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REPORT

The Life Extension Foundation

At the Forefront of Longevity Research

By Dave Tuttle



The Life Extension Foundation supports groundbreaking research on therapies to extend the healthy human life span. While commercial companies fund research to develop profitable drugs, the Foundation seeks out projects that have the maximum potential to extend our lives radically, committing its research dollars in areas that would be difficult or impossible to fund with government dollars, institutional grants, or commercial financing sources.

Recent projects include studies to determine the genetic basis of why we age and what can be done to slow or reverse it. The Foundation also funds tissue and organ cryopreservation research, which one day will lead to banks of compatible tissues for transplants to treat aging and diseased patients. Another project funded by the Foundation is identifying less toxic methods of delivering chemotherapy drugs to cancer patients.

These and other areas of study are helping scientists to better understand the mechanisms of aging and disease—bringing the Life Extension Foundation closer than ever to its objective of extending the healthy human life span indefinitely.

In this article, we bring readers up to date on the latest and most promising Foundation-funded research projects.

THE PROMISE OF “LONGEVITY GENES”

One of Life Extension’s most important initiatives is determining the molecular mechanisms of aging and the retardation of aging, and understanding how longevity genes are altered by interventions that mimic the effects of caloric restriction, a method that has been shown to significantly extend life span in mammals. This is the primary research objective of BioMarker Pharmaceuticals, an organization funded almost exclusively by Life Extension.

“We are developing therapeutic interventions to extend the healthy life span,” says Dr. Zhao-Wilson, BioMarker’s CEO and lead scientist. “Longevity genes identified in yeast, worms, flies, and rodents are directly relevant to humans. BioMarker is seeking to develop products that mimic both the gene expression and life-span-extending effects of caloric restriction. Our objective is to slow and reverse aging, and to prevent the diseases of aging.

“The average American now spends the last 10 years of life in a disabled state,” adds Dr. Zhao-Wilson. “By slowing aging and preventing disease and disability, we should be able to extend the average human life span to over 100 years. We also aim to extend maximum life span in humans to 150 years or above.”



PROVEN BENEFITS OF CALORIC RESTRICTION

While BioMarker has conducted a variety of gene-expression studies of caloric restriction, two stand out as being particularly important.

BioMarker scientists discovered that caloric restriction stimulates a rapid response in gene expression and in the organism itself.¹ This study showed that when caloric restriction was initiated in 19-month-old mice, it increased the mean time to death by 42% and prolonged the mean and maximum life spans by 4.7 and 6.0 months, respectively—within only two months. Tumors as a cause of death decreased from 80% to 67%.

Another study examined caloric restriction’s benefits for the heart.² Once again, mice responded quickly to a regimen of caloric

restriction. Eight weeks of restricted food intake reproduced 19% of the gene-expression changes associated with long-term restriction. Heart remodeling and fibrosis were reduced, while contractility and energy production were enhanced. Smaller cardiomyocytes were seen in the left ventricle of the older mice, suggesting reduced age-related cell death. The improvements proved to be short lived—just eight weeks after the calorie-restricted animals went back on the control diet, fully 97% of the genes returned to their previous expression levels.

Clearly, these studies indicate that you are never too old to begin a program of caloric restriction, and that it is likely that therapies that mimic the benefits of caloric restriction will work even late in life.

GENE-EXPRESSION STUDIES

BioMarker uses a technology that can check the impact of a nutrient or drug on all 45,000 gene probe sets, representing a complete set of over 34,000 genes of the mouse genome. The company is now working to apply this technology to humans. The first goal is to develop a method to test for changes in gene expression that would enable doctors to determine the biological age of a person rather than just relying on his or her chronological age. The second goal is to study the impact of nutrition and specific nutrients on gene transcription and protein expression. This will eventually lead to the development of nutrigenomics, in which a person's genetic expression will be used to personalize care to help prevent aging and disease.

"The human body is a complicated circuit, and its pathways interact," explains Dr. Zhao-Wilson. "It is hard to believe that such a sophisticated system can be switched on and off by a single chemical compound, especially when there are several diseases present. Life Extension's funding will help us to dissect these chronic diseases at the molecular level. No one size fits all, which is why standard drugs can have differing effects on different people. We will take an approach to evaluate how genes are responding to intervention, and also look at nutrients that Foundation members can use to assist this process. This will help determine which health interventions are most appropriate, so we can live longer, healthier lives."

BioMarker investigated the benefits of Life Extension's grape extract with resveratrol and found that it protects mitochondrial function and prevents protein oxidation in vitro. Whole grape has a complex mixture of nutrients, such as resveratrol, quercetin, and proanthocyanidins—each of which has diverse biological activities. Moreover, BioMarker's in vitro and in vivo studies on rodents have shown a statistically significant overlap between the benefits of caloric restriction and the use of grape extract.

BioMarker is also looking at the benefits of a combination of ginkgo biloba, grape extract, and green tea. Scientists have already completed in vitro and in vivo animal studies on this combination, and the company is now conducting a randomized, double-blind, placebo-controlled human study, with results due later this year.

