

HARNESSING THE NATURAL POWER OF AGING

In 1996, the world was introduced to a sheep named Dolly, a clone created by scientists in Roslin, Scotland; she was not the first clone in history, but the first to be cloned from a fully grown adult animal. Dolly was created from udder cells that had been isolated from a six year old sheep and stored in a laboratory prior to the actual cloning (1). In effect, Dolly began development with DNA that had undergone six years of mitotic replication before being degraded as a result of the culturing process; with each replication cycle, a portion of each chromosome, called a telomere, is cut off at the end and is not copied into the daughter cells – it is depleted thusly until it is gone, causing cells to become senescent and stop dividing (2). It is also important to note that it is the telomere that is typically degraded during in vitro cultures (3). Early analysis of Dolly's telomeres revealed that they were approximately 20 percent shorter than those of normal sheep, meaning that she was older genetically than she was chronologically (3). Any speculation as to whether this would affect Dolly's aging or lifespan was settled in 2003 when Dolly died of lung disease at the age of six, which is approximately half of the average sheep's lifespan. This would suggest that, since the sheep's telomerase had been subject to six years of depletion, its cells only needed another six years of division until they reached senescence and ceased their functions at a much earlier than normal – time did not kill this sheep, a shortage of telomerase did.

Three years before Dolly's death, she was purchased, along with the technique used to clone her, by the California-based biopharmaceutical company Geron, which

specializes in the development of telomerase technologies. Telomerase is the enzyme responsible for preserving telomeres during mitosis (4). It is difficult to say whether or not the company's scientists learned anything new about the enzyme from Dolly, but she had indeed captured their interest enough to further their research of the enzyme with respect to its activation; this process had recently been attributed to a catalytic protein subunit of telomerase called human Telomerase Reverse Transcriptase (hTERT) which activates the RNA template subunit of telomerase, which is called human Telomerase RNA (hTR) (5). Geron has spent the years since researching ways to create recombinant hTERT products capable of controlling telomerase expression in normal cells in the interest of treating age-related diseases; they are experimenting under the assumption that a controlled activation of the telomerase enzyme within a given cell will prevent or slow the mitotic loss of telomerase by delaying cellular senescence (6). Their search for recombinant hTR treatments has met with some success in combating malignant cellular phenotypes (7), but their endeavor to find an effective recombinant hTERT treatment has yet to bear considerable publishable fruit. It would appear that Geron has made much more progress in their telomerase activation's converse: telomerase inhibition.

The shortening of telomeres, as seen in Dolly's case, has frequently been correlated with cellular aging and senescence (4). Cells that express telomerase activity are not typically subject to this form of chromosomal degradation, and are thus theoretically capable of indefinite proliferation without senescence. Though not all tumor cells express active telomerase (8), it has been suggested that telomerase is necessary for the immortality of many, if not most, cancer cells (9); the implication of this is that inhibiting telomerase activity in these cells could potentially leave them all too mortal,

since the cancer cells' telomeres would shorten at an accelerated rate due to their rapid, uncontrolled proliferation. When scientists working for the biotech company Amgen tested this hypothesis by cloning human tumor cells with induced mutations, they made two observations: (i) that clones with shorter telomeres divide normally until they exhibit abnormal mitotic behavior and then die of apoptosis, and (ii) that clones with longer telomeres displayed a rate of shortening comparable to that of normal human cells (10). In a similar vein, Geron aims to develop a commercially marketable telomerase inhibitor drug to treat various forms of cancer, as their official website (6) advertises.

The biopharmaceutical company may be much closer to reaching its goal of developing effective inhibitors than they are to producing viable activator treatments. Orally administered telomerase inhibitors have been observed to hinder tumor growth *in vivo* in immunodeficient mice without adversely affecting the organism's normal cells (11). In other words, a telomerase-inhibiting pill may be the next viable progression in the treatment of cancer.

There are, however, major caveats to this direction of research. In more recent years, there has been an increasing concern that telomerase inhibitors may negatively affect the lifespan and mortality of normal cells because the enzyme's activity is not limited to an organism's tumor cells; though telomerase activity is rare in the normal cells of mature organisms, it can be expressed in any area of cell proliferation (12). Such cells would likely be just as vulnerable to an inhibitor drug as the tumor cells are. More research is required to determine if this does indeed pose a problem for the application of telomerase inhibitor treatments and, if so, new efforts must be taken to ensure the inhibitor's specificity for tumor cells. As the study of telomerase's role in normal cells

advances, scientists may stumble upon new information that could prove crucial in advancing the field of telomerase activator therapies. If Geron can manage these feats, they may stand to create an entirely new class of cancer treatment and harness the natural power of aging in the early part of the 21st century.

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