Taking Aim At Recurrence: Targeting Cancer Stem Cells To Stop Proliferation

An emerging field of oncology drug development offers the potential for eradicating all remaining cancer cells following treatment—and thus preventing recurrence—by targeting the so-called cancer stem cells that are thought to be involved in cancer proliferation, treatment resistance, and metastasis.

Cancer stem cells are malignant cells within tumors that can proliferate, continually self-renew and, like other stem cells, differentiate. They also seed new cancer growth in spite of all anti-cancer treatments. That’s because unlike cancer cells, they may divide very slowly and thereby elude treatments used to target other cancer cells, which are generally rapidly dividing cells and are often identified by over-expression of growth factors.

Identified in small numbers in some solid and blood tumors, cancer stem cells have been reportedly isolated by scientists in glioma, leukemia, breast, ovarian, colorectal and pancreatic cancers. They are resistant to chemotherapy, targeted drugs, and radiation.

Many scientists believe that they are the major reason for cancer recurrence, although some avoid the “stem cell” label because of the potential to confuse them with other stem cells, referring to them instead as “cancer-driving” cells. Because they are not eradicated by current cancer treatments, residual cancer stem cells/cancer-driving cells remain to proliferate and repopulate tumors.

A handful of companies are trying to target these cells with modalities ranging from vaccines to peptides to monoclonal antibodies, with no indication yet which of these might prove effective. The most promising are focusing on certain developmental signaling pathways that are reactivated in cancer, and telomerase, an enzyme involved in the immortalization of stem cells and cancer cells.

The hope is that eliminating cancer-driving cells will drastically reduce or eliminate the chance of cancer recurring following treatment, a problem for every anti-cancer modality. Several companies are developing treatments that target both cancer cells and cancer stem cells, a double-barreled approach which could prove more effective than targeting each separately.

Investment in drug development in this area has been relatively modest so far, however, perhaps in part because the academic community is not unanimous that these cells are true stem cells and in part because the field is still in a relatively early stage. While a few proof-of-principle studies in animals show that attacking cancer stem cells reduces recurrence, more clinical data are needed before Big Pharma and other financing sources step forward to make major investments.

Recent data presented last winter and this spring by a number of companies— with more expected over the next year or so—are strengthening the hypothesis that attacking these cells may hit cancer’s Achilles heel. Advances could bring new interest and investment into this area.

Monoclonal Antibodies Offer A Way In

To date, pharma firms have invested little in the space, mostly through collaborations with academia. Only one large Big Pharma-biotech collaboration exists, according to Elsevier’s Strategic Transactions Database. Venture capital and stock offerings account for other sources of financing for this relatively new area of cancer drug development.
Among the few Big Pharma deals is a research collaboration that Sanofi-Aventis signed in September 2007 for an undisclosed sum, with China’s Institute of Hematology and Blood Diseases Hospital and the Chinese Academy of Medical Sciences in Tianjin. In 2008, Roche acquired Arius Research of Toronto, Canada for over $190 million, which gave it control of its antibody and cancer stem cell programs.

In the biggest cancer stem cell deal to date, GlaxoSmithKline agreed in December 2007 to pay OncoMed potentially up to $1.4 billion for rights to its cancer stem cell antibodies. “We believe that the use of antibodies gives our drugs greater specificity than other stem cell targeting therapies,” said OncoMed CEO Paul Hastings.

Founded in 2004 with University of Michigan stem cell scientists Max Wicha and Mike Clarke, OncoMed is targeting the Wnt and Notch signaling pathways and has an extensive patent portfolio covering mAb-related intellectual property relating to cancer stem cells. It had received venture capital from Latterell Venture Partners in San Francisco early on – a $13.9 million first round in September 2005, half of which was provided before the company had generated its first lead (“Cancer Stem Cells: A New Approach To Treating Cancer,” Start-Up, March 2006). Genentech was also an early investor.

