

About this study: Josh Zhu, Ph.D., M.D., senior director of research and development at Pharmanex, was the lead scientist on the research. Angela Mastaloudis, Ph.D., (Pharmanex senior scientist), presented this research at the Oxygen Club of California 2010 World Congress at Santa Barbara, CA. March 17-20, 2010, and was awarded the prestigious DSM Nutraceutical Research Award.

Conclusions of the three-year lifespan and antioxidant laboratory studies found that:

- Cs-4 extended the maximal and average lifespan of the population studied; and
- Cs-4 supplementation significantly improved antioxidant protection and reduced oxidative damage caused by an oxidative stressor.

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#### ABSTRACT

#### Anti-oxidation and lifespan-extension activities of *Cordyceps sinensis* Cs-4 in oxidative stress and aging models

*Cordyceps sinensis* is traditionally believed as an anti-aging herb in China. We have reported the effects of *Cordyceps sinensis* Cs-4 (Cs-4), a mycelia fermentation product of *C. sinensis*, in glucose-lipid energy metabolisms, anti-fatigue and endurance enhancement. In this study we examined the effect of Cs-4 in antioxidant and lifespan extension in mice. The antioxidant activity was tested in mice (6 months old) that received 60 days of vehicle or Cs-4 (0.5, 1.0, or 1.5 g/kg) and a single dose of 11 Gy 60Co gamma-radiation on Day 60. Compared to controls, Cs-4 increased plasma total thiol groups, GSH and GSH-oxidase, and liver CAT, SOD and GSH reductase ( $p < 0.05$ ). Cs-4 reduced liver protein carbonyl groups and 8-OHdG ( $p < 0.05$ ). For examining the lifespan-extension effect of CM, 250 mice of 12 months of age (both sexes) were received either vehicle or Cs-4 (0.5, 1.0, or 1.5 g/kg) mixed with the forage. Calorie intake was adjusted to match the levels for controls twice per week. Compared to controls, the 75% survival time was extended 94-108 days in the Cs-4 dosage groups, the 50% survival time extended 10-66 days, the 25% survival time extended 29-44 days and the 12.5% survival time extended 7-50 days (86 wks so far; treatment continues). The Kaplan-Meier Survivor analysis revealed the extended lifespan and the reduced risks of death by Cs-4 ( $p < 0.05$ ). In conclusion, Cs-4 therapy significantly improves the body's antioxidant capacity and extends the lifespan in mice, supporting the traditional belief on the anti-aging function of Cs-4 in humans.

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Authors: Barger JL<sup>1</sup>, Wood SM<sup>2</sup>, Weindruch R<sup>1</sup>, Prolla TA<sup>1</sup>.

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## ABSTRACT

### Transcriptional Biomarkers of Age and Their Modulation by Dietary Interventions.

Studies using whole-genome transcriptional profiling have identified thousands of genes that are changed in expression with age. However, many of these age-related changes are not universal, but instead are specific to the genetic background of the organism being studied. Thus, there is great interest in identifying robust biomarkers of age across multiple experimental models that are applicable to human aging. We use gene expression profiling to identify transcripts that were consistently changed in expression with age (5 vs. 28-30 month old) in seven mouse strains. This analysis was performed in four tissues (heart, cerebral cortex, gastrocnemius and adipose tissue) and RT-qPCR was used to confirm a panel of 10-20 genes in each tissue. Interestingly, we found minimal overlap across the four tissues studied, suggesting that aging at the individual gene level is tissue-specific. We then assessed whether the age-related change in these biomarkers was effected by caloric restriction (CR), the only intervention known to extend lifespan by slowing the aging process. Depending of the tissue studied, CR opposed 3-24% of the overall aging change. Finally, we assessed the ability of dietary ingredients to attenuate age-related changes in these biomarkers. An extract of pomegranate was the most effective compound tested, opposing 32-65% of the overall aging change depending on the tissue studied. In summary, we have identified robust, tissue-specific panels of the transcriptional biomarkers that are relevant to human aging. We are currently using these biomarkers in a large-scale screen of compounds to determine if they have efficacy in preventing aging at the transcriptional level.

Presented at: Biology of Aging, Determinants of Health-Span: From Cells to Humans.  
Les Diablerets, Switzerland August 22-27, 2010.

