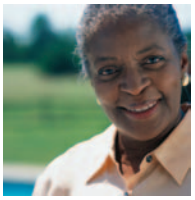
KRONOS LONGEVITY RESEARCH INSTITUTE

Research to promote a longer, healthier life for you, your children, and your grandchildren.





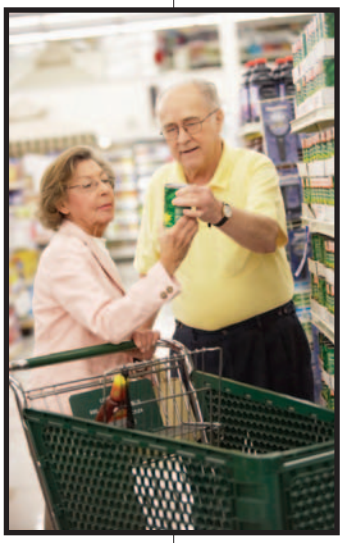


Fourth Quarter 2005 Vol. 4, Issue 10

WHY SHOULD YOU BE INTERESTED IN AN OMEGA ENRICHED DIET?

Many factors determine human longevity. It is a widely accepted "common-sense" fact that diet is one factor. Increasingly, medical research supports the important role of a healthy diet in extending life. Good nutrition is critical for a high quality of life in our older years, as well.

The first nutritional target is maintenance of a normal body weight. Obesity can contribute to the development of a variety of chronic diseases that lead to early death or disability, such as diabetes, heart attacks, strokes, and some forms of cancer. In addition, obesity can lead to faster progression of other chronic age-related diseases, such as osteoarthritis, low back pain, incontinence, respiratory problems and sleep impairments. These diseases increase disability, dependence and suffering, and impair quality of life. A body weight below normal is also unhealthy because it can lead to impaired immune functions and infections, osteoporosis, bone fractures, loss of muscle mass and strength. In extreme cases, low body weight is a sign of generalized malnutrition leading to anemia, vitamin deficiency diseases, poor wound healing and a host of other problems.



It is extremely important to keep our weight within the normal range. For persons over 60, a Body Mass Index (BMI) in the 19 to 30 range is acceptable (see BMI calculation table on page 4).

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Kronos Longevity Research Institute

2222 E. Highland
Suite 220
Phoenix, Arizona
85016

Tel: 602.778.7499

www.kronosinstitute.org

DIRECTOR'S MESSAGE

Biomarkers Of Aging

Most chronic diseases occur mainly in the elderly, such as, arthritis, diabetes, cancer, cardiovascular and neurodegenerative diseases (such as Alzheimer's and Parkinson's disease), as well as blindness and deafness. Even in those without a chronic disease, so called "normal aging changes" bring about losses of muscle and bone, and reduce the function of the immune system, leading to frailty and vulnerability. An important fact about today's population is the expected increase in the elderly (over 65). To improve health and independence for the growing number of elderly, we desperately need a deeper scientific understanding of aging and its relationship to disease and functional status.

Aging involves more than the length of time that an individual lives. It is clear that different species age at different rates. Mice look "old" (white hairs, slow movements, reduced appetite, patchy coat) at 24 months of age, most dogs at 12 or 14 years, and humans by 65-80 years of age. Ultimately, death from "old age" or its associated diseases occur, much earlier for mice than for dogs, and for dogs than for humans. Thus, for different species, the concept of "Biological Age" is more valid and informative than just giving a calendar age. That is, if one says, "a species is 2 years old," the statement tells us nothing about his or her Biological Age, unless one knows whether they are discussing a mouse (biological age = very old), a dog (biological age = young adult) or a human (biological age = juvenile).

Less obvious are the rates of aging that may differ markedly between members of the same species. The best example is the large versus small breeds of dogs. A Toy Poodle is old at 15 or 16 years of age, but a Great Dane is already a tottering geriatric case by the age of 7. We know that humans also age at different rates. If the factors responsible for such differences can be identified, interventions in the course of aging and delay of onset of age-related diseases may be possible. Such intervention holds tremendous promise for improved human health.

