# Dankesrede

# von

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**Es gilt das gesprochene Wort.**

**Telomeres & Telomerase**

The story of telomerase is one of curiosity driven science; Liz Blackburn and I simply wanted to understand how chromosomes are maintained, we did not set out to study specific diseases. However, having a fundamental understanding of how cells work is the basis to understand all disease. Today we know that telomere function plays a major role in human disease.

In 1984 Dr. Blackburn, and I set out to examine how telomeres are maintained. We chose to study telomeres in Tetrahymena because a single cell contains 40,000 telomeres; so Tetrahymena was an excellent source of material. Fundamental systems in biology are conserved - what we have learned about telomeres in Tetrahymena is conserved in eukaryotes through to humans.

Telomeres are required to protect chromosome ends. During normal cell division the telomeres shorten because the ends cannot be completely copied during chromosome duplication. Telomerase is the enzyme that solves this end replication problem by balancing the sequence loss with lengthening. Telomerase adds telomere sequences onto chromosome ends. Thus telomeres in all cells are maintained by a constant balance between sequence loss and addition that establishes length equilibrium. The maintenance of this telomere length equilibrium is critical for cell viability.

In 1990, working together with Dr. Calvin Harley, we found that human cells show progressive telomere shortening as they divide. In some cases this is because cells lack telomerase while in others it is because the amount of telomerase in the cell is not enough. When telomeres become short, telomere function is lost and cells either stop dividing or die. The consequences of the loss of telomere function turns out to have a fundamental role in human disease, in cancer, and in aging.

Cancer cells express high levels of telomerase which prevents telomere shortening in these cells. To understand the consequences of telomere shortening in cancer, we generated mice that lack telomerase. These mice show progressive telomere shortening with each generation. Because cancer cells divide many times more than most normal cells, telomere shortening occurs rapidly in these cells when telomerase is absent. We and our colleagues found that blocking telomerase in this way will stop the growth of tumor cells, while having little effect on normal cells that divide less frequently. This work provides strong evidence that telomerase inhibitors may be useful in some settings as a treatment for cancer.

While the increased telomerase activity in cancer cells can allow too many cell divisions and thus tumor growth, on the other hand, not having sufficient telomerase can also be deadly. Genetic evidence from the group of Dr. Inderjeet Dokal showed that mutations in telomerase lead to the disease called dyskeratosis congenita. Patients with this disease die of bone marrow failure due to the limited cell divisions bone marrow cells can undergo due to short telomeres. Since this initial discovery of inherited telomerase mutations in disease, it is now apparent that a common lung disease is also associated short telomeres.

Dr. Mary Armanios found that the lung disease idiopathic pulmonary fibrosis is due to short telomeres. This observation, and the growing number of diseases now attributed to telomerase mutations, led Dr. Armanios to define a syndrome of telomere shortening that recognizes the underlying etiology of a loss of regenerative capacity due to short telomeres that is common amount these diseases.

Work from our lab and others indicates that it is the telomere shortening in stem cells that leads to disease. The tissue specific stem cells are required for tissue renewal. If a tissue is damaged, stem cells divide and generate replacement cells for tissue repair. Cell division in the bone marrow stem cells is required to replenish the blood cells that must be replaced each day. We developed a strain of mice to study the effects of telomere shortening and stem cell failure. In mice that have half of the normal level of telomerase, telomere length cannot be maintained. These mice share many features of the disease that patients with short telomere syndromes display. Indeed short telomeres are passed on from one mouse generation to the next, resulting in a worsening of the symptoms in the next generation. This *genetic anticipation* can also be seen in human families with telomere shortening. Each successive generation shows earlier onset and greater severity of disease. This mouse strain will be very valuable in studying the underlying mechanisms of human disorders of stem cell failure.

Remarkably with this mouse strain, we found that when short telomeres accumulate over many generations, restoring the normal level of telomerase does not immediately restore telomere length. These wildtype mice (termed wildtype*) have the same extent of disease seen in mice with only half the level telomerase. Therefore, short telomeres in these mice limit cell division capacity, even though telomerase is present. This implies that people with short telomeres may have limited cell renewal capacity even if they are not from families with inherited mutations in telomerase.

Understanding telomere dysfunction goes beyond families with inherited disorders. Many of the diseases associated with telomere shortening syndromes resemble certain age related disease, such as, immune dysfunction, bone marrow failure, pulmonary fibrosis, osteoporosis and hair graying. Studying telomere function will help us understand the mechanisms of age related diseases that occur in tissues that have to undergo continual renewal.