The role of telomerase in allowing the immortal growth of reproductive cells is well established in the scientific literature.

In the laboratory dish, the introduction of telomerase into cultured human cells transforms otherwise aging mortal cells into immortal cells without transforming them into cancer cells. On the heels of this discovery, small molecule activators of telomerase are being developed for use in treating cellular aging and at least one nutritional supplement is being marketed for the treatment of aging.

Do these compounds really work and are they safe? That is the question that was posed to two leaders in the field.

Arguing in favor of the marketing of telomerase activators for nutritional use is William H. Andrews, PhD, president & CEO, Sierra Sciences, who previously was director of molecular biology at Geron Corporation where the telomerase genes were first isolated.

Taking the opposing position is Michael D. West, PhD, who was the founder of Geron Corporation, and is currently the CEO of BioTime, Inc, which focuses on the stem cell biology and the resetting of cell life span by cellular reprogramming.

Until more human data are compiled, the Life Extension Foundation does not have a position, one way or another, on the use of this particular telomere-extending therapy. The information for this article is written by two highly respected scientists. Some members may find this material technically challenging to comprehend.

DR. ANDREWS WRITES IN FAVOR OF …

There is now compelling evidence that the length of a person’s life span is dictated by the limited number of times a human cell can divide. Though the immortal reproductive cell can divide a limitless number of times, once the human reproductive cell, in the developing embryo, turns into a developmental cell the clock starts ticking and the cell’s fate is doomed to a limited 75-100 number of cell divisions (the Hayflick Limit). Once that limit has been reached, the cell and all of its progeny completely lose the ability to divide and then enter a phase called senescence.

The ticking clock in this case is found at the tips of the cell’s chromosomes in a region called the telomere. It is believed that telomeres may have evolved to prevent the unlimited growth of cells by limiting their life span. Telomeres are made up of subunits (or bases) of DNA called A, C, G, and T. In the telomere, these bases are arranged in six base repeat units of TTAGGG. When a human is first conceived, the length of the telomeres averages about 15,000 bases (up to 2,500 TTAGGG repeat units) as measured by a process called terminal restriction fragment length analysis. The length then begins to decrease at a rate of about 100 bases per cell division. By the time a person is born, the average telomere length has already dwindled to about 10,000 bases and then throughout the rest of a person’s lifetime the average length of the telomeres gradually decreases to about 5,000 bases at which time the person’s cells lose the ability to divide. These cells are then senescent, and the person suffers and dies of old age.
About 85-95% of all cancers express telomerase activity. Many research labs are working very hard to develop inhibitors of telomerase activity to cure cancer. So, one might think that we must be out of our minds to now want to intentionally turn telomerase activity on. But, the data show that telomerase is, in fact, not the cause of cancer. Instead, cancers turn on telomerase expression only to extend their life span; just like we want to turn on telomerase expression in our non-cancer cells to extend their life span. So, we’ve learned a lesson from cancer cells on how to extend cellular life span. But, true cancer cells already have telomerase activity. Giving someone a telomerase inducer isn’t going to make an immortal cancer more immortal. So, it’s not actually the true cancers we are concerned about. The cancers that are really at issue here are the pre-immortal cancers; that is, the cells that have lost growth control but that don’t express telomerase activity or some other immortal pathway (such as the ALT [alternative lengthening of telomeres] pathway).

Fortunately, TA-65 is a transient inducer of telomerase activity. Cessation of taking TA-65 will shut down the expression of telomerase activity in cells, including the pre-immortal cancer cells, thus providing opportunities to still treat the pre-immortal cancer cells. Though, on one hand, the risk of cancer has still been elevated because of the extended telomere lengths, there are also strong reasons to believe that the longer telomeres have also significantly reduced the cancer risks; especially in the people suffering from later stages of aging. That is, short telomeres may actually be one of the major causes of cancer. When telomeres are short, they have a higher propensity to induce chromosome rearrangements. This can lead to aberrant expression of oncogenes and aberrant repression of tumor suppressor genes. In addition, our immune cells show decreased abilities to target and destroy cancer cells when telomeres are short. Keeping telomeres long should therefore decrease the incidence of cancer and help our immune systems to fight cancer. It’s hard to know if the “pros” outweigh the “cons” when considering the cancer issues. The lack of a good animal model that ages by telomere shortening makes these issues almost untestable. So, at this time we can only speculate.