A major roadblock to carrying out research on human aging is the lack of intermediate measures or biomarkers of aging. Why is this? Suppose that a laboratory working on fruit flies (lifespan about eight weeks) has found that some combination of dietary chemicals fed to adult flies doubles their lifespan and delays signs of functional old age until flies have lived 12-14 weeks. Then the same combination is tried in mice (lifespan about 2 years) beginning at 4-6 months of age (young adults) and the treated mice still appear vigorous and youthful at 24 months and do not become frail or die out until 40-48 months of age. How can we determine if the same intervention could double the human lifespan? We could start giving the treatment or a placebo to groups of 30-40 year old humans and wait for them to exhibit signs of frailty and increased mortality. However, we would have to wait 40 years or more before we know whether our experiment has been successful. This would simply be too expensive and impractical.

To do this experiment successfully, we would need a certain criteria that we can measure accurately which would provide an "index" of aging. This measure or measures would have to change progressively more than the adult lifespan and, to be valid, would have to predict the onset of frailty, chronic illness, and,

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BODY MASS INDEX CHART

BMI (kg/m^2)	19	20	21	22	23	24	25	26	27	28	29	30
Height (in.)	Weight (lb.)											
63	107	113	118	124	130	135	141	146	152	158	163	169
64	110	116	122	128	134	140	145	151	157	163	169	174
65	114	120	126	132	138	144	150	156	162	168	174	180
66	118	124	130	136	142	148	155	161	167	173	179	186
67	121	127	134	140	146	153	159	166	172	178	185	191
68	125	131	138	144	151	158	164	171	177	184	190	197
69	128	135	142	149	155	162	169	176	182	189	196	203
70	132	139	146	153	160	167	174	181	188	195	202	207
71	136	143	150	157	165	172	179	186	193	200	208	215
72	140	147	154	162	169	177	184	191	199	206	213	221
73	144	151	159	166	174	182	189	197	204	212	219	227
74	148	155	163	171	179	186	194	202	210	218	225	233
75	152	160	168	176	184	192	200	208	216	224	232	240
76	156	164	172	180	189	197	205	213	221	230	238	246

Components of Our Diet

The main components of our diet are proteins, carbohydrates (sugars) and fats. The proper balance between them is essential for our health; any "diet" that attempts to nearly eliminate any of these categories from our daily food intake is considered unhealthy.

From the energy (caloric) perspective, fat is the most important, since each gram of fat has approximately two and a half times as many calories as one gram of protein or carbohydrate.

Calories do count! Once we have consumed food that can be oxidized as fuel in our cells, we must either use it to produce energy (calories) or store it. There is no other way for our bodies to get rid of it. Eating more calories than we burn will make us gain weight and, if continued for a long period, will lead to obesity. On the other hand, if we eat less calories than we burn, we will lose weight and, over time, this may lead to underweight conditions (common in people over 70).

Most people on Western type diets take 1/3 to 2/3 of their daily calories in the form of various fats. Therefore, if you have reasons to watch your weight, you have to closely watch how much fat you eat.

Types of Fat: The Good, The Bad and The Ugly

Not all fats are created equal as far as health and longevity are concerned.

An easy way to tell what fats are considered healthy or unhealthy is to look at them at normal room temperatures. Fats in liquid form fall into the reasonably healthy category. Such fats are the monounsaturated fats (MUFA) and the polyunsaturated fats (PUFA). Fats that appear solid are, usually, unhealthy and include the saturated fats (SFA) and the trans-fatty acids (TFA).