Authors: SM Wood<sup>1</sup>, JL Barger<sup>2</sup>, TA Prolla<sup>2</sup>, R Weindruch<sup>2</sup>, A Mastaloudis<sup>1</sup>, SB Ferguson<sup>1</sup>.

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## ABSTRACT

### Transcriptional Biomarkers of Mitochondrial Aging and Modulation by *Cordyceps sinensis* Cs-4.

**Introduction:** One of the earliest manifestations of human aging is a decline in energy which begins as early as 30 years of age. The source of this decline is multi-factorial yet changes in mitochondria (ie. function and number) have been implicated as an integral component of the age-associated decline in humans. Therefore, we set out to identify mitochondrial-related nuclear encoded genes that consistently change in expression with aging. *Cordyceps sinensis* Cs-4 (Cs-4) is a natural ingredient that has been shown to have anti-aging properties and positive effects on energy including maximal oxygen consumption ( $VO_{2max}$ ). Therefore, we examined whether age-related gene expression changes could be opposed by Cs-4.

**Methods:** Mice (C57Bl/6), aged 5 (n = 5; young control (YC)) and 22 (n = 10; old) months of age were fed an AIN 93M diet. The old animals were divided into two groups and fed either the diet alone (old control (OC)) or supplemented with Cs-4 (300 mg/kg body weight)(old supplemented (OS)), for three months. Tissues were collected from skeletal muscle (gastrocnemius) and brain (cerebral cortex); gene expression was analyzed using microarrays. Gene expression profiling was used to identify mitochondrial-related transcripts that consistently changed with age in brain and muscle. Gene ontology terms were used and Parametric Analysis of Gene set Enrichment (PAGE) performed to determine effects of age (YC vs. OC) and supplementation with Cs-4 (OC vs. OS).

**Results:** We identified 393 out of 1241 mitochondria-related nuclear encoded transcripts in the muscle (220) and brain (173) that changed in expression with age. Cs-4 opposed the age-related changes in 52 of the genes ( $P < 0.05$ ). In addition, Cs-4 opposed the effects of aging in several gene ontology pathways.

**Conclusion:** We identified mitochondrial-related nuclear encoded genes which changed consistently in expression with age. Using this methodology, we found that Cs-4 opposed many of these changes in aging brain and muscle. Ongoing studies are utilizing this technique to investigate the effects of a variety of natural ingredients in brain, muscle and other tissues.

## Introduction:

- Mitochondrial changes occur with aging (i.e. function and number).
- Skeletal muscle and brain tissue show signs of aging and also contain high concentrations of mitochondria.
- *Cordyceps sinensis* is traditionally believed to have anti-aging activities and to promote longevity:
  - Improvements in endurance, anti-fatigue, maximal oxygen consumption ( $VO_{2max}$ ), glucose and lipid metabolism (Dai et al. *J Altern Compl Med.* 7:231, 2001; Zhao et al. *J Altern Compl Med.* 8:309, 2002; Xiao et al. *Chin J Integrat Med.* 10:187, 2004; Li et al. *Chin J Clin Pharmacy* 16:274, 2007; Li et al. *Shanghai J Prevent Med.* 20:367, 2008; Wang et al. 2008 Symposium Chin Assoc Med Mycol. pp157-164).
- The purpose of this study was to examine whether or not age-related changes in gene expression in mitochondrial-related nuclear encoded genes could be opposed by Cs-4.

## Methods

C57Bl/6 Mice fed AIN 93m diets (n = 15; 5/group)

- Fed for 3 months
- Skeletal muscle (gastrocnemius) and brain (cerebral cortex) tissue harvested
- Gene Expression (Affymetrix Chips)
- Parametric Analysis of Gene set Enrichment (PAGE)

