No end in sight for telomerase-targeted cancer drugs

On paper at least, the telomerase enzyme seems like a perfect cancer target. Telomerase expression is essential for the proliferation of most cancer cells, but the enzyme is inactive in the majority of normal human tissues. That means that inhibiting the chromosome-elongating enzyme should, in theory, be a relatively safe and effective way to, if not directly kill, at least weaken cancer cells before treating with other agents. Putting that idea into practice has proven more difficult than drug companies expected, but a new wave of clinical trials testing novel combinations of drugs and new patient populations is finally providing evidence that telomerase inhibitors might be an effective cancer treatment, at least when it comes to some tumor types.

It took some time for this idea to take root, however. One setback came in 2008, when Denmark's Pharmexa prematurely halted a phase 3 trial that was testing GV1001, a vaccine designed to prime the immune system to recognize telomerase, in 520 people with pancreatic cancer. Then, in September of last year, California's Geron announced that it was discontinuing a phase 2 study of imetelstat, a small-molecule telomerase inhibitor, in 166 patients with breast cancer. In both cases, interim analyses of the clinical data showed no survival benefit from the drugs. However, both agents have since advanced, albeit with revised protocols or in different indications, and promising results are starting to emerge.

"We're at this stage where there's still more basic science of telomerase we need to understand to be able to make better telomerase-specific therapeutics," says Jerry Shay, a molecular biologist at the University of Texas Southwestern Medical Center in Dallas who previously worked with Geron but is no longer associated with any commercial telomerase inhibitor pursuits. "But it's not over for telomerase by a long shot."

Just last month, for instance, at the American Society of Hematology meeting in Atlanta, Geron reported the results of a small phase 2 trial showing that 13 of 14 people with essential thrombocythemia, a hematological malignancy characterized by an excess of platelets, achieved target platelet counts after receiving imetelstat. "The fact that we saw molecular responses and the fact that it seems to be modifying the [mutated] clone gives us hope that the drugs have some true antitumor activity," says Olatoyosi Odenike, a hematologist-oncologist at the University of Chicago Medical Center and an author of the

Never-ending story: Telomerase activity can help sustain tumor cells.

new study on essential thrombocythemia. "I would say the field is very positive right now."

A decrease in platelets was actually noted as an adverse effect in earlier failed phase 2 trials of imetelstat in people with breast and lung cancer. Yet, whereas this is an unwanted side effect for solid tumors, it's exactly the desired effect for some blood cancers, in which the bone marrow produces an excess of blood cells. In addition to thrombocythemia, this is seen in multiple myeloma. Also last month, Geron published an abstract in the journal *Blood* reporting that, in eight of nine patients with multiple myeloma who took imetelstat, the number of circulating cancer stem cells decreased approximately fourfold on average over the course of two months.

Buoyed by all these recent findings, Geron plans to advance imetelstat for hematological malignancies as its lead therapeutic candidate, according to a company announcement made on 3 December.

But the company is not giving up entirely on solid tumors quite yet. In a recent conference call with analysts, Geron revealed subgroup analyses from a failed lung cancer trial showing that imetelstat was most effective in people whose lung tumors had the shortest telomeres at the outset of the study. Following up on this observation, Geron scientists are now planning to study tumor banks to identify other subtypes of solid tumors with routinely short telomeres that may respond optimally to imetelstat. They also hope to develop a companion diagnostic test that could be marketed in conjunction with imetelstat to determine telomere length.

From chromosome cap to thinking cap

In another tactic, Geron is combining imetelstat with other agents. In a phase 1 trial involving ten women with breast cancer reported at the annual San Antonio Breast Cancer Symposium last month in Texas, Brittney-Shea Herbert and her colleagues at the Indiana University School of Medicine in Indianapolis gave imetelstat together with Herceptin (trastuzumab) to women who didn't respond to the antibody therapy alone. "By adding imetelstat to their regimen, we are seeing decreases in HER2 like we would expect for Herceptin-sensitive patients," says Herbert.

Meanwhile, GV1001, which was licensed to South Korea's KAL-GemVax in 2008, is now in phase 3 testing for the treatment of non-small-cell lung cancer and of pancreatic cancer in combination with chemotherapy, rather than alone as the previous failed trial was designed, and other telomerase vaccines, including products from France's Vaxon Biotech and New Jersey's Merck, are earlier in clinical development. All these vaccines encode peptide fragments of hTERT, a catalytic subunit of the telomerase enzyme. In addition, Japan-based Oncolys has completed phase 1 trials of telomelysin, an oncolytic vaccine designed to stop expression of telomerase by enoding an hTERT promoter.

"We still think of telomerase as the Achilles' heel of cancer," says Herbert. "It's just a matter of optimizing the delivery methods and drug combinations."

Sarah C P Williams