Trans Fats - We have disscussed with trans-fatty acids and their problems in previous issue (Volume 4, Issue 9.) To review, TFA's are the unhealthiest and most ubiquitous of the fats in our twentieth century American

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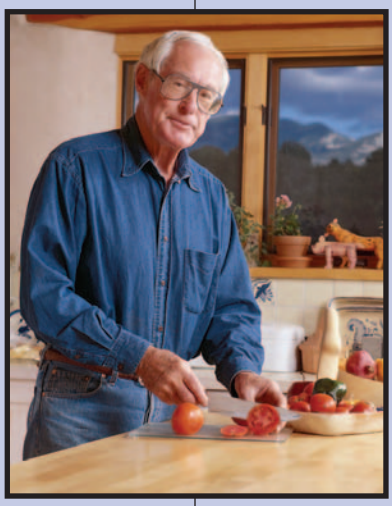
diets. TFA's may be up to twice as potent, compared to SFA's, in accelerating heart and arterial diseases, leading to heart attacks and strokes. A short survey of food labels on prepared foods looking for the terms "hydrogenated" or "partially hydrogenated" will demonstrate the pervasiveness of the use of TFAs. A new FDA rule requires food labels to indicate TFA content. There are encouraging signs that the food industry is, also, responding. We can now find products marked as "trans-fatty acid free." Even McDonald's announced that they will shift from using hydrogenated oils to vetgable oils to fry their famous French fries.



Saturated Fatty Acids - The SFA's have been a part of the human diet for thousands of years. They are the predominant fat in most beef, pork, lamb and many birds, and are found in large quantities of milk and dairy products.

For most of our history, animal and dairy fats constituted, on the average, less than 12% of the daily caloric consumption (with the exception of rare societies such as ancient Rome and Greece, mostly the Athenians). A rapid explosion of meat and dairy consumption occurred in the last 100 to 150 years in Europe and North America; SFA consumption increased three to five fold. It was not until the last 40 to 50 years that we discovered that eating SFA-rich foods can raise the bad cholesterol (LDL) and can lead to increased risk for heart disease, high blood pressure, strokes and cancer.

The liquid oils are not all equal from the health perspective. The two main categories are monounsaturated oils (MUFA) and polyunsaturated oils (PUFA). The PUFA are further divided into two subcategories: the omega-6 PUFA and the omega-3 PUFA.

The monounsaturated fatty acids (MUFA's) are found primarily in olive oil. Other sources of MUFA are canola oil, avocados and some nuts (e.g. almonds, pecans, cashews, hazelnuts). Populations whose diet is very high in MUFA and low in SFA have fewer heart attacks, fewer deaths from heart disease, and, possibly, fewer cases of certain cancers. MUFAs (and especially olive oil) appear to be excellent substitutes for SFAs in our daily diet. The scientific observations regarding the benefits of olive oil keep coming in and this type of fat looks better all the time.

A recent report from Spain suggests that in order to achieve significant protection from heart disease, we must consume at least 50 grams (about three and one-half tablespoons) per day of olive oil without increasing the total number of our daily calories.

Olive oil may be more beneficial than other MUFAs because it contains strong antioxidant substances (the main one is called hyrdohytyrosol). Although all types of olive oil contain some antioxidants, their final amount depends on the method of olive oil extraction from olives. Regular olive oil (marked as "Pure" or "Pomace") is produced using hot pressurized water and these high temperatures destroy some of the antioxidants; in contrast, virgin olive oil (marked as "Virgin" or "Extra Virgin") is produced using cold water and, therefore, contains much higher amounts of antioxidants. Consuming olive oil increases antioxidant levels in the blood, reduces the excretion of oxidative damage products in the urine, increases the good (HDL) cholesterol in the blood and reduces a particularly harmful form of the bad cholesterol (oxidized LDL or oxLDL).

In addition, virgin olive oil contains a substance called oleocanthal (one of the substances that gives virgin olive oil stronger taste and aroma) was just reported, in the *Nature journal* to have pharmacological actions and

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properties similar to Ibuprofen, one of the most commonly used anti-inflammatory pain medications.

