Will TA-65 Increase the Risk of Cancer?

TA-65 is a proven telomerase activator.
Telomerase makes telomeres longer.
*There are **no** known studies linking long telomeres with cancer.*

However, there are dozens of studies that link short telomeres to higher incidence rates of cancer.

We believe the preponderance of the evidence strongly supports transient telomerase activation as not only being safe, but it is actually beneficial for overall health.

Many well respected telomere biologists (Cal Harley, Bill Andrews, Mike Fossil, etc.) and widely followed oncologists (Mark Rosenberg, Khalid Mahmud, etc.) personally use TA-65. Obviously they believe it to be both safe and effective.

TA-65 is shown to be safe based on human cell data, animal data, and data from thousands of people taking TA-65 over several years. Telomerase activation helps maintain healthy telomeres and may reduce the risk of cancer by preventing degenerative changes (e.g. aging of the immune system and multiple other tissues and organs) that contribute to cancer initiation or progression [1-3]. Other published data shows telomerase can increase longevity without increasing cancer risk in old mice [4]. Nevertheless some individuals falsely believe that telomerase could cause cancer. The following Q&A is intended to give the reader a new perspective of the potential risks of telomerase activation in general and TA-65 specifically.

Is telomerase a cancer-causing gene?

The short answer is no, telomerase is not an oncogene. Many normal cells have, or can be made to have, relatively high levels of telomerase, and these cells are not tumorigenic (reviewed in reference [1]:

- Normal human cells such as fibroblasts, endothelial cells, or retinal pigmented epithelial cells that have low or no detectable levels of telomerase can be made to have high levels of permanently active telomerase by gene transduction, i.e. inserting a highly active telomerase gene into otherwise aging normal cells. These cells are immortal, but are not tumorigenic. They show no signs of growth deregulation or any of the hallmarks of cancer cells other than cellular immortality [5,6].
- Normal stem or progenitor cells in highly proliferative compartments such as bone marrow, gut, liver, lung, and skin have relatively high, active telomerase, but they are not tumorigenic in healthy individuals.
- Embryonic stem cells which develop into all cells of the body have constitutively active telomerase, but they are not tumorigenic.
- Most cells in a developing fetus are telomerase positive, but they are not tumorigenic, even though the fetus is growing faster than most tumors.

- The male germ line tissue in testes has high constitutively active telomerase, but these cells are not tumorigenic, even though sperm telomere length actually increases with age in males. (In most other proliferative tissues there appears to be insufficient telomerase to maintain or increase telomere length with age).

Can you have cancer without any telomerase?

Yes. Some aggressive, metastatic human cancers have no detectable telomerase [7], and mice that have telomerase totally "knocked out", can still get lethal cancer [8]. You can have growth deregulated tumor cells that have relatively long telomeres and hence long cellular lifespan, and these cells may survive long enough to form lethal cancers even though they have no telomerase activity.

These observations, that telomerase does not cause cancer, and that you can get cancer without telomerase, tell us that telomerase is neither sufficient, nor necessary for cancer.

What else supports your belief that TA-65 does not pose a cancer risk?

- The Blasco group, which had previously shown that permanent active telomerase in the presence of mutagens increased the probability of tumors in mice [12] has since reported data that challenges their earlier work. Dr. Blasco recently conducted a long term study with TA-65 fed daily to aged mice that had about 50% lower telomerase than normal young mice. The dose of TA-65 was chosen to mimic dose exposures of TA-65 in humans. Comparisons of the TA-65 treated mice to the control mice without TA-65 revealed health-related benefits in numerous tissues (for example improved glucose tolerance, reduced osteoporosis and increased skin fitness) without significantly increasing global cancer incidence. [13]
- TA-65 is a natural product derived from a Traditional Chinese Medicinal plant (Astragalus, or Huang-Qi). As such, the TA-65 molecule has been used by humans for centuries, albeit at lower doses and not in the same high purity compared to TA-65, without reports of adverse effects.
- TA-65 and TA-65MD (an improved formulation of TA-65) have been taken daily over the past 7 years by thousands of humans under the supervision of physicians, with only a handful of reports of new cancer cases being reported by attending physicians and all of those except for one were believed to be pre-existing, but undiagnosed. Compared to the average American population, this would indicate a statistically significant decrease in new cancer incidence in the TA-65 population. It is possible that the TA-65 population is different from the general American population in ways other than TA-65 consumption, but the data to date show no indication that taking TA-65 is contributing to cancer.
- Laboratory studies conducted at independent academic institutions and contract research facilities showed that TA-65 did not cause cancer-like changes in normal or pre-malignant human cells in culture at doses much higher than those seen in humans taking TA-65 orally (Fauce et al., J. Immunol, 2007, and unpublished data).
- Studies conducted with human tumor cells (from breast, colon, prostate, and colorectal cancers) in immune compromised mice taking TA-65 daily show no evidence for

increase growth rates or increased size of the tumors compared to control mice without TA-65. These studies were conducted by an independent contract lab.