Its major alliance with GlaxoSmithKline is for four Notch pathway antibodies: two compounds partnered through Phase II, and two through the clinical candidate stage. OncoMed also has two Wnt-targeting antibodies in its pipeline which it is looking to partner, Hastings said.

According to the 2007 deal, the Redwood City, Calif.-biotech received an undisclosed initial payment of cash from GSK and an equity investment, and is eligible to earn additional milestone payments up to $1.4 billion based on the achievement of specified discovery, development, regulatory and commercial milestones. OncoMed will also receive double-digit royalties on all collaboration product sales.

GSK, for its part, has an option to invest in a future IPO by OncoMed. (GSK also contributed to a February 2008 $168 million financing.) It has an exclusive option to license the monoclonal antibody, and would then fund further worldwide clinical development. OncoMed retains the option to participate in development and commercialization of OMP-21M18, its lead antibody candidate.

OMP-21M18 targets the anti-delta-like 4 ligand, DLL4, an important part of the Notch pathway, which mediates stem cell self-renewal and vascular development. The company is about to begin a Phase Ib clinical trial in combination with chemotherapy for triple-negative breast cancer. Preclinical studies demonstrated that OMP-21M18 works well as a single agent and in combination with paclitaxel in a triple-negative breast cancer xenograft model.

“This antibody has multiple mechanisms of action,” Hastings noted. Gene expression analysis showed that the drug blocks Notch signaling in both tumor and stromal cells. It reduces cancer stem cell frequency, inhibits proliferation of bulk tumor cells, and disrupts productive angiogenesis.

Similar to findings that cancer cell growth increases following high-dose chemotherapy and rest periods, researchers have found that cancer stem cells proliferate following chemotherapy. Depleting cancer stem cells delays regrowth of cancer cells. The implication is that cancer stem cell volume decrease is related to recurrence rate.

Significantly, breast cancer stem cell volume increased following treatment with just chemotherapy – but combining chemo with OMP-21M18 delayed and decreased the growth rate of recurrence after paclitaxel had been stopped. The combination also reversed paclitaxel-related increase in cancer stem cells.

In another preclinical study, combining its anti-DLL4 drug with irinotecan inhibited the growth of K-ras-mutated colorectal tumors. These mutations in colorectal cancer are associated with resistance to EGFR-inhibiting antibodies.
Then, wanting to see if its drug could also restore sensitivity to EGFR inhibitors, OncoMed tested OMP-21M18 in K-ras-mutant colorectal xenografts. OncoMed found that while its antibody alone was not effective, adding it to cetuximab, an EGFR inhibitor, restored the tumor’s sensitivity to EGFR inhibition in both wild-type and mutant K-ras colon tumors.

The company now plans to test OMP-21M18 in colorectal patients with K-ras mutations. Ultimately, the anti-DLL4 drug will also be tested in lung cancer, pancreatic cancers and melanoma.

OncoMed is planning to file an IND for a second Notch-directed antibody, OMP-59R, by the fourth quarter. “This drug blocks Notch signaling without damaging normal colon stem cells,” Hastings explained. The company also plans to test the drug in breast and pancreatic cancers.

OncoMed will file another IND for its first Wnt-directed antibody, OMP-18R, by the fourth quarter of 2010 or early 2011. “To date, no one but us has produced an antibody to the Wnt pathway,” said Tim Hoey, VP of cancer biology. A partial antagonist of the Wnt pathway with a good side-effect profile, this candidate has shown robust anti-cancer stem cell activity in preclinical studies of pancreatic, breast and colon cancers.

**Targeting Stem Cells and Tumor Cells**

The cancer stem cell field gained ground with the presentation of Phase I data on Boston Biomedical’s first-in-class BBI-608 as a late-breaking abstract at the American Association for Cancer Research annual meeting on April 19.

BBI-608 produced stable disease in 9 of 12 evaluable advanced cancer patients at eight to 57 or more weeks, with early signs of tumor regression. Essentially, the trial offered clinical proof that targeting both types of cells has a positive clinical effect.

