndrome. He found that these mice, although short-lived, display many key adaptive metabolic and physiologic features of dietary restriction, an intervention best known for extending lifespan in organisms as diverse as roundworms, fruit flies, and rodents. These studies sparked his interest in the benefits of dietary restriction and its potential translation to the clinic. Dr. Mitchell started his own lab at the Harvard T.H. Chan School of Public Health in Boston in 2008, where the main focus remains on the use of dietary restriction to protect against acute inflammatory stressors ranging from ischemia reperfusion injury to metabolic syndrome to experimental rodent malaria.

James M. Mullin received his BS degree in Biology from St. Joseph’s University (Philadelphia) in 1976. His PhD in Physiology was awarded from the University of Pennsylvania School of Medicine in 1980. A postdoctoral fellowship in the Department of Human Genetics, Yale University (1982-84), was followed by a Research Associate position at the Wistar Institute (Philadelphia). In 1986, Dr. Mullin joined the Lankenau Institute for Medical Research (Wynnewood, PA). He is currently also the Director of Research, Division of Gastroenterology, Lankenau Medical Center, and Professor, Kimmel Cancer Center, Thomas Jefferson University Medical School. Dr. Mullin has authored over 80 research publications and reviews on the regulation of epithelial transport processes, tight junctions, and epithelial barrier function. His current research interests focus on the role of epithelial barrier compromise in various gastrointestinal diseases and the regulation/enhancement of epithelial barrier function by various micronutrients and nutraceuticals. Ongoing research projects by his group encompass studies on HIV, Ebola, aging, Barrett’s esophagus, Ulcerative Colitis, Crohn’s Disease, and colorectal cancer. The Mullin research group utilizes epithelial cell culture models, animal tissue models, and patient-based studies in their research. Through the Mullin group, Lankenau Institute for Medical Research is the holder of numerous patents on micronutrients and epithelial barrier function in a variety of gastrointestinal diseases.

Arlan Richardson earned his PhD in biochemistry from Oklahoma State University and has devoted the past 40 years to aging research. He is the Founding Director of the Barshop Institute for Longevity and Aging Studies at the University of Texas Health Science Center at San Antonio and is currently Director of the Oklahoma Nathan Shock Aging Center at the University of Oklahoma Health Science Center. He also holds the appointment of Senior Career Research Scientist with the Oklahoma City VA Medical Center. Dr. Richardson’s laboratory is a major contributor in studying the role of gene expression in
aging, showing for the first time that caloric restriction alters gene expression at the level of transcription, and that these changes in gene expression enhance the ability of animals to respond to stress. Dr. Richardson’s group has developed novel genetically-modified mouse models to study the roles of oxidative stress and damage in aging and age-related diseases, such as cancer, neurodegeneration, and diabetes. His current research focuses on experiments into the role of rapamycin on aging. His leadership roles include serving as president of both the Gerontological Society of America (GSA) and the American Aging Association. Among his honors are the GSA’s Robert W. Kleemeier Award, the Lord Cohen Medal for Services to Gerontology from British Society for Research on Ageing, the Harman Research Award for research contributions in the field of aging and dietary restriction from the American Aging Association, and the Irving S. Wright Award of Distinction from the American Federation for Aging Research. The NIA has honored his research with the highly competitive MERIT award. He currently holds the Donald W. Reynolds Endowed Chair of Aging Research.

John Richie is Professor of Public Health Sciences and Pharmacology at Penn State University College of Medicine in Hershey, PA. For the past 30 years, his research goal has been to understand the link between the biological aging process and the development of aging-related diseases and disorders, including cancer. Using an interdisciplinary research approach, he has focused on the role of oxidative stress, generated both endogenously and from environmental exposures, as a mechanism for enhanced susceptibility during aging. His research has also investigated the impact of both endogenous and dietary antioxidants in protection against oxidative stress and its resulting damage, with the ultimate goal of designing and developing targeted prevention strategies. Dr. Richie received his PhD in Biochemistry from the University of Louisville in 1985. Prior to joining Penn State College of Medicine, he developed and led a Program on Cancer Susceptibility and Aging at the American Health Foundation (Institute for Cancer Prevention) in Valhalla, NY.

