Telomerase-Based Therapies Emerging Slowly

By Vicki Brower

Scientists are targeting telomerase in various ways to kill cancer cells.

Most recently, a team led by John Nemunaitis, M.D., at Mary Crowley Medical Research Center in Dallas, used an adenosivirus carrying a telomerase-targeted drug to search out and destroy malignant cells. The phase I study included 16 patients who received injections of the adenosivirus with the drug telomelysin, or OBP-301. Eleven had partial responses.

The trial, reported in February in *Molecular Therapy*, is one of the latest attempts to target the enzyme that maintains the tips of chromosomes, or telomeres, regions of repeated DNA that keep chromosomes from deteriorating.

Telomerase drew attention recently when its discoverers, Elizabeth Blackburn, Ph.D., of the University of California, San Francisco; Carol Greider, Ph.D., of Johns Hopkins in Baltimore; and Jack Szostak, Ph.D., of Harvard University in Cambridge, Mass., won the 2009 Nobel Prize in Physiology or Medicine. Since their discoveries in the early 1980s, telomerase has been considered a potential drug target because it is present at high levels in nearly all cancers but generally in small quantities in normal cells. It is active in embryonic development, present to a lesser degree in stem cells, and reactivated in carcinogenesis. When normal cells divide, telomeres shorten; when they reach a very short length, cell division stops and the cell enters senescence. Telomerase added to normal cells restores telomere length and extends cell lifespan. When it is reactivated in cancerous ones, it enables them to divide indefinitely. In many animal studies, inhibiting telomerase activity shortens telomeres and causes cancer cell death.

Greider and Blackburn continue to lead basic telomerase research, but three decades of work in the field has produced few drug candidates. “Many questions remain about how telomeres and telomerase function and how telomerase should be used in the clinic,” said Jerry Shay, Ph.D., at University of Texas Southwestern Medical School in Dallas. The number of candidates has actually fallen since 2001, according to Pharmaprojects. And new research is showing that telomerase may play roles in normal physiology, raising questions about safety. Today, only one telomerase-targeting drug and a few immunotherapy vaccines are in clinical development.

Commercially, Geron Corp., in Menlo Park, Calif., dominates the landscape, having made early, substantial investments in telomerase research and amassing a broad and deep patent position. But Geron and other companies have had trouble finding a compound that robustly and specifically targets telomerase. “Several major pharmaceutical companies screened millions of compounds, and none were specific for telomerase that were not toxic at dosages that could be used clinically,” Shay said.

Inhibiting Telomerase

Strategies for telomerase inhibition entail targeting one of three major components necessary for telomerase activity and telomere lengthening. One is the telomerase reverse transcriptase protein, or hTERT, which is the component that telomelysin targets. That drug’s developer, Oncolyx Biopharma of Tokyo, will begin a phase II study shortly in liver cancer, said company director Toshiyoshi Fujiwara, M.D., Ph.D.

Another target is the RNA component that acts as a template for TERT. This is the strategy that Geron favors in its current oligonucleotide-based therapy. Geron’s drug, GRN163L, or imetelstat, is a short-chain lipidated oligonucleotide that binds to the catalytic site of telomerase; it is now in six early-stage trials. The company completed four phase I and phase I/II studies in 2009 and plans to begin four randomized, phase II trials during the second quarter of 2010 in breast and lung cancers, myeloma, and chronic leukemia, all of which are driven in part by cancer stem cells, CEO Tom Okarma said. GRN163L is also in phase II in acute myelogenous leukemia (AML). An upcoming trial will test GRN136L with paclitaxel and bevacizumab in breast cancer.

Geron is casting a wide net by targeting cancers with unmet needs and those for which stem cells play a role in carcinogenesis and relapse, said Okarma. The rationale for targeting cancer stem cells is to reduce recurrence in cancers in which cancer stem cells are known players, he said. Recent preclinical data, discussed at the American Association for Cancer Research Special Conference on the Role of Telomeres and Telomerase in Cancer Research in Fort Worth, at the end of
February, suggested that imetelstat had anti-cancer stem cell activity in a range of models.

Other recent preclinical research by Shay suggests that imetelstat crosses the blood–brain barrier and inhibits telomerase in human glioblastoma cells, including glioblastoma cancer stem cells. Others have shown that glioblastomas contain cancer stem cells that resist many treatments and may be responsible for recurrence. Telomere length and telomerase activity were reduced in Shay’s study, which appeared in January in *Clinical Cancer Research*, leading to cell death. Temozolomide and radiation boosted the drug’s effects.