- A skin tumor formation study using oral or topically applied TA-65 in a UV-induced skin tumor mouse model was conducted by an academic center in a blinded fashion. No significant change in tumor frequency or size of tumors was noted in either of the TA-65 groups compared to the control groups.
- Genotoxicity studies by the standard FDA approved tests (bacterial Ames mutagenicity test, chromosomal aberrations, and the micronucleus test) conducted by an independent contract research organization were negative (no signs of genotoxic potential).

Are there other studies that support that TA-65 is safe?

A number of general toxicity studies have been conducted to date showing that TA-65 is extremely safe, and as mentioned earlier, the data in mice and humans so far indicate that TA-65 can improve markers of health.

- *Acute toxicity studies in rodents.* These studies conducted in a research setting at a California biotechnology company and a Contract Research Organization, showed that single intravenous or oral doses of TA-65 in mice and rats had no gross short-term toxicity unless the dose was extremely high (e.g. 1000-2000 mg/kg, which is about 1000-times higher than the highest recommended dose in humans.
- *Chronic (90 day) toxicity in rats*. No signs of toxicity to any of the multiple organ and tissue systems investigated were reported at low, mid or high doses of TA-65 compared to the control rats. For this chronic (90-day study), the high dose (150 mg/kg/day) was designed to be about 100 times higher than the maximum recommended human dose (100mg/day, which is about 1.5 mg/kg/day for a 70-kg person). This study was conducted under GLP by an independent contract laboratory.
- *Other safety studies completed.* A number of other standard studies were conducted to evaluate potential toxicity from topical (skin) exposure to TA-65 in various liquid, gel, or cream formulations. These included studies in animal models (guinea pig, rabbits, and pigs) as well as humans ranging in duration from single exposure to multi-month exposures. The studies were conducted at academic and contract research laboratories. No significant adverse effects were attributed to TA-65 in any of these studies.
- *Human exposure.* Since its launch in 2007 more than 20,000 people have taken TA-65 adding up to more than 25,000 person years of exposure. To our knowledge there have been no serious adverse effects attributed to TA-65 by the attending physicians.

What do the recent studies showing that senescent cells can contribute to cancer tell us about potential benefit from TA-65?

Several recent studies have shown that while cellular senescence can be a strong tumor suppressive mechanism when tumor cells first become growth deregulated, senescent cells, which accumulate with age, also have increased genomic instability, and they produce inflammatory cytokines that can cause tissue damage, contributing to degenerative conditions of aging, including cancer [14-19]. Baker et al. [20] discovered that eliminating senescent cells in aging mice delayed tissue dysfunction and extended health span. Eliminating senescent cells as

was done in this experiment is currently not possible in humans, but delaying or preventing cellular senescence with a telomerase activator like TA-65 is feasible. However the benefits of telomerase activation in relation to senescence need further investigation.

Harley et al [21,22] and Campisi [23] have proposed that telomere shortening (and other mechanisms of tumor suppression) may be examples of antagonistic pleiotropy, i.e. pathways that are beneficial early in life, but detrimental late in life. In young humans, with relatively long telomeres, telomere shortening and cellular senescence in rapidly dividing cancer cells is beneficial as a tumor suppressive mechanism. However in older individuals with low telomerase and a high frequency of short telomeres and near senescent cells, this pathway (senescence) is expected to have a net negative benefit to health. This is a reasonable supposition because evolutionary pressure to prevent cancer would seemingly only take place in younger humans. Mechanisms to control cancer in aging humans would not have been selected for because cancer occurring later in life would have occurred after the reproductive age.

In conclusion, we believe that TA-65 should have a net positive benefit to aging humans.

