



Public Lecture by Dr. Maurizio Zanetti
Aging and Advances in Cancer Vaccine Development
Wednesday, May 21, 2003 at 6:00 p.m. Garren Auditorium, Basic Science Building
Sponsored by the Sam & Rose Stein Institute for Research on Aging, UCSD

Summary of topics that will be covered:

The genetic determination of life-span should be equated with the action of a genetic program but such a program, from birth to death, is not by evolutionary theory. In contrast aging is a stochastic process, genetically determined only in the sense that the genetic constitution determines its course. Because it encompasses stereotypical biochemical responses to particular cellular states, aging may superficially appear to be programmed. In reality no genetic instructions are required to age animals, just as no instructions on how to age inanimate machines are included in their blueprints.

Normal cells have limited proliferative potential in culture, a fact that has been the basis of their use as a model for replicative senescence for many years. Telomeres, the repeated sequences found at the end of chromosomes inside the nucleus of all cells shorten in many normal human cells with increased cell divisions. Statistically, older people have shorter telomeres in their skin and blood cells than do younger people. Experiments have shown that telomere length plays a role in determining cellular life span in human cells. Increasing the number of times a cell can divide, however, may predispose to tumor formation.

The biological clock inside a cell is disregulated during the process of tumor transformation, which invariably begins with short telomere shortening. To compensate for this phenomenon the cell activates an enzyme called telomerase that promotes elongation of telomeres. In fact telomerase activity has been documented in the vast majority of tumor cells of different origin in humans. For this reason a constituent of telomerase which, as seen, is over expressed in tumor cells serves as beacon for specialized cells of the immune system called killer T cells.

Based on this reasoning we have spent the past four years studying the interaction between the immune system, and its killer T cells, and telomerase. We have gathered convincing evidence that normal individuals as well as patients with cancer have retained the ability to recognize telomerase, including telomerase-expressing tumor cells. We have also been able to incite the

reactivity of lymphocytes present in the blood against telomerase in the majority of individuals tested. These lymphocytes educated to recognize telomerase also recognize telomerase-expressing tumor cells.

Telomerase is unique among the various types of cancers in humans. Therefore, we have suggested that it can serve as substrate for vaccination against cancer, not just one type of cancer but in principle all types of cancer. Efforts in this direction have already begun. We have designed a strategy of vaccination based on telomerase as the target on tumor cells, which will be discussed and exemplified in the final part of the lecture. Finally, we will briefly discuss the current efforts to bring to the bedside this new type of treatment for patients with cancer.

In conclusion, the lecture will illustrate how in less than fifteen years the study of the molecular mechanisms that control cell senescence has spontaneously merged into studies on the causes of tumor transformation, and from there to the possibility to vaccinate against cancer through a new generalized approach.