George Roth was formally affiliated with the National Institute on Aging from 1972-2004 and currently continues collaboration in an advisory capacity. After receiving a BS in Biology from Villanova University (1968) and a PhD in Microbiology from Temple University School of Medicine (1971), and post-doctoral work with Dr. Richard Adelman at the Fels Research Institute, he progressed from Staff fellow, to Research Chemist, to Chief of the Molecular Physiology and Genetics Section, to Acting Chief of the Laboratory of Cellular and Molecular Biology. Dr. Roth then served as Senior Guest Scientist at NIA from 2000-04, and became CEO of GeroScience Inc. He also served as Co-executive Director of the American Aging Association from 2002-03. His research interests continue to be basic mechanisms of aging; has worked in the area of signal transduction for many years, he now focuses on anti-aging strategies. The most visible projects in this area have been an examination of the effects of dietary caloric restriction in nonhuman primates and, more
recently, the development of caloric restriction mimetics. Dr. Roth has received a number of honors and awards. These include the Sandoz (now Novartis) Prize for Gerontological Research, the Research Award of the American Aging Association, Chair of the Gordon Conference on the Biology of Aging, Chair of the Biological Sciences Section of the Gerontological Society of America, the Merit Award and Equal Employment Opportunity Award of the NIA, and the Third Age Award of the Intl. Assoc. of Gerontology. In addition, he has been the Sigma Xi Scholar in Residence at Miami University, an NIH Visiting Professor at Meharry Medical College and the University of Puerto Rico Medical School, as well as Alpha Omega Alpha Professor at the University of Puerto Rico, the Ben Cohen Memorial Lecturer at the University of Michigan, Keynote Lecturer at the Nagoya International Symposium on Aging and Health, the Israel Endocrine Society, and the Orentreich Foundation for the Advancement of Science Symposium. Dr. Roth has been granted numerous patents in the caloric restriction mimetic area.

**Jacob Selhub** is a senior scientist and Director of the Vitamin Metabolism Research Laboratory at the Jean Mayer USDA Human Nutrition Research Center on Aging and a professor in the Friedman School of Nutrition Science and Policy. He received a BS in Agriculture at Hebrew University & Rehovot in Israel and a PhD in Biochemistry (Major) and Organic Chemistry and Microbiology (Minor) at Case Western Reserve University. He is a nutritional biochemist with expertise in folic acid and other B vitamins. His early work dealt with the metabolism, intestinal absorption, and physiology of folic acid and biological folate. In 1987, he used his basic science work as platform to study the epidemiological associations between one-carbon nutrients, homocysteine, and health outcomes in the aging population. His collaboration with other investigators made him realize that many diseases, including cancers, cardiovascular disease, and rheumatoid arthritis (RA) are associated with low plasma pyridoxal-5’ phosphate (PLP), the active form of vitamin B independent of homocysteine. His studies suggesting the existence of potential interaction between excessive folate intake and low vitamin B12 status that could adversely affect health and biochemical outcome in the elderly prompted exploration of possible mechanisms and whether excessive folic intake per se is potentially detrimental. Dr. Selhub is now collaborating with investigators in the Cardiovascular Inflammation Reduction Trial at Brigham and Women’s Hospital to study the role of methotrexate as an anti-inflammatory agent in patients with cardiovascular disease and metabolic syndrome.

**Martha Harney Stipanuk** is the James Jamison Professor in Nutrition in the Division of Nutritional Sciences at Cornell University, where she has been a faculty member since 1977. She received her BS from the University of Kentucky, her MS from Cornell University, and her PhD from the University of Wisconsin-Madison. Dr. Stipanuk’s research focuses on the study of amino acid metabolism, particularly the metabolism of the sulfur-containing amino acid cysteine. Her work played a major role in elucidating the intermed-
ary pathways of cysteine metabolism in mammalian cells, as well as the regulation of these pathways. Her research on cysteine dioxygenase, an iron-dependent enzyme that catalyzes the first step in the dominant pathway for cysteine disposal, involved approaches ranging from solving crystal structures to knockout mouse models. More recently, the Stipanuk laboratory has investigated cellular responses to amino acid deficiency, which has provided insights into potentially unique roles of methionine. Dr. Stipanuk also has a long-standing interest in teaching in the area of macronutrient metabolism. She is currently working on a 4th edition of her textbook Biochemical, Physiological, and Molecular Aspects of Human Nutrition (Saunders/Elsevier).

Suresh Tyagi received his PhD from the University of Aligarh (India) in 1980 and began his research career as a biophysical scientist during his graduate and post-graduate training in India and Ireland. He explored the dynamics of molecular biology of metalloproteinase homeostasis in cardiovascular remodeling in several post-doctoral fellowships (1984-1991). He was an assistant professor of medicine and biochemistry at the University of Missouri-Columbia (1992-6) and associate professor (1998-2003) at the University of Mississippi Medical Center. Currently, he is Professor of Physiology & Biophysics at the University of Louisville and holds the Stodghill Endowed Chair in Biomedical Sciences. Dr. Tyagi has consistently pursued a research program aimed at elucidating the role of metalloproteinase in cardiovascular disease and stroke. His work has impacted the view of metalloproteinase in cardiovascular remodeling and dysfunction. His research has great significance for many diseases, especially heart failure, Alzheimer’s disease, renal disease, Types 1 and 2 diabetes, and hypertension. Currently, he is a regular member of the NIH-MIM study section and is supported by four NIH-RO1 grants to study the homocysteine homeostasis and matrix remodeling in cardiovascular and cerebral vascular diseases.
Reception/Banquet
Breakfast/Lunch
BBQ
Symposium

If you have any questions on the Symposium, please contact:
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