Another mainstay of the Mediterranean diet is tomatoes. Tomatoes contain a very potent antioxidant, called lycopene, that has been shown to provide some protection from prostate and, perhaps, lung cancer. Recent studies have indicated that eating tomatoes cooked in olive oil achieves a 4 to 10 times higher lycopene levels in the blood as compared to eating the same amount of tomatoes cooked without olive oil. In another study consuming tomato products with olive oil increased the antioxidant capacity of the blood substantially. There was no increase in antioxidant capacity when sunflower oil (an n-6 PUFA - see below) was used instead of olive oil.

Some observational studies have suggested that high consumption of olive oil may offer some degree of protection from age-related memory decline and Alzheimer's disease. Using olive oil can also help reduce high blood pressure.

Some data suggests that the protective effects of virgin olive oil are most important in the first decades of life, which suggests that for maximum preventive benefits increased consumption of olive oil should be initiated before puberty.

The **Polyunsaturated Fatty Acids (PUFA's)** are divided into two subcategories:

- **Omega-6 PUFA (also written as n-6)** are almost all the vegetable oils (including corn oil, soybean oil, sunflower oil and cottonseed oil).
- **Omega-3 PUFA (also written n-3)** can be found in fatty (usually cold water) fish, such as salmon, mackerel, sardines, anchovies and herring, and, in lesser amounts, in walnuts and flax seeds.

In the Paleolithic ages, the human diet contained about equal amounts of n-3 and n-6 PUFA. About 10,000 years ago, with the establishment of agriculture, the proportion changed to a ratio of a little more than twice as much n-6 as n-3 because of the increased consumption of grains and legumes. It remained about the same until 100 years ago, when we developed the efficient technology for the extraction of oil from corn and cotton seeds. The availability of cheap vegetable oils, together with the concern (in the second half of the century) for the deleterious effects of saturated fats, lead to an explosion of n-6 oil consumption. Now the ratio of n-6 to n-3 in North America and most of Europe (with the exception of Southern European olive oil producing countries, such as Spain, Greece and Italy) is about 12-18:1. This means that for each portion of omega-3 in our diet, there are 12 to 18 portions of n-6 oils. Such a huge imbalance is not healthy. Although replacing SFA with n-6 PUFA reduces total serum cholesterol and may lead to some reduction in heart disease, it also impairs the function of the immune system promoting inflammatory diseases like asthma and ulcerative colitis. In addition, certain substances produced in the body as a result of n-6 metabolism can contribute to the formation of thrombus (clot) and atheromas (plaques in the arteries) that may lead to heart disease and strokes. In contrast, many population studies have suggested many beneficial effects from higher n-3 content in the diet. The most impressive are the findings related to heart disease. It appears that high consumption of n-3 PUFA (mostly by increasing fish in the diet and/or by adding fish oil supplements) can reduce heart attacks, reduce even more deaths associated with heart attacks and sudden deaths, and generally reduce overall death rates. These studies resulted in a recommendation by the American Heart Association for increased omega-3 in the diet (by eating more fish and adding fish oil supplements).

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WHY... AN OMEGA ENRICHED DIET?

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KLRI Study on the Effects of Omega-3 PUFA

Large population studies are a good guide of proper nutrition, but they also have several limitations. The most important one is that a diet very high in n-3 PUFA (like the Mediterranean diet), also includes high amounts of MUFA (olive oil), more vegetables and fruits, and more complex carbohydrates. In contrast, a diet high in n-6 (like the North American diet) also involves higher consumption of SFA, less vegetables and fruits, and more refined sugars. It is difficult, therefore, to draw any firm conclusions by studying populations by their daily eating habits.

A way to reduce this variability is to control the amount and type of foods/supplements that the study population consumes during the study.

Another issue with epidemiological studies is that if an association is found with the frequency or progression of a certain disease, we cannot conclude that there is a cause and effect relationship since we do not have a clear indication of how this is achieved (the mechanism).

