

LE Magazine November 1998

## REPORT

Continued from A Dynamic Partnership in The Fight Against Aging

Dr. Minoru Sugawara, of the Agene Research Institute Company, in Kamakura, Japan, held out that the "wrn" mutation-which causes Werner's syndrome, a disease characterized by rapid premature human aging-is a single-gene mutation that overlaps aging.

Michael Rose, a University of California, Irvine, professor, who also consults with private industry, submitted that energy metabolism is a common theme and an example of what could be universal. Kenyon countered that mice live for only two years, but that animals with much higher rates of energy metabolism can live much longer (for example, bats can live 15 years and canaries 13 years).

Huber Werner, with the National Institute on Aging, suggested that mitochondrial aging could be important, and that birds make fewer superoxide radicals per oxygen used than rodents. Werner's comments were rebutted by Vijg, who noted that there are so many mitochondria that the loss of a few mutated mitochondria may not be important, and that the mitochondrial mutation rate is not different from the nuclear DNA mutation rate in several cases. Werner drew attention to an NIA request for proposals on genes and gene regions that are candidates for aging modulators.

Vijg explained his system for screening rodent DNA for background mutations that might underlie the aging process. His results showed that the number of mutations present in the DNA at any given time was constant between the time of sexual maturation and the time rodents die, about 35 months.

Therefore, mutations do not accumulate during the time that aging takes place, making mutations an unlikely cause of aging. The hypothesis that the exponentially rising incidence of cancer might be due to an exponentially rising number of mutations was also contradicted by these results. Clearly, something else is controlling cancer incidence besides mutations or even DNA repair. In any case, Vijg is now shifting his attention to changes in gene expression that lead to aging.

Another compelling avenue of aging research is the telomere theory of aging. As detailed extensively in *Life Extension*, telomeres are regions of DNA at the end of each chromosome that are thought to shorten each time a cell divides. Michael West, at the time of the meeting vice president for new technologies for Geron Corp., of Menlo Park, Calif., explained Geron's hypothesis: That telomere shortening is the clock of cell aging, which leads to several types of product possibilities. One of these is the use of naturally immortal primordial stem cells to rejuvenate other cells. Another possibility is to find a way to inhibit telomerase-the enzyme that maintains telomere length in cancer cells-as a universal anti-cancer target, to prevent cancer cells from being immortal. In support of this concept, the death or cure of neuroblastoma patients is predictable based on their cancers' telomerase activity, and 85 to 90 percent of malignancies studied have turned-on telomerase activity. Collected urine can be checked for telomerase activity to detect bladder cancer.

A therapeutic use of telomere biology could entail removing cells from a patient, recharging them with telomerase, and putting them back to replace old, dividing cell types.

West noted that prolonging the lives of cells used for making biotechnological pharmaceuticals would be another therapeutic use of telomere biology. Further, cells could be removed from a patient, recharged with telomerase, and put back in the body to replace old, dividing cell types. This would be easy to do with bone marrow cells. Similarly, reversing senescent gene expression by restoring telomere length should reduce wrinkling, fragility, and other age-related changes in skin.

West also spoke of using known, naturally immortal primordial stem cells that, when injected into muscle, spontaneously give rise to blood cells, neurons, various kinds of muscle cells, hair follicles, intestinal cells, teeth, and other complex tissues. He said there is no other known technology for making complex tissues, and that this could be an inexhaustible resource for making cells and tissues for transplantation. West's new company, Origen, will develop primordial stem cells to make therapeutics.

West said the dream is to manipulate the human genome as we wish. This stem cell technology opens the door to that because if

we can put genes into specified areas of the genome and overcome cell senescence, we can do gene targeting without limit and make any kind of cells we want. Therefore, this is a technology platform for very open-ended gene therapy and gene augmentation. West also contemplated transgenic cell-based screening, using a product he called Lifescreen. In this assay, cells of various kinds are put onto a biochip.

