Preface

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Recent advances in aging and cancer research have established that most somatic human cells have a lifespan dictated by the size of their telomeres. The telomeres, specialized structures that cap and protect the ends of mammalian chromosomes, shorten at each round of cell division until they reach a threshold size, at which point they trigger senescence, a viable state of permanent quiescence. Resetting this clock can be achieved through the action of telomerase, a specialized reverse transcriptase whose function is to maintain the size of telomeres. The aberrant expression of this enzyme, whose presence is normally limited to rare cells of the blood, skin and digestive track, can cause human cells to avoid senescence and become immortal. This special issue of *Cytotechnology* on Telomere Biology is intended to give the reader an overview of recent advances in this field, with particular attention to the application of these discoveries to the treatment of cancers and degenerative diseases. Telomere shortening is a double-edge sword, as it contributes to the aging process and the progression of degenerative diseases while protecting the organism against the emergence of cancer cells. This ambivalence is a recurrent theme of this special issue of the Journal. Written by Dominique Broccoli, the first article of this special issue is an introduction to the structure, function, and replication of the mammalian telomere. Initially described as a stretch of (TTAGGG)_n ds-DNA repeats that cap the ends of chromosomes, the telomere has since been revealed as a protein–DNA structure of great complexity. In her article, Dominique Broccoli illustrates this complexity by describing its individual components, their distinct functions, and their physical interactions. This first article additionally introduces the reader to the ‘end

replication problem’ responsible for the shortening of the telomeres and the limited lifespan of telomerase-negative cells.

Telomerase is present in rare cells of renewal tissues, where it is required to sustain the continued proliferation of these tissues. In the second article of this special issue, Amanda Walne and Inderjeet Dokal describe the consequences of telomerase dysfunction in these tissues. This hereditary disease, Dyskeratosis congenita, is a multi system bone marrow failure syndrome characterized by muco-cutaneous abnormalities, which reiterate the importance of endogenous telomerase for continued proliferation. In recent years, methods have been developed to harness the regenerative capability provided by telomerase. In an article written by us, the use of exogenous telomerase to extend the lifespan of primary human cells is discussed, as well as the value and unique properties of these telomerase-immortalized cells. In the following article, Moustapha Kassem’s group extends this topic to include a discussion of the novel clinical applications made possible by the availability of telomerase-immortalized cells, in particular the development of tissue engineering and cell-based therapies to treat degenerative diseases and age-related illnesses.

While the expression of exogenous telomerase in normal cells may serve therapeutic purposes, telomerase has a darker side and plays a vital role in the development of cancers, during which it is almost always expressed aberrantly. This aberrant expression of telomerase, detected in more than 85% of malignant tumors, is among the most frequent alterations detected in cancers. In their article, Eiso and Keiko Hiyama describe the current methodologies for telomerase detection, and elaborate on the value of this unique marker

for the diagnosis and prognosis of cancers. In a related article, Carl Barrett's group discusses the transcriptional regulation of the hTERT gene, and how these regulatory mechanisms are altered to cause the aberrant expression of telomerase during cancer development. The demonstration that the enzyme is needed to sustain the growth of malignant tumors has identified telomerase as a potential new target for cancer therapy. Two distinct approaches that target telomerase for the purpose of cancer therapy are discussed in this special issue of *Cytotechnology*. The first approach, covered by Jean-Louis Mergny's group, uses inhibitors to block the enzymatic activity of telomerase and/or its interactions with native telomeres. The second approach, covered by Kunal Patel and Robert Vonderheide, exploits telomerase as a tumor-associated antigen for cancer immunotherapy.

Most of our knowledge pertaining to the effects of individual genetic lesions on cancer development has been inferred from *in vitro* studies performed in rodent cells. Until recently, the spectacular resistance of human cells to oncogenic

transformation had prevented their use as model systems to study cancer development. But, the recent cloning of the catalytic subunit of human telomerase (hTERT) and the realization that this subunit is required for the transformation of human cells has removed this unique obstacle. In an article co-authored by Jesse Boehm and William Hahn, the use of hTERT-immortalized human cells as experimental models to study cancer is extensively discussed.

I wish to thank wholeheartedly all the authors who contributed manuscripts to this special issue of the Journal for the high quality of their contributions and/or their willingness to consider my many suggestions. I thank Dr Otto-Wilhelm Merten, Editor-in-Chief of *Cytotechnology*, for allowing me to edit this special issue of the Journal and for his encouragement. I, like all investigators in this exciting field, hope that the better understanding of the biology of telomeres will result in the development of improved technologies for the diagnosis of cancers, cancer therapy, and the treatment of degenerative diseases.