In the meantime, people are aging, and people are dying of old age. Many cancer survivors will tell you that cancer is a fate worse than death. Many elderly people will tell you that suffering old age is a fate worse than death. There is little doubt that the potential for increased risk of cancer due to TA-65 is real. But the potential for increased risk of suffering from old age due to not taking TA-65 is more real.

DR. WEST WRITES AGAINST...

Recent advances in molecular and cell biology have allowed spectacular progress in our understanding of the molecular machinery of human aging. With this new information come insights into how that clockwork can be modified to slow or even reverse various facets of human aging. The discovery of the telomerase gene as a central regulator of replicative immortality and the “key” that winds and sets the length of telomeres (and hence cell replicative life span) in human cells has led to great optimism about the prospects of turning on the gene in the body to extend telomeres and potentially human life span.

Many scientists believe that the reason telomerase, and hence cellular immortality, is repressed in the majority of cells in the body while being left on in the reproductive cells is that this allows the human species to continue indefinitely, while repressing the unlimited growth of cells in the process of cancer formation. This conclusion is based in part on the observation that approximately 90% of human malignant tumors show the abnormal expression of telomerase compared with normal tissues.
The role of telomerase in cancer is best summarized by the car analogy. A cancer cell is like a runaway car on the freeway. Imagine a car with an accelerator stuck to the floorboard. That would be similar to the activation of oncogenes that drive cancer cells to divide rapidly even when inappropriate. Now imagine a car that in addition to the aforementioned mechanical difficulty also has a broken brake. This is analogous to the loss of tumor suppression also seen in many human cancers. The driver of such a runaway car could at least hope that he could avoid a collision long enough to run out of gas and safely steer the car to the shoulder of the road.

However, now imagine that the car somehow acquired the capacity for an unlimited fuel supply (telomerase activation). Collision and death would then be the nearly certain outcome. In the same way, it has been demonstrated that a normal human cell can be transformed into a cancer cell by introducing oncogenes (broken accelerator), interrupting tumor suppression genes (broken brake), and then introducing human telomerase (infinite fuel supply).

The downside of nature’s anticancer program, of course, is that our skin, bone, and blood cells, as well as many others, have a deadly clock ticking away that puts an absolute limit on their capacity for renewal and repair. To overuse the car analogy, in aging we see a highway littered with cars that have run out of gas, so to speak. So the question is can we find a way to fill up the gas tank of the aging cells in our body, to reawaken telomerase just enough to rewind the clock of cellular aging without causing an undue risk of runaway cells and cancer.

The nutritional supplement TA-65 is a single naturally occurring small molecule derived from the root of the plant Astragalus. Geron discovered that this molecule was capable of reawakening telomerase expression in mortal human cells in the laboratory dish, and there is now some published evidence of its utility in human beings. However, it should be pointed out that there is still no published evidence that this molecule results in a profound extension of telomere length or cell life span. The plant and extracts of the root of the plant have apparently been consumed safely by people for many years. However, the highly purified form of the compound, the administration at doses and for the length of time of 6-12 months in what is called the Patton Protocol (www.tasciences.com/pattonprotocol.html), has no precedent in normal nutrition.

If indeed TA-65 can induce telomerase expression sufficient to extend telomere length in human cells, then the long-term expression of telomerase in the entire human body may, in my opinion, expose a person to an unsafe risk of cancer. The data suggest that the adult human body has many “runaway” cells that have activated oncogenes and inactivated tumor suppressor genes but have stalled due to being mortal (pre-malignant growths). Examples of pre-malignant tumors would be colon polyps, growing prostates, or that large, but not yet malignant mole on your back. A protocol to reset cellular aging to benefit human health in aging needs to be carefully designed to increase the probability of human longevity without exposing people to unnecessary risk of cancer by allowing all of these pre-malignant cells just long enough to take off in unbridled growth.

In mice, which live only a couple of years, the genetic up-regulation of telomerase (which turns on telomerase throughout the body) clearly leads to an elevated risk of tumors such as breast cancer. So the bottom line, the mouse model suggests that long-term global elevation of telomerase in the mouse increases, not decreases, the risk of cancer. The one-year Patton Protocol is intended to activate telomerase throughout the human body for up to a year (approximately half of a mouse life span). One could therefore reasonably conclude that given the fact that the mass of a human is over 2,400 times that of a mouse, a year of continuous telomerase activation could reasonably allow occult pre-malignant lesions in the human body to expand into larger tumors that then could mutate into overt and immortal malignancies on their own even after the drug was removed.