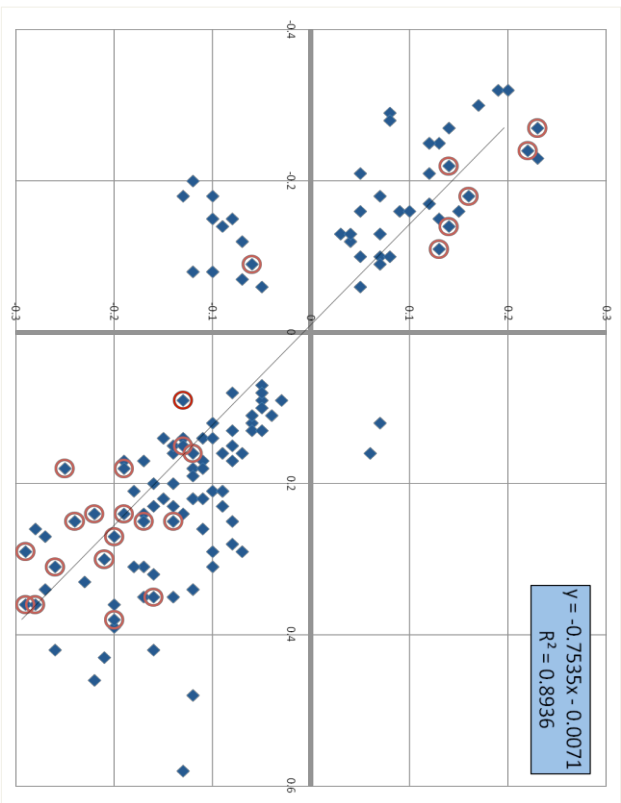
## Groups:

1. Young Control (YC); 5 months of age
2. Old Control (OC); 22 months of age
3. Old Cs-4 Supplemented (OS)(300 mg/kg body weight); 22 months of age

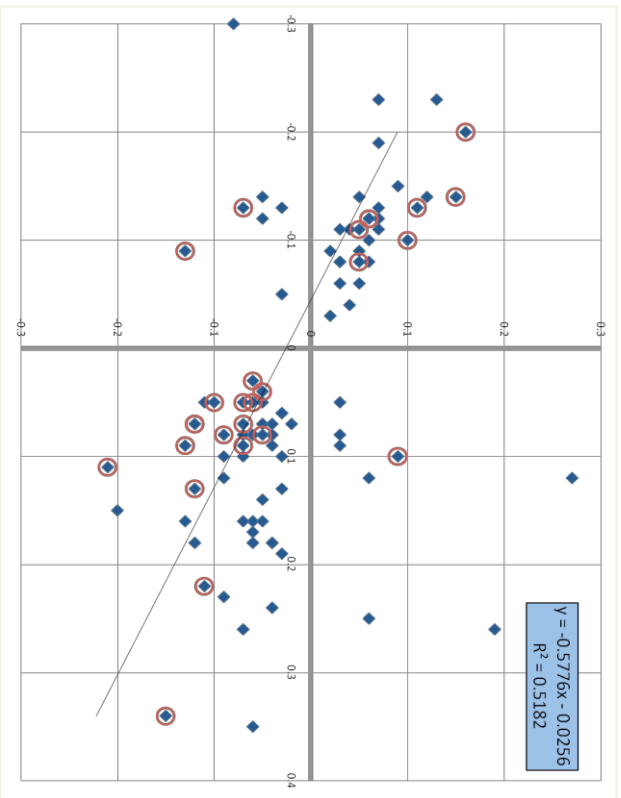
## Results

- Expression of 20,696 genes examined
- Genes associated with Mitochondria structure/function (1,241, ~6%)
  - Genes which changed with age, YC vs. OC ( $P < 0.05$ )
    - ✓ Brain: 173, Muscle: 220; 21 genes overlapped in both brain and muscle
  - Genes influenced by Cs-4
    - ✓ Brain: 27, Muscle: 25 (no overlap)
    - ✓ 48 of 52 (92%) opposed aging

### Muscle Mitochondrial Related Nuclear Encoded Gene Changes, Aging vs. Cs-4



### Brain Mitochondrial Related Nuclear Encoded Gene Changes, Aging vs. Cs-4



Figures of Gene Expression (fold change) as influenced by aging (x-axis) vs. Cs-4 (y-axis). Each point represents one gene. Those that are statistically different ( $p < 0.05$ ) with Cs-4 supplementation are circled in red.