These research efforts will have a dramatic effect over time, helping reveal the true causes of aging and how to slow the aging process.

CREATING A TISSUE AND ORGAN TRANSPLANT BANK

When a person's kidney, heart, or other organ gives out, doctors try to find a replacement organ. Currently, the only available resource is an organization that acts as a broker, trying to find an organ donor who is compatible with the patient in need. Even if such donors can be found, often there are only poorly compatible organs available, and many times individuals waiting for an organ transplant die before one can be found. There are long lists of patients waiting for kidney, heart, and liver transplants. Moreover, today's limited technology dictates that even patients who receive organ transplants must take expensive anti-rejection drugs—with serious side effects—for the rest of their lives.

"With successful cryopreservation methods, complex tissues and organs could be stored on a long-term basis in banks, which would increase the time that doctors would have to get organs," notes Dean Barry, CEO of 21st Century Medicine, another California-based company funded by the Life Extension Foundation. "Transplants could become standard procedures instead of emergency surgery. There would be better matches because of greater availability, and less need for anti-rejection drugs that have side effects."

Several companies and university laboratories are working on ways to overcome the rejection problem of transplanted tissues and organs. Once scientists develop a successful technology to overcome rejection, it will become possible to transplant almost every organ and tissue in the body (including many portions of the brain) to treat age-related diseases such as atherosclerosis, maturity-onset diabetes, Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (Lou Gehrig's disease), as well as manifestations of aging such as wrinkled skin, cross-linked collagen, weakened bones, sexual dysfunction, energy depletion, and muscular debilitation.

When methods to cryopreserve complex tissues are perfected, it will become possible to store virtually every tissue in the body—whether taken from human donors, grown in the laboratory from stem cells, or combined with artificial components to form bioartificial organs. Such banks will be used to cure diseased or severely injured patients and to reverse aging in humans. These

efforts will be guided by much greater knowledge of the mechanisms of aging, as discovered by BioMarker and other laboratories.

With Life Extension funding, 21st Century Medicine now has six scientists working on an ice-free preservation technique known as vitrification, in which water in cells is replaced with cryoprotectant solutions that do not freeze but instead preserve tissue in a glass-like state, with little or no structural damage. To date, the company has vitrified human kidneys, corneas, blood vessels, ova, ovaries, brain slices, and cartilage, as well as rat hearts and testes. It has made considerable progress toward perfecting the vitrification of these organs and tissues.

21st Century Medicine's most advanced research project involves the vitrification of corneas. It has worked on several hundred corneas, transplanting them into animals after they have been preserved for months. Despite the time lag, these corneas have had outstanding clarity, thickness, and endothelial function. The company is now ready to begin transplanting vitrified corneas into humans in emergency situations. The vitrified cornea will act as a "patch" to save the sight of an eye, if a standard cornea transplant is not available. 21st Century Medicine is now establishing relationships with several teaching universities to launch this project.

LEADING THE LIFE EXTENSION FOUNDATION: JAMES L. CUNDIFF



The Life Extension Foundation is a 501(c)(3) nonprofit organization whose long-range goal is radical extension of the healthy human life span.

James L. Cundiff serves as the Foundation's chief development officer. In his more than 20 years of experience working for nonprofits, Cundiff has held senior positions in local and national organizations, where he has used his expertise in nonprofit management and fund raising for public and private ventures. Additionally, Cundiff has coauthored training manuals on nonprofit management and fund raising, and has served as a public speaker and national trainer.

James Cundiff provides new vision and leadership necessary to help Life Extension achieve its strategic objectives.

For information about how your tax-deductible contributions can help further Life Extension's research programs, please contact James Cundiff at jcundiff@lef.org or 954-202-7676.

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SPEEDING DRUG DEVELOPMENT TO EXTEND LIFE

Life Extension is also funding research into the cryopreservation of animal tissue to permit faster drug discovery and development. Drug companies always conduct tissue tests to determine the effects of drugs before they begin animal testing. Currently, companies have to kill a new research animal every day to get fresh tissue for these experiments. Soon, they will be able to use vitrified tissues instead. This will reduce the use of research animals while increasing the supply of available animal tissue, so that more drugs can be screened faster. 21st Century Medicine is in co-development projects with several pharmaceutical companies to offer slices of kidneys, brains, and livers for drug development.

“This research is directly related to life extension,” says 21st Century Medicine’s Barry. “I can’t thank Life Extension enough for funding these efforts. It would have been difficult—if not impossible—to pursue these research goals without them. The transplant market is not big enough monetarily to attract investors into cryopreservation research. Since Life Extension cares about longevity—not profits—they are willing to assist us. Only a foundation with the vision to see how this research will extend life would step forward and fund us.”

REVIVING DISEASE AND ACCIDENT VICTIMS

The Life Extension Foundation has also funded studies of resuscitation, helping to develop procedures that will allow for the revival of traumatized, near-death victims of disease or accidents.

“There has been little support from traditional sources for this research,” says Dr. Steve Harris, director of research for Critical Care Research, also based in California. “Most people don’t think they will ever need it, and when they do, they are unconscious. Much brain damage could be stopped if these procedures were used to a greater extent.”

