Cancer is a category of disease caused by myriad genetic and cellular derangements. The search for effective anticancer strategies in the 1990's lead to the discovery of a small core of common genetic defects and alterations in normal regulatory pathways that result in malignant transformation of cells. One of these requisite conditions is cellular immortalization, usually due to the upregulation of an enzyme called "telomerase". Telomerase is a ribonucleoprotein that normally acts as a reverse transcriptase to extend telomeres during embryonal development, in germ cells, and in select populations of stem cells in the body.

Eukaryotic cells must maintain telomeres, the non-coding hexanucleotide repeats at chromosome ends, in order to retain chromosomal integrity. Virtually all cancers express the telomerase enzyme as a primary defense against the progressive degradation of the chromosome ends that occurs during every round of cell replication. Thus, inhibition of telomerase presents an attractive anticancer strategy.

However, telomerase enzyme expression and activity may be linked to normal cell cycling, and telomerase may be constitutively expressed in normal stem cells and in cells with continuous cell cycling. Telomerase inhibition may therefore be associated with significant acute and chronic toxicities. Traditional preclinical murine models of cancer treatment strategies may prove inadequate or inappropriate to evaluate the positive and negative impacts of telomerase inhibition on patient health.

For this reason, we have pursued the development of a large, outbred animal cancer model, the tumor-bearing dog, for evaluation of the concept of telomerase inhibition. We have characterized the presence of telomerase activity in spontaneous canine tumors and normal tissues, and have determined that virtually the same tumor types express telomerase with the same relative frequency in both canine and human cancer patients.

In 33 solid tumors of dogs, we found that 24/26 malignant, 1/4 benign, and 0/3 normal tissues were telomerase positive. In 46 canine effusions (including bronchoalveolar lavage fluid, abdominal fluid, and thoracic effusion), 12/16 malignant and 1/30 benign samples contained telomerase activity. Overall, in canine cells, the telomerase assay in our laboratory has 86% sensitivity and 95% specificity for malignancy.

Furthermore, we have demonstrated that telomere length, on average, ranges from 9-25 kb in normal and neoplastic canine tissues. We found major differences in telomere length, as determined by terminal restriction fragment digest, between different tissues within individuals. Samples of the same tissue type from different dogs also displayed variability. Additionally, telomere length from tumors varied with respect to normal adjacent tissue.

For example, tissue from a hepatic carcinoma showed an average length of 13.7 kb (range 25 to 5.3 kb) whereas the normal adjacent hepatic tissue was 14.8 kb in length (range 22 to 9.2 kb). This supports the findings of others that malignant tissues possess similar or slightly shorter telomeres than their normal counterparts, but are much more heterogeneous in length. In normal dogs, telomere length varies by up to 33% between tissues, with those tissues containing germ cells (such as ovary) showing much more heterogeneity in telomere length (i.e., wider ranges). We found that, on average, canine telomere lengths range from 3.3 kb to approximately 20 kb, with the average falling around 8.6 kb in the tissues we sampled. Canine telomeres appear to lose approximately 100 - 200 bases per round of cell division, according to our preliminary results of primary canine fibroblasts in cell culture. The rate of loss of telomerase erosion with each round of cell replication is approximately 75 bases per population doubling, which roughly corresponds to the rate of telomere erosion with cell replication in human
This is in contrast to the situation in classical murine tumor models, because rodents have extremely long telomeres as compared to humans (150 kb) and express telomerase activity constitutively in a variety of somatic cells. We hope to characterize the impact of telomerase inhibitors tumor bearing dogs to better define the positive and negative impacts of such therapy in advance of human testing, as well as to provide a novel therapeutic avenue for companion dogs with cancer.