## Targeting a Killer

While much of the IBC conference discussions concerned the search for the genetic sources of aging, one of the primary illnesses of aging, Alzheimer's disease, was not neglected. Aileen Anderson, of the University of California, Irvine, noted that Alzheimer's disease is the fourth leading cause of death in the elderly, affecting 47 percent of individuals over the age of 85. One possible cause of Alzheimer's disease has been identified as a buildup of beta amyloid peptides in effected parts of the brain. These peptides have been shown to kill neurons in culture, as occurs in the late stages of the disease.

Anderson noted that the mechanism of death is via apoptosis, that is, a cell suicide cascade triggered by the aggregated beta amyloid protein.

Using a type of staining procedure that identifies cells that are committing suicide by apoptosis in the whole brain, she found tremendous staining in the entorhinal cortex, but not in the cerebellum, of postmortem Alzheimer's brains. This agrees with the pattern of injury expected in Alzheimer's disease. The staining did not follow all aspects of Alzheimer's pathology, however, such as the location of the paired helical filaments of neurofibrillary tangles, and was not related to DNA damage. The staining was accurate after postmortem without fixation up to at least 12 1/2 hours, but depended on the time the brains were held in a preserving formaldehyde solution.

Anderson pointed to a study (*Neurology* 48: 626-632) showing that the risk of contracting Alzheimer's disease is reduced by non-steroidal anti-inflammatory drugs taken for at least two years, and concluded that a promising intervention could be the blockade of apoptosis. The antioxidant vitamin E has been shown to reduce Alzheimer's pathology, but Anderson believes that free radicals are not the cause of Alzheimer's disease.

Despite the exciting discoveries made by Geron and research scientists associated with the company's efforts, not all scientists agree with the telomere theory of aging. Cynthia Kenyon, for one, challenged West's statement that telomere shortening is the clock of cell aging. She noted that while her worms age, all of the cells in the worm are non-dividing cells. Since telomeres shorten only when cells divide, Kenyon argued that telomere shortening doesn't appear to be a factor in aging *C. elegans* worms.

Similarly, she noted, mice grow old and die while still having long telomeres, and when telomerase is removed from mice, they live just fine for six generations despite the resulting telomere shortening. She also said that low levels of telomerase are, indeed, found in human tissues and that you need very little to maintain telomere length. She was concerned that lengthening telomeres to help aging cells would interfere with anti-cancer therapy.

West agreed that not all aging is cell aging (replicative senescence). But immunosenescence, age-related macular degeneration, and other human aging processes appear to be related to cell senescence. Telomere shortening is probably not germane to Kenyon's worms, but is germane to aging in yeast. As for mice, these animals do not get heart disease and other conditions that are characteristic of human aging and thus may not die or age for the same reasons that humans do. Further, mice have very long telomeres compared with humans, and so can get by better without telomerase. Mouse cells are easy to immortalize, whereas human and bird cells are classically hard to immortalize.

Walter Funk, also from Geron, noted that many changes in gene expression have been documented as cells approach the "Hayflick limit"-the replicative senescence point during reproduction in tissue culture dishes in the lab-but the relevance of these findings to aging in the whole body needs to be better established.

Funk reported it is possible to restore telomerase activity to human cells, and implied that he would be using such rejuvenated cells in his future experiments to show that cell rejuvenation can allow old cells to give rise to young (and, by implication, natural) human skin.

Funk concurred with Francis Bacon, who noted several hundred years ago, "The lengthening of the thread of life itself" has not received enough attention.

These statements have not been evaluated by the FDA. These products are not intended to diagnose, treat, cure or prevent any disease. The information provided on this site is for informational purposes only and is not intended as a substitute for advice from your physician or other health care professional or any information contained on or in any product label or packaging. You should not use the information on this site for diagnosis or treatment of any health problem or for prescription of any medication or other treatment. You should consult with a healthcare professional before starting any diet, exercise or supplementation program, before taking any medication, or if you have or suspect you might have a health problem. You should not stop taking any medication without first consulting your physician.