KLRI investigated the role of n-3 PUFA's in the function of cells during aging. It is known that certain changes that take place as we age are the result of loss of sensitivity of our cells to messages generated inside the body or from the environment. Such loss of cell responsiveness can contribute to the development of many age-related diseases, including diabetes, heart disease, loss of muscle mass and strength, and impaired sexual function.

To understand what we are studying, we must have a general idea of what our cells look like. We can roughly visualize our cells like a peach. In the middle there is a nucleus (like the pit), around the nucleus is the cytoplasm (like the pulp) and the whole cell is contained inside the cell membrane (like the skin of the fruit).

The cell membrane is extremely important because any message directing the cell to change its activities must be transmitted across or through the cell membrane. It turns out that complex fat molecules in the cell membrane help control the rate at which messages can be transmitted across it. The fat composition of the membrane determines (to a large extent) its physical properties. A very important property, influenced by the type of fats in the membrane, is fluidity. The higher the fluidity, the more efficient the membrane is at transmitting messages. A high content of SFA in the membrane causes a reduction in fluidity, while a high content of n-3 PUFA increases the fluidity making the cell membrane more responsive to hormones, electrical pulses, etc.

Aging has been associated with a loss of membrane fluidity, leading to reduced cell responsiveness to hormones and other factors. KLRI decided to test whether it is possible to counteract age-related loss of cell response by increasing n-3 PUFAs in the diet.

KLRI recruited 12 healthy volunteers (6 men and 6 women) over 60 years of age to participate in this study. Each volunteer had a comprehensive physical examination and blood tests to make sure that they did not have any significant health problems. Then each

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volunteer was placed on a controlled Western-type diet for six weeks. This diet was designed to provide 30% of the calories from fat, from which 30% was omega-6 PUFA, 30% MUFA and 40% SFA. In addition, they were taking one tablespoon a day of a placebo supplement (50% corn oil/50% olive oil). During the last week on this diet, the volunteers came to KLRI's Clinical Studies Center for three days of extensive clinical testing. These tests included evaluation of all major hormonal systems and blood samples to analyze the types of fatty acids in the red cell membrane. We tested the systems that control the production of reproductive hormones, growth hormone, cortisol and DHEA, the release of free fatty acids in response to stress hormones, and sensitivity to insulin. We tested insulin sensitivity by giving a substance (sandostatin) that blocks the body's own production of insulin (the hormone that controls blood sugar levels); immediately afterwards, the volunteers were given a known amount of sugar and insulin (calculated according to body size) through a vein continuously for three hours. During this period, blood samples were taken to measure the blood sugar levels. During the last hour, blood sugar levels off. By calculating the average blood sugar level, we could estimate how sensitive the body cells are to insulin; the lower the average blood sugar level, the higher the insulin sensitivity. This is an important measurement because insulin resistance is an indicator of a predisposition to the development of diabetes and, also, for the development of coronary (heart) disease.

After the tests were completed, each volunteer was switched to an eight-week high omega-3 PUFA diet. This diet was 30% of the fat which included omega-3 PUFA, 30% MUFA and 40% SFA. This was achieved by including 20 ounces per week of fatty fish and a tablespoon per day of salmon oil supplement in the diet. During the last week of the study, all tests described in the previous paragraph were repeated. The analysis of the data of the hormonal studies and the red cell membrane fatty acid composition tests were recently completed.

The major findings are as follows:

1. Eight weeks of high omega-3 diet produced a major improvement in the amount of omega-3 fatty acid in the red blood cells, with nearly twice as much omega-3 fatty acid being present in the outer lining (membrane) of red cells compared with omega-6.
2. After eight weeks on the high omega-3 diet, we found that insulin had a better effect on lowering blood sugar, suggesting that increased omega-3 consumption could reduce the risk for diabetes and heart disease.

Current scientific evidence suggests that we should:

1. Eliminate TFA's from our diet.
2. Reduce, as much as possible, the consumption of SFA's.
3. Use MUFA's as our primary source of dietary fat.
4. Reduce the consumption of omega-6 PUFA's and increase omega-3 PUFA's (eat more fish or use fish oil supplements).