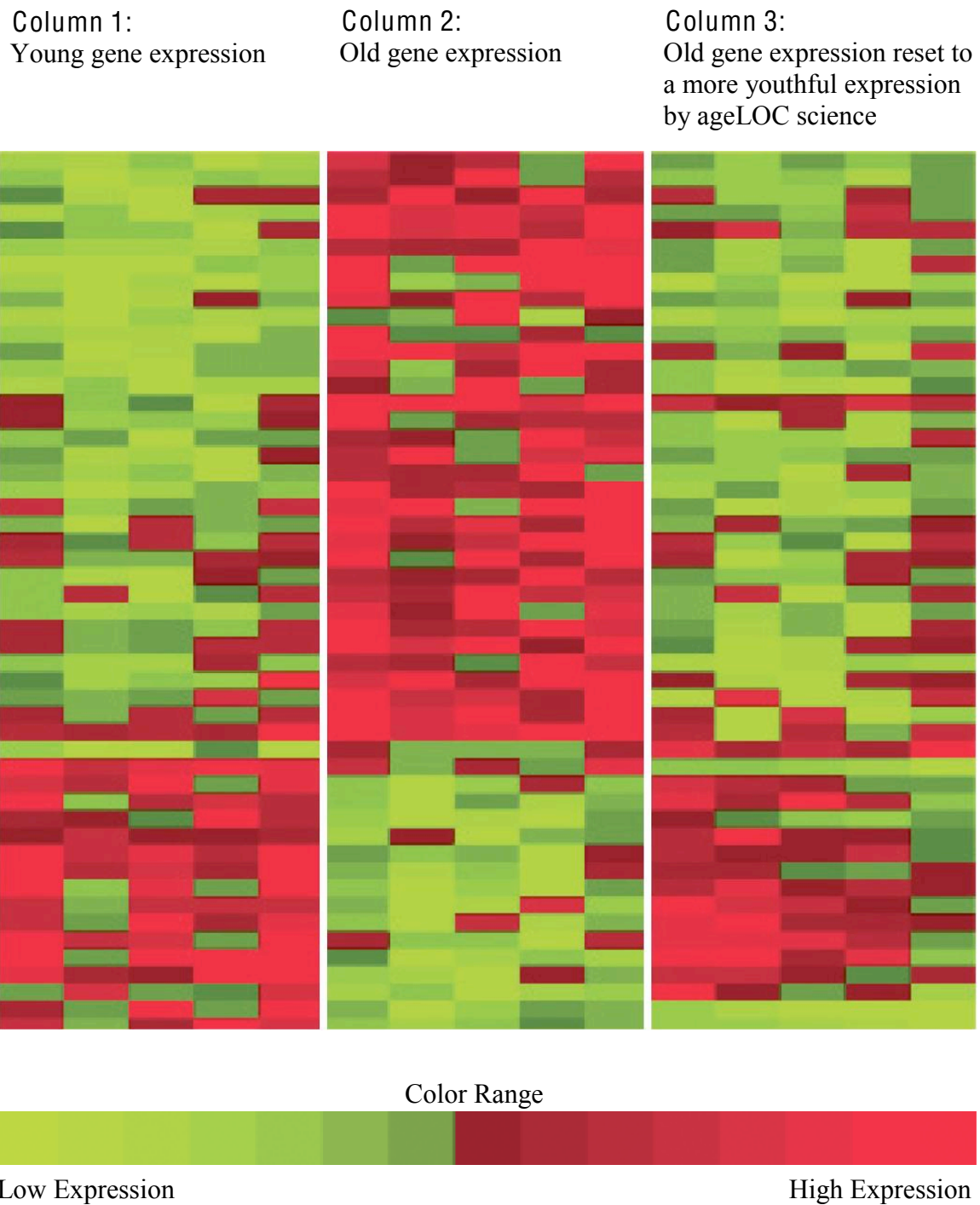


Figure description: This heatmap illustrates gene expression of three groups from a pre-clinical test with one of the ageLOC Vitality ingredients: young (column 1), old (column 2), and old with ageLOC science (column 3). Each row represents one of 52 genes comprising the mitochondrial Youth Gene Cluster. Columns 1 and 2 show that each of the 52 genes became more or less active during the aging process. In column 3, the YGC activity pattern of the old with ageLOC science group has been reset (92%) to a gene expression pattern similar to the young group in column 1.