Two series of experiments highlight the company’s research focus. In one, scientists cooled dogs using a perfluorocarbon solution. Because this fluid is capable of conducting both heat and cold, as well as carrying oxygen and removing carbon dioxide, it can be used to fill an anesthetized dog’s lungs, cooling the animal by a half-degree Celsius per minute. This experiment demonstrated that the animals could be cooled more rapidly than ever before, without the use of cardiopulmonary bypass, and without the animals experiencing pain. Because cold slows down the degeneration process, it offers hope that humans can one day be maintained in hypothermic stasis until the body can be delivered to a medical facility staffed to save the individual.

In another line of experimentation, scientists were able to revive dogs that had been in cardiac arrest with no blood pressure for more than 14 minutes. The dogs—which were given a drug cocktail including heparin to prevent brain damage—were resuscitated by a defibrillator, and then put on a ventilator. It took up to 60 minutes for them to start breathing on their own. The dogs survived the ordeal with no apparent harm, despite the fact that they were in cardiac arrest so long that most conventional doctors would have considered resuscitation to be impossible.



“All of these studies were financed entirely by the Life Extension Foundation,” says Dr. Harris. “We are very grateful for the funding, which a drug company would never have even considered doing. Life Extension supports cutting-edge research that needs to be done, but that no one else is doing.”

MAKING CHEMOTHERAPY LESS TOXIC

The Life Extension Foundation also funds more traditional research that could lead to less harmful ways to treat cancer.

A Phase I study was recently completed, comparing various dosages of two chemotherapy drugs that are often administered together. This study showed that the best compromise between response and toxicity occurred when 2000 mg of gemcitabine (Gemzar®) per square meter of body mass (m²) was alternated on a weekly basis with 50 mg/m² of docetaxel (Taxotere®). A

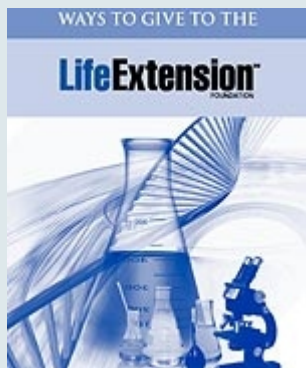
Phase II follow-up study on the effects of these two drugs on women with Stage IV breast cancer was recently begun at the Cancer Treatment Center of Oklahoma in Oklahoma City. Under the direction of lead investigator D. Richard Ishmael, MD, this study will alternate the two drugs on a weekly basis for six weeks, with a one-week break. The regimen will then be repeated every eight weeks until the study's conclusion.

"We started the study in February 2007," notes Orn Adalsteinsson, PhD, president and CEO of the International Cancer Alliance, who is coordinating the study's implementation. "Depending on how quickly we can sign up 25 people who meet the rigorous qualification criteria, we expect to be completed in a year to a year and a half. The researchers hope to reduce the side effects of the gemcitabine and docetaxel combination, while maintaining and hopefully maximizing the efficacy of the drugs. The findings of the Phase I study were very positive, and we expect that the Phase II study will confirm these findings. We are grateful for the assistance of the Life Extension Foundation, which is totally funding this study."

STAYING ON THE CUTTING EDGE

The Life Extension Foundation seeks out research projects that will help to make a difference in optimizing health and extending life span. Rather than funding "copycat" studies that break no new ground, the Foundation explores the frontiers of scientific research. Whether it is determining how caloric restriction enhances longevity at the genetic level, or helping ensure that organ transplants will be available on demand, the Foundation follows an independent path, leading the way in innovative research. Behind these efforts is a fundamental goal: to push the limits of research in a way that will one day make radical life extension a reality.

SUPPORTING LIFE EXTENSION RESEARCH



A gift to the nonprofit Life Extension Foundation is an investment in your future—one that promises to be long, healthy, and disease-free. Your tax-deductible contribution supports scientific and medical research by the world's leading experts in preventing or treating degenerative disease, aging, and death. Today, your contributions are at work funding the following innovative research initiatives:

- Caloric-restriction studies
- Gene-expression studies
- Creation of a tissue and organ bank
- Speeding the process of drug development
- Reviving victims of accidents and disease

- Developing less toxic chemotherapy methods.

There are many ways you can support the Life Extension Foundation's mission to extend the healthy human life span. You may make charitable contributions through a variety of means, including:

- Cash contributions
- Gifts of securities and real estate
- Donating tangible personal property
- Charitable remainder trusts
- Gift annuities
- Life insurance.

For more information on how your contribution can help fund longevity research, please request our free booklet, "Ways to Give," by calling Life Extension at 1-800-544-4440. Free to members, the booklet reviews the benefits of various forms of charitable giving (Product code: WAYSTOGIVE).

References

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2. Dhahbi JM, Tsuchiya T, Kim HJ, Mote PL, Spindler SR. Gene expression and physiologic responses of the heart to the initiation and withdrawal of caloric restriction. *J Gerontol A Biol Sci Med Sci*. 2006 Mar;61(3):218-31.

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