These findings were presented at the Annual Meeting of the Endocrine Society in June 2004.

We are now in the process of analyzing more data from this study. We will keep our readers informed of any other new findings.

Panayiotis D. Tsitouras, MD
Clinical Director, KLRI

DIRECTOR'S MESSAGE ... *Continued from Page 2*

ultimately, mortality in the population studied. The changes would have to occur rapidly enough that we could detect differences between treated and untreated research participants within 10 (or, better yet, 5) years. There are many measures that scientists have observed to change systematically with aging in humans. However, no single measure or combination of them has been proven to be a valid predictor or index of biological aging. Hence, we have no scientifically accepted "biomarkers of aging."

Recent biomarkers of aging discussion and action group were convened by the not-for-profit Alliance for Aging Research. The Alliance invited over a dozen scientific and policy leaders to participate in a half-day planning meeting to explore the feasibility of developing valid markers of aging. This panel included experienced researchers familiar with the biology of aging, technical hurdles and opportunities in this area. The leaders also were skilled in organizing and monitoring scientific enterprises. Kronos Longevity Research Institute was among the invitees.

At the meeting, the group developed a general approach and research outline. The proposed research has the goal of developing an index of biological aging. This will facilitate the scientific study of human aging and anti-aging interventions. The steps necessary to lay the groundwork toward achieving this goal are as follows:

1. Identify candidate biomarkers through both scientific consensus building and data evaluation;
2. Assemble available data on candidate biomarkers from multiple high quality, population-based, longitudinal studies on aging;
3. Develop a valid methodology for building a biological aging index and assuring its coherence with knowledge and theory on aging (construct validity) and usefulness for forecasting adverse outcomes of aging (predictive validity);
4. Refine candidate indices by cross-validation using data from multiple cohorts; and
5. Disseminate methodological and substantive findings through organized meetings and scientific publications, so asto encourage broad-based research to reach the ultimate goal.

Past efforts to develop biomarkers of aging have failed because they have not included sufficient depth and breadth of data from studies of human aging and have not organized the necessary biological, epidemiological, and gerontological expertise to integrate available data. The proposed research would overcome these shortcomings by:

1. Employing multiple large sets of data on human aging;
2. Acquiring leadership by a biostatistician with internationally recognized expertise in complex measurement, modeling for large longitudinal data sets, and gerontology;
3. Locating the effort in a leading interdisciplinary center of research on biostatistics, public health and aging; and
4. Providing oversight from an advisory panel comprised of world-renowned scientists on aging.

This project would, if successful, be one of the most important scientific achievements of the century while providing the critical tools needed for clinical investigators to perform interventional research on human aging. KLRI will participate in this effort.

S. Mitchell Harman, MD, PhD
Director and President , KLRI

The Importance of Translational Research on Aging

Prior to being approved for widespread use by the general pubic, the effectiveness and safety of potential treatments to numerous diseases and disorders are thoroughly evaluated using translational research methods. Statistically significant results from large, randomized, placebo-controlled, double-blind trials – the current "gold standard" of research – are required before the Food and Drug Administration will approve drugs for treatment.

So it should come as no surprise that billions of dollars are pumped into the research arena annually. Research is funded through several channels – be it through grants from the government or private foundations, financial support from pharmaceutical companies or gifts from private individuals.

Why is translational research needed?
Translational research is the critical link between findings from the basic research laboratory and corresponding improvements in clinical care. Translational research focuses on taking the wealth of new data available and translating it into direct benefits for patients. These benefits may include the development of novel therapeutics, prognostics and diagnostics, all of which promote patient health.