## Parametric Analysis of Gene set Enrichment (P.A.G.E. Overview)

Muscle		Z-Age *	Z-OS
Gene Ontology Term			
RNA metabolic process	10.63	-8.35	
RNA processing	9.58	-7.04	
RNA binding	9.01	-5.92	
Nuclear part	7.95	-3.48	
Protein transport	7.94	-4.08	
Establishment of protein localization	7.93	-4.02	
mRNA metabolic process	7.66	-4.24	
Protein localization	7.46	-3.47	
Intracellular transport	7.23	-3.55	
Macromolecule localization	6.94	-2.94	
Chromatin modification	6.76	-4.3	
ncRNA metabolic process	6.58	-7.62	
Serine hydrolase activity	-4.14	3.8	
Structural constituent of eye lens	-4.16	3.24	
Serine-type peptidase activity	-4.2	3.9	
Wnt receptor signaling pathway	-4.24	4.36	
Substrate-specific transporter activity	-4.47	3.26	
Cation transmembrane transporter activity	-4.49	2.94	
Ion transport	-4.49	3.26	
Ear morphogenesis	-4.51	3.79	
Cation channel activity	-4.56	2.88	
Amine receptor activity	-4.7	4.49	
Ear development	-4.71	4.02	
Inner ear morphogenesis	-4.73	3.69	
Ion transmembrane transporter activity	-5.03	3.19	
Ion channel activity	-5.11	2.91	
Keratin filament	-5.12	6.43	
Cell-cell signaling	-5.22	4.3	

Brain		Z-Age *	Z-OS
Gene Ontology Term			
Defense response	7.64	4.22	
Immune response	7.19	5.02	
Antigen processing and presentation of peptides	6.53	2.71	
Response to biotic stimulus	6.35	3.38	
Response to other organisms	6.25	4.31	
Defense response to bacterium	6.12	3.86	
Antigen processing and presentation	5.98	2.85	
Response to wounding	5.97	3.48	
Inflammatory response	5.78	3.45	
Positive regulation of immune system process	4.99	3.58	
Response to bacterium	4.94	3.89	
Regulation of response to stimulus	4.93	4.31	
Regulation of immune response	4.89	3.75	
Response to external stimulus	4.88	3.79	
Cell surface	4.69	4.65	
Amino acid ligase activity	-4.21	-2.85	
RNA binding	-4.35	-4.81	
Translation	-4.41	-3.43	
RNA metabolic process	-4.48	-6.77	
Chromosome organization	-4.69	-3.75	
mRNA processing	-4.72	-3.51	
RNA processing	-5.21	-5.54	

\*Z-scores from PAGE are highlighted in RED or BLUE to indicate pathways that are up- or down-regulated by age and treatment ( $p < 0.01$ ). Age refers to YC vs. OC; OS refers to OC vs. OS.

## Summary & Conclusions

1. Cs-4 supplementation opposed age-related changes in gene expression in mitochondrial-related nuclear encoded genes.
  - a. We identified 393 out of 1241 mitochondrial nuclear encoded genes in the muscle (220) and brain (173) that changed in expression with age.
  - b. Several age-related changes in mitochondrial nuclear encoded gene expression were opposed in the muscle and brain by Cs-4.
  - c. Of those genes that were changed in expression by Cs-4, 92% changed statistically significantly ( $P < 0.05$ ) in the direction of a more youthful pattern.
2. The gene expression pattern changes following Cs-4 supplementation provides mechanistic evidence of anti-aging effects noted by other researchers.
3. PAGE revealed that Cs-4 opposed age-related changes in multiple gene expression pathways in skeletal muscle; a different pattern in brain tissue was observed.
4. Analysis of changes in expression of individual genes and PAGE analysis each provided unique insights into the anti-aging effects Cs-4. It is recommended to utilize multiple data analysis tools when conducting gene expression profiling experiments.
5. Nutritional strategies to oppose the effects of aging will most likely require several ingredients to address age-specific gene expression changes in specific tissues.
6. Ongoing studies are utilizing gene expression profiling in brain, muscle and other tissues to investigate potential effects of natural ingredients in opposing the effects of aging.

Presented at: International Symposium on Aging and Anti-Aging; Tokyo, Japan. Sept 24, 2010.

About this symposium: Leading international scientists gathered at the University of Tokyo to share research and insights on how to remain youthful as we age. The International Symposium on Aging and Anti-Aging: From Molecular Biology to Nutritional Science was hosted by the Graduate School of Agricultural and Life Sciences at the University of Tokyo and sponsored by Nu Skin Japan.

Richard H. Weindruch Ph.D.

Professor of Geriatrics and Gerontology,

Department of Medicine, University of Wisconsin

Presented on behalf of Weindruch by his colleague Tomas A. Prolla, Ph.D.

## ABSTRACT

### Slowing the Aging Process by Caloric Restriction: Studies in Mice and Monkeys

It is widely accepted that caloric restriction (CR) without malnutrition delays the onset of aging and extends lifespan in diverse animal models including yeasts, worms, flies and laboratory rodents. The mechanism underlying this phenomenon is still unknown. We have hypothesized that a reprogramming of energy metabolism is a key event in the mechanism of CR (Anderson RM, Weindruch R, Trends Endocrinol Metab, 2010).