Since pre-malignant tumor cells have activated oncogenes and inactivated tumor suppressor genes, they are thought to be dividing faster than their normal counterparts, and therefore even a modest extension of telomeres in the whole body could be expected to give a preferential extension of cell life span to these pre-malignant cells. Therefore, in my opinion, our best available mouse data argue that there is an unreasonable risk to treat a healthy individual with telomerase-activating compounds. Some would counter that current telomerase activators are weak enough that they would not be expected to extend telomeres to the point where they would increase cancer risk. However, one would then ask why they would be useful for the treatment of aging.

The concerns I am voicing regarding the reactivation of telomerase are restricted to: 1) the long-term continuous administration of these agents, 2) the administration to the whole body, and 3) the treatment of patients who are otherwise young and healthy. It seems reasonable that for patients who are very old and/or are at high risk of death from age-related disease within five years, the Patton Protocol may be a reasonable trade-off of risk and reward. Similarly, if telomerase activators could be given for shorter periods of time, or administered to localized tissues that are a specific near-term problem for the patient, such as the use of telomerase gene therapy to reset cell life span in a non-healing geriatric skin ulcer, the trade-off might again make sense.

The good news is that modern advances in medical research are leading to unprecedented discoveries into the actual mechanisms of human aging that lead to rational strategies for intervention. Even 15 years ago, few researchers would have predicted that such technologies were even possible. Those who have an interest in using these new and unregulated therapies either in a personal program of life extension or for a loved one should carefully consider the trade-off of risks versus benefits.
Hanging in the balance is not only the life of the individual patient, but the well-being of the emerging field of interventional gerontology.

COMMENTS FROM THE MANUFACTURER OF TA-65

The “against” article is not entirely negative. Dr. West says, “It seems reasonable that for patients who are very old and/or are at high risk of death from age-related disease, the Patton Protocol may be a reasonable trade-off.” The issue boils down to the risk/reward ratio for those of us who are aging, but are not yet seriously compromised by the ravages of old age.

A study published in the September 2008 online edition of the prestigious journal Lancet Oncology shows that a healthy lifestyle increases telomerase and is beneficial in controlling the aging process. The study was conducted by Dr. Elizabeth Blackburn, the famed UCSF biochemist who discovered telomerase, and Dr. Dean Ornish, well-known author and head of the Preventive Medicine Research Institute in Sausalito, CA. This study included 30 men with low-risk prostate cancer who improved their diet, exercised moderately, and reduced stress. At the end of the study, the men had 29% higher levels of telomerase than when they began. The researchers also reported that gene expression in cells taken from the men had been modified and that the activity of disease-preventing genes increased and some disease-promoting genes including those involved in prostate and breast cancer had shut down.

We don’t hear anyone condemning Blackburn and Ornish’s findings or even suggesting that raising telomerase by an improvement in lifestyle might result in an undue cancer risk. Since TA-65’s mechanism of action is also to raise telomerase levels, why should raising telomerase by taking TA-65 be any different?

HOW TO ACCESS TA-65

The TA Sciences Center is located in Manhattan, NY. The Patton Protocol with TA-65 costs approximately $2,500 for initial tests (including extensive blood work, telomere length measurements, and seven biomarkers of aging). The first six months of the protocol is approximately $6,725. Members of the Life Extension Foundation receive a 10% discount off of these prices. TA Sciences can be contacted at:


FINAL COMMENTS FROM LIFE EXTENSION®

We live on the very frontiers of achieving a radically extended life span. The molecular data presented in this article should impress anyone who understands the remarkable strides scientists are making in understanding the fundamental mechanisms of aging. While Dr. Michael West is a board member of the Life Extension Foundation®, we as an organization don’t as of yet have a formal position or recommendation as it relates to the use of TA-65.

If you have any questions on the scientific content of this article, please call a Life Extension Health Advisor at 1-800-226-2370.

*These statements have not been evaluated by the Food and Drug Administration. These products are not intended to diagnose, treat, cure or prevent any disease.