Why is longevity research needed?
For now, anti-aging medicines may be questionable at best, but reputable research on nutrition and exercise and the effects of hormones and other supplements on aging will pay off in the long run and ultimately serve to strengthen your golden years. The following facts illustrate the reasons why we need more money spent on longevity research:

- **Americans are living longer, but not healthier.** Those over age 85 – the oldest of the old – will increase from 4 million today to nearly 19 million by 2050. This group will include more than 1 million centenarians.
- **There is a significant lack of qualified health-care providers for the elderly.** By 2030, the United States will need up to 36,000 geriatricians and will fall far short of that figure by as many as 25,000 unless effective steps are taken to train new providers.
- **Older Americans will soon account for half of all health-care expenditures.** Currently, this population accounts for 36 percent of hospital stays, 49 percent of all days of hospital care and 50 percent of all physician hours.

How can you help?

KLRI is a not-for-profit 501(c)(3) organization that conducts state-of-the-art clinical translational research on the prevention of age-related diseases and the extension of healthier human life. Your financial support ensures the continued success of our research programs.

Congress recently passed a major new tax provision that allows donors to write off up to 100 percent of their income for cash donations they make prior to the end of 2005. This limited time tax break is significant. Usually donors cannot write off more than 50 percent of their adjusted gross income in deductions for charitable gifts. Now, for the first time ever, donors are able to double their tax advantage if contributions are made before December 31, 2005.

The new measure was created to encourage people to give generously in response to recent world events as well as in support of nonprofit organizations that might experience a resulting reduction in their donation pool. Fortunately, KLRI is a qualified 501(c)(3) nonprofit and our donors are eligible for this doubling tax benefit.

Contact your tax advisor for more information on exactly how this new tax law will benefit you. For more information on how you can support KLRI, please call at (602) 778-7481.

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DIRECTOR'S FORUM

Save the Date!

The Director's Forum is an event held to communicate the latest scientific discoveries in longevity research, study status and potential studies being considered. The industry's update also will include information on government issues that may affect the progress of longevity research. The Forum is comprised of our valued friends.

The next Forum is on April 6, 2006 • To attend the Director's Forum, please call (602) 778-7499.

Who we are!

Kronos Longevity Research Institute (KLRI) is a not-for-profit, 501(c)(3) organization conducting state-of-the-art clinical translational research on the prevention of age-related diseases and the extension of healthier human life. KLRI tests new strategies to detect and prevent chronic diseases associated with aging and investigates the effects of innovative interventions to slow the aging process and improve health outcomes for older persons. In addition, KLRI helps the medical and lay communities understand important aging issues. KLRI research findings support a healthier quality of life and a robust lifestyle in our senior years.

KLRI also performs research to increase our healthy years by improving muscle strength, understanding the role of various nutritional components in our diets, and achieving a better grasp of human aging physiology.

There are many "anti-aging" remedies and recommendations on the market today. However, most lack scientific evidence, and have potential side effects. We need reputable scientific organizations to spearhead research to further our understanding of treatments developed to increase our healthy years.

Our world-renowned scientific team is comprised of experts in their fields, who are conscience driven to perform at their highest potential to ensure that all research projects are safe, carefully performed and accurately communicated. The KLRI studies performed differ from those of many narrowly focused institutions because we have a wide range of scientific expertise and our focus is on aging itself rather than a single disease.

OUR MISSION

To perform and foster clinical translational research aimed at healthier human longevity and communicate results to the professional and lay communities.

OUR GOVERNANCE

A distinguished board of directors, with a unique mix of scientists, longevity specialists, and community leaders governs KLRI. There is also a scientific advisory board of recognized international experts in medical and scientific fields, including nutrition, exercise, hormones, bone and joint diseases, cancer and heart disease.

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To contact us,

please call

(602) 778-7499

visit our website at

www.kronosinstitute.org

or write to

2222 E. Highland Ave.

Suite 220

Phoenix, AZ 85016

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Phyllis Wise, PhD
Provost and Vice President for Academic Affairs
University of Washington

Note: Individual is participating in a personal capacity and does not represent the NIH, NIA nor the Federal Government.

Kronos Longevity Research Institute

2222 East Highland Avenue
Suite 220
Phoenix, Arizona 85016

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