Data will be presented from studies of mice on CR that lend support to this hypothesis. A robust area of CR research concerns the search for drugs or nutrients that mimic the actions of CR in normally fed animals.

We have investigated resveratrol and other nutrients in this context (Barger et al., PLoS ONE, 2008; Barger et al., Exp Gerontol, 2008) and will present data suggesting slower cardiac aging in treated mice. Whether aging retardation occurs in primates on CR has long been a major research question in the biology of aging. We have been investigating this issue in rhesus monkeys subjected to CR since 1989 and will discuss the current status of this project. We have found that CR reduces the rate of age-associated muscle loss (sarcopenia) (Colman et al., J Gerontol Biol Sci, 2008).

CR in monkeys also improves survival, reduces (by 3-fold) the risk of developing diseases of aging and opposes the development of age-associated brain atrophy (Colman et al., Science 2009). Human trials of CR are ongoing and will be briefly described. (Supported by NIH P01 AG11915).

## Profile

Richard Weindruch, Ph.D.

Professor of Geriatrics and Gerontology,  
Department of Medicine, University of Wisconsin  
Co-founder, LifeGen Technologies



Dr. Weindruch earned his Ph.D. in Experimental Pathology at UCLA in 1978. He is the author and co-author of more than 170 publications and his scientific awards include the Harman Research Award, American Aging Association (2000) and the Glenn Award, GSA (2000). Dr. Weindruch's research career has focused on the biology of aging and age-related diseases, studying caloric restriction, which slows the aging process and retards the appearance of a broad spectrum of diseases in diverse animal populations. In 2001, he and Dr. Tomas Prolla founded LifeGen Technologies, LLC, a company focused on nutritional genomics, including the impact of nutrients and caloric restriction on the aging process.

Dr. Weindruch has published several articles in *Science* and other prestigious scientific journals.

Presented at: International Symposium on Aging and Anti-Aging; Tokyo, Japan. Sept 24, 2010.

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Tomas A. Prolla, Ph.D  
Professor, Departments of Genetics and Medical Genetics,  
University of Wisconsin-Madison

### ABSTRACT

#### Role of Mitochondria in age-related hearing loss and its prevention by Caloric Restriction

Age-related hearing loss (AHL, also known as presbycusis) is a universal feature of mammalian aging and is the most common sensory disorder in the elderly population, affecting 50% of individuals over 60 years of age. AHL is a complex disorder, but it is widely accepted that AHL is generally caused by degeneration of the inner ear (cochlea). AHL is associated with age-dependent loss of sensory hair cells, which function as mechanosensory transducers, and spiral ganglion neurons, which relay information from the hair cells to the CNS. Because these cells do not regenerate in mammals, cochlear cell loss eventually leads to AHL.

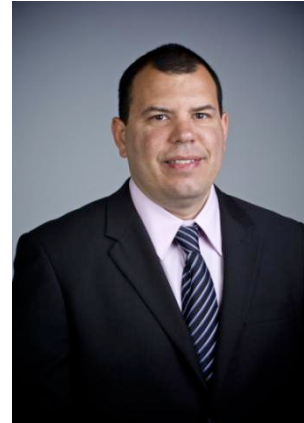
We have recently demonstrated that AHL can be prevented in mice by deletion of Bak, a mitochondrial pro-apoptotic protein. Bak-mediated cell death of cochlear cells is induced by oxidative stress, and prevented by overexpression of a mitochondrial-targeted catalase, or dietary antioxidants that target mitochondria.

We have also shown that caloric restriction can prevent AHL, and that prevention is associated with the induction of mitochondrial transcripts, and reduction in the expression of genes involved in the mitochondrial apoptotic pathway. Induction of the mitochondrial sirtuin Sirt3 appears to be essential for the positive effects of CR, since sirt3 gene deletion prevents the beneficial effects of CR. These findings suggest novel pathways for intervention in aging and AHL through the development of CR mimetic compounds.

