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 adenovirus carrying a telomerase-targeted drug to search out and destroy malignant cells. The phase I study included 16 patients who received injections of the adenovirus 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 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 and 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, Oncolyts Biopharma of Tokyo, will begin a phase II study shortly in liver cancer, said company director Toshiyoshi Fujiiwara, 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 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 telom-
erase 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 inves-
tigating 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 ran-
donized trials. Cancer Research UK is
testing it in a projected 1,100 pancreatic can-
cer patients who are receiving gemcitabine
and capecitabine and then sequential or con-
comitant 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 leuke-
mia 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 tech-
nology 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 mole-
ular 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. Vaxxon 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 mono-
clonal 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 telom-
erase in normal and progenitor cells, accord-
ing to new research. “We are seeing that
telomerase play a more important role in nor-
mal 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 con-
sidering telomerase-based therapies, no data
to suggest stopping trials exist, he added.

Dr. Shay holds stock in Geron Corp.

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