A third way to inhibit telomerase is to target associated proteins, such as TRF1, the subject of a new study by Ming Lei, Ph.D., of the University of Michigan (online Feb. 15, 2010, in *Developmental Cell*). Lei found that the amount of TRF1 in a cell correlates with telomere length, and Lei is now investigating small peptides to block TRF1.

**Immunotherapy Vaccines**

Other strategies that involve telomerase use therapeutic vaccines. Of these, GV-1001 is the most advanced and the first to enter randomized trials. Cancer Research UK is testing it in a projected 1,100 pancreatic cancer patients who are receiving gemcitabine and capecitabine and then sequential or concurrent granulocyte–macrophage colony-stimulating factor with GV-1001. Developed by Gustav Gaudernack, Ph.D., professor and head of immunotherapy at Norway’s Oslo University Hospital, the vaccine is an hTERT peptide fragment that targets the active site of telomerase and elicits helper T-cell and cytotoxic T-cell responses.

To date, these “TeloVac” trials have enrolled 629 patients of a projected 1,100. GV-1001 has previously been tested in more than 230 patients in nine phase I/II trials in different cancer types alone or in combination with chemotherapy, with a 50%–80% response rate, said Gaudernack. A new study in chronic lymphocytic leukemia will begin in March at the Karolinska Hospital in Stockholm. South Korean Kael GemVax is now developing GV-1001.

Geron’s autologous vaccine, GRNVAC1, uses dendritic cells transfected ex vivo with the whole coding sequence of hTERT RNA and is administered intradermally. The technology is licensed from Duke University. Interim phase II data with 20 AML patients announced in December 2009 at the American Society of Hematology meeting showed safety and tolerability. Several high-risk patients who have been in clinical and molecular remission from 4 months to 2 years have entered the extended boost phase of the regimen, and analyses of minimal residual disease showed that the 14 in complete remission are negative for AWT1, a tumor gene associated with AML proliferation.

Its second vaccine, GRNVAC2, is an allogenic dendritic cell product produced from embryonic stem cells. Merck is also developing a nondendritic cell vaccine with technology licensed from Geron.

Rather than using dominant hTERT peptides, which are abundant on the cell surface and exhibit high human leukocyte antigen (HLA) 1 activity, Vaxon Biotech of Paris uses two cryptic peptides that have low HLA-1 affinity, are nonimmunogenic, and generate stronger immune responses. Its vaccine, VX-001, received orphan drug status from the U.S. Food and Drug Administration in February for non–small-cell lung cancer (NSCLC) in HLA-A-positive patients. It had been granted orphan drug status in Europe in 2007.

VX-001 completed a phase I/II study in 33 patients with NSCLC, and the trial was extended to 83 others with breast, prostate, and pancreatic cancers. It was safe and well tolerated and produced an immune response in 70% of patients. The response, with boosts, continued for 4 years. One patient in the extension had a complete response, three had partial responses, and 33 had disease stabilization for more than 6 months.

Clinical outcome correlated with immune response. In the initial cohort, survival was 18.8 months versus 10 months in matched control subjects, which correlated with early immune response. Vaxon will begin a pivotal phase III trial in locally advanced and metastatic NSCLC by mid-2010.

Robert Vonderheide, M.D., D.Phil., and Susan Domchek, M.D., both at the University of Pennsylvania School of Medicine in Philadelphia, are testing a full-length hTERT peptide vaccine, now in a phase I trial in solid tumors. Vonderheide said that the goal is to use telomerase as a universal tumor antigen and circumvent characteristic problems with cancer vaccines, namely, antigens that are too restricted in expression and irrelevant to oncogenesis. To address immunosuppression in cancer patients, Vonderheide administers a monoclonal antibody against CD25, daclizumab, before the vaccine, to mobilize CD4 and CD8 cells and maximize immune response.

“Our long-term goal in the next 5–10 years is to use this vaccine for prevention in women at high risk for breast cancer,” Vonderheide said.

Vonderheide notes that caution is necessary inhibiting even low levels of telomerase in normal and progenitor cells, according to new research. “We are seeing that telomeres play a more important role in normal physiology than initially appreciated,” said Vonderheide. “That telomerase may play roles other than in cancer and aging, such as in the Wnt signaling pathway and in RNA processing, reminds us to be vigilant about side effects.” Although new, important information must be factored in when considering telomerase-based therapies, no data to suggest stopping trials exist, he added.

Dr. Shay holds stock in Geron Corp.

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