## Profile

**Tomas A. Prolla, Ph.D**

Professor, Departments of Genetics and Medical Genetics,  
University of Wisconsin-Madison  
Co-founder, LifeGen Technologies



Tomas A. Prolla, Ph.D., performed his graduate studies in the Department of Molecular Biophysics and Biochemistry at Yale University, receiving his doctoral degree in 1994. He completed post-doctoral training at the Human and Molecular Genetics Department at Baylor College of Medicine, then joined the faculty of the Department of Genetics and Medical Genetics at the University of Wisconsin in 1997. Dr. Prolla has received several awards of scientific excellence, including the Shorb Lecturer Award, the Burroughs Wellcome Young Investigator Award, the Basil O'Connor Starter Scholar Research Award, and the Howard Hughes Medical Institute New Faculty Startup Award. Dr. Prolla's work currently focuses on the genetic basis of aging. In 2001, he and Dr. Richard Weindruch founded LifeGen Technologies, LLC, a company focused on nutritional genomics, including the impact of nutrients and caloric restriction on the aging process. Dr. Prolla has published several articles in prestigious scientific journals such as *Science*, *Nature Genetics* and *Cell*.

*From the sponsor of this symposium*

Joseph Y. Chang Ph.D  
Chief Scientific Officer and Executive Vice President,  
Product Development  
Nu Skin Enterprises, Inc.



## TO AGE OR NOT TO AGE

In Greek mythology, Tithonus, upon the request by his lover, Eos, was granted immortality by Zeus. Eos' request for immortality, unfortunately, failed to include health as a prerequisite. Tithonus, while living an immortal life, deteriorated with age, becoming frail and old. This cautionary tale of immortality suggests that any anti-aging intervention should include the most critical of elements, i.e. the preservation of health and vitality over the life of an individual.

A discussion of aging issues and to find a way to make our lives as rich and full as possible as we age is, therefore, timely. Only through this process of scientific discovery can the real contributors to aging and age-related diseases be identified and, when possible, reversed. As it will become evident, nutrition plays a vital part in achieving the goal of living healthier longer. Aging is not an episodic process; instead, it is the consequence of a continuum of cumulative and excessive damage occurring at the molecular level. Attenuation of aging is entirely dependent on mitigating such molecular damage by augmenting compensatory repair mechanisms or slowing the degenerative processes. At its core, this view makes clear that aging indeed starts early and the rate of aging rests on factors (internal and external) that can either positively or negatively influence the delicate balance between tissue repair and damage. If we are to widen the gap between chronological and biological age, we, therefore, have to understand the various mechanisms that control this delicate balance between tissue repair and damage, and to devise effective strategies that turn these mechanisms in favor of tissue repair and regeneration.

This symposium, therefore, provides an excellent forum to bring together several international scientists who have devoted their lives to researching the aging process. Their research has contributed significantly to our understanding of aging at the physiological and genetic level. Caloric restriction (CR) is the best documented nutritional intervention for extending lifespan in many species ranging from yeasts to primates. Genetic and physiological analysis after CR provide clues to functionally relevant mechanisms that lead to aging and offers a means to develop anti-aging strategies. Indeed, by exploring gene patterns of anti-aging, the role of the mitochondria in modulating the aging process is gaining recognition as a major causal factor. It is also becoming clear that crosstalk among multiple genes plays a more important role than the action of a single gene in mediating the survival of an organism.

Other speakers will focus on oxidative stress and antioxidants at the organ level, e.g. heart and brain. Such metabolically active tissues should provide further insights into the way that nutritional supplementation can be an effective modality for slowing the aging process. Through these and other studies, we look forward to a new understanding of aging and a new paradigm of "old age." Certainly, the polymorphic nature of aging highlights the need to analyze aging at all levels although this symposium suggests that we are getting closer to the "secret of youth". When complete, this clearer understanding of aging will lead us to formulate anti-aging products that provide a better quality of life as we age.

## Supporting Research for ageLOC Vitality's benefits of physical, mental, and sexual vitality

### Physical Vitality

1. Weindruch R, Prolla TA, Barger JL. Effect of the ageLOC ingredient Cordyceps Cs-4 on gene expression profiles, and effects of caloric restriction and the ageLOC ingredient pomegranate on supermarkers of aging. LifeGen Technologies, unpublished work, 2010.
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## Mental Vitality

1. Weindruch R, Prolla TA, Barger JL. Effect of the ageLOC ingredient *Cordyceps* Cs-4 on gene expression profiles, and effects of caloric restriction and the ageLOC ingredient pomegranate on supermarkers of aging. LifeGen Technologies, unpublished work, 2010.
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