REFERENCES (ENDNOTE FORMAT)

1. Harley CB (2002) Telomerase is not an oncogene. Oncogene 21: 494-502.
2. Harley CB (2005) Telomerase therapeutics for degenerative diseases. Curr Mol Med 5: 205-211.
3. Harley CB, Liu W, Blasco M, Vera E, Andrews WH, et al. (2011) A natural product telomerase activator as part of a health maintenance program. Rejuvenation Res 14: 45-56.
4. Bernardes de Jesus B, Vera E, Schneeberger K, Tejera AM, Ayuso E, et al. (2012) Telomerase gene therapy in adult and old mice delays aging and increases longevity without increasing cancer. EMBO Mol Med.
5. Jiang XR, Jimenez G, Chang E, Frolkis M, Kusler B, et al. (1999) Telomerase expression in human somatic cells does not induce changes associated with a transformed phenotype. Nat Genet 21: 111-114.
6. Morales CP, Holt SE, Ouellette M, Kaur KJ, Yan Y, et al. (1999) Absence of cancer-associated changes in human fibroblasts immortalized with telomerase. Nat Genet 21: 115-118.
7. Hiyama E, Hiyama K, Ohtsu K, Yamaoka H, Ichikawa T, et al. (1997) Telomerase activity in neuroblastoma: is it a prognostic indicator of clinical behaviour? Eur J Cancer 33: 1932-1936.
8. Blasco MA (2003) Telomeres in cancer and aging: lessons from the mouse. Cancer Lett 194: 183-188.
9. Ding Z, Wu CJ, Jaskelioff M, Ivanova E, Kost-Alimova M, et al. (2012) Telomerase reactivation following telomere dysfunction yields murine prostate tumors with bone metastases. Cell 148: 896-907.
10. Rudolph KL, Millard M, Bosenberg MW, DePinho RA (2001) Telomere dysfunction and evolution of intestinal carcinoma in mice and humans. Nat Genet 28: 155-159.
11. Gonzalez-Suarez E, Flores JM, Blasco MA (2002) Cooperation between p53 mutation and high telomerase transgenic expression in spontaneous cancer development. Mol Cell Biol 22: 7291-7301.
12. Gonzalez-Suarez E, Samper E, Ramirez A, Flores JM, Martin-Caballero J, et al. (2001) Increased epidermal tumors and increased skin wound healing in transgenic mice overexpressing the catalytic subunit of telomerase, mTERT, in basal keratinocytes. EMBO J 20: 2619-2630.
13. Bernardes de Jesus B, Schneeberger K, Vera E, Tejera A, Harley CB, et al. (2011) The telomerase activator TA-65 elongates short telomeres and increases health span of adult/old mice without increasing cancer incidence. Aging Cell 10: 604-621.
14. Choi D, Whittier PS, Oshima J, Funk WD (2001) Telomerase expression prevents replicative senescence but does not fully reset mRNA expression patterns in Werner syndrome cell strains. FASEB J 15: 1014-1020.
15. Rodier F, Campisi J, Bhaumik D (2007) Two faces of p53: aging and tumor suppression. Nucleic Acids Res 35: 7475-7484.
16. Coppe JP, Patil CK, Rodier F, Sun Y, Munoz DP, et al. (2008) Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor. PLoS Biol 6: 2853-2868.

17. Rodier F, Coppe JP, Patil CK, Hoeijmakers WA, Munoz DP, et al. (2009) Persistent DNA damage signalling triggers senescence-associated inflammatory cytokine secretion. Nat Cell Biol 11: 973-979.
18. Velarde MC, Flynn JM, Day NU, Melov S, Campisi J (2012) Mitochondrial oxidative stress caused by Sod2 deficiency promotes cellular senescence and aging phenotypes in the skin. Aging (Albany NY) 4: 3-12.
19. Capparelli C, Chiavarina B, Whitaker-Menezes D, Pestell TG, Pestell RG, et al. (2012) CDK inhibitors (p16/p19/p21) induce senescence and autophagy in cancer-associated fibroblasts, "fueling" tumor growth via paracrine interactions, without an increase in neo-angiogenesis. Cell Cycle 11.
20. Baker DJ, Wijshake T, Tchkonia T, LeBrasseur NK, Childs BG, et al. (2011) Clearance of p16Ink4a-positive senescent cells delays ageing-associated disorders. Nature 479: 232-236.
21. Harley CB (1990) Aging of cultured human skin fibroblasts. Methods Mol Biol 5: 25-32.
22. Harley CB (1991) Telomere loss: mitotic clock or genetic time bomb? Mutat Res 256: 271-282.
23. Campisi J (2005) Senescent cells, tumor suppression, and organismal aging: good citizens, bad neighbors. Cell 120: 513-522.

UPDATED 9/5/2014