Curriculum Vitae

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Education/Training:

M.D. 1986. University of Occupational and Environmental Health, Japan.

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Positions and Employment:

07/1986-06/1987 Clinical Staff, Department of Obstetrics and Gynecology, Osaka University,
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Recent advances in telomerase-based medicine for targeting cancers

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Telomerase activation is a critical part of multistep carcinogenesis. A thorough understanding of telomerase regulation may provide a molecular basis of cancer progression as well as technologies to manipulate telomerase activity as potential therapeutic modalities. Several strategies have been proposed to inhibit telomerase activity in cells, including antisense DNAs or ribozymes against *hTERT*. Introduction of a dominant negative form of hTERT are the powerful approaches to directly inhibit telomerase. As a novel technology to target *hTERT*, we developed siRNA-based hTERT inhibition in cancer cells. By retroviral introduction of siRNA against *hTERT* into HeLa cells, we successfully isolated clones that lack hTERT expression, of which molecular characteristics will be presented and discussed. For more practical application to clinical medicine, these clones were allowed to investigate the cooperative actions of hTERT inhibitors with radiation or anti-cancer drugs. Recent progress in our understanding of the controlling mechanisms of *hTERT* has prompted the use of the hTERT promoter for vectors for cancer gene therapy. This strategy is based on the expectation that the *hTERT* promoter can confer strong tumor-specific transgene expression, minimizing toxicity to normal cells. As a novel cancer-specific vectors, we developed hTERT-specific replication-competent adenoviruses (TRAD), in which hTERT promoter drives expression of E1A and E1B genes linked with an internal ribosome entry site. TRAD induced selective E1A and E1B expression only in cancer cells but not in normal cells and exhibited marked cell killing in a panal of cancer cell lines. In *nu/nu* mice carrying s.c. human lung tumor xenografts, intratumoral injection of TRAD resulted in a significant inhibition of tumor growth. No evidence of TRAD was identified in normal tissues outside of the tumors, despite the presence of TRAD in the circulation. Notably, TRAD replication in the distant, non-injected tumors was demonstrated, suggesting the possible efficacy to metastatic foci.