Calling the drug a “stemness inhibitor,” Boston Biomedical’s CEO Chiang Li explained that BBI-608 blocks a number of key signaling pathways known to keep cancer stem cells alive and active. These pathways include c-myc, beta catenin, and stat-3. That means “BBI-608 is active in a broad range of types of cancer stem cells,” he said.

To date, the Norwood, Mass.-based company has enrolled 18 patients, with data available for 12. It has administered BBI-608 to six groups at doses ranging from 20 mg to 600 mg per day. Patients received the oral drug twice daily for 4 weeks, with cycles repeated every 28 days until progression or unacceptable toxicity occurred. Blood concentration of BBI-608 exceeded the level needed to destroy cancer stem cells and heterogenous cancer cells in the lab.

The drug has so far shown an excellent safety profile and signs of clinical activity, Li said, pointing to few side effects and stable disease in treated patients. Boston Biomedical plans to begin a Phase II trial later this year, he noted.

While a range of other cancer stem cell therapies are in development, BBI-608 is the first drug designed to block multiple cancer stem cell pathways, Li said. BBI-608 has advantages over other cancer stem cell drugs in development because it also kills other, non-stem cancer cells, he said. “We believe it is necessary to target both populations of malignant cells,” he said.

**Testing Out Telomerase**

BBI and OncoMed’s approaches to targeting cancer stem cells are to hit certain key signaling and developmental pathways, respectively. A third approach, taken by Geron Corp., Vaxon Biotech, and Kael GemVax, entails targeting telomerase, an enzyme involved in the immortalization of cells, a hallmark of cancer cells, stem cells, and cancer stem cells *(see sidebar).*
Of these, Geron, of Menlo Park, Calif., has the highest profile. Its approach is entirely different from its peers. Best known for its high profile regenerative medicine work with embryonic stem cells, the company is also a leader in on telomerase-targeting drug and vaccine development. The company has extensive patents on intellectual property related to this enzyme beginning in the 1990s. So far, it is the only company with a telomerase-targeted drug in the clinic.

Telomerase is central in both stem cell and cancer cell immortalization. Its inhibition can stop abnormal replication of cancer cells and, in contrast to an unlimited number of antigens, it could be a universal cancer target because it is present in high levels in most cancer cells, but at very low levels in normal cells after birth, according to Geron researchers. Its significance was recognized when its three discoverers received 2009’s Nobel Prize in medicine.

Telomerase maintains telomeres, the tips of chromosomes containing regions of repeated DNA, which keep chromosomes from deteriorating. As normal cells divide, telomerase shortens telomeres until they stop dividing and cells enter senescence.

When telomerase is added to normal cells, they divide indefinitely and become immortalized. Because the telomerase enzyme is reactivated in carcinogenesis, it is a target that, when inhibited, can arrest the abnormal replication of cancer and cancer stem cells. Preclinical research shows that inhibiting telomerase shortens telomeres and causes cancer cell death. However, scientists have had difficulty identifying a compound that specifically inhibits this enzyme. To date, researchers have identified three telomerase-related targets with which they are working: hTERT, the telomerase reverse transcriptase protein; the RNA component that acts as a template for hTERT; and telomerase-associated proteins, such as TRF1.

Geron is pursuing the RNA template strategy and is testing a drug and vaccine in cancers known to be stem cell-driven and have large, unmet needs, said CEO Tom Okarma. His company has cloned both the genes for hTERT and hTR, and designed and produced a new class of short-chain nucleic acid molecules, or oligonucleotides, that target the active site, or template region, of telomerase. The drug has high inhibitory power at low concentrations, and binds with high affinity to the RNA template of human telomerase, which lies in the active site of hTERT.

**Funding For Geron**

Numerous preclinical studies presented at an AACR meeting on telomerase last winter indicated that Geron’s drug, imetelstat (GRN-163L), targets cancer stem cells in a number of cancer models. It is the only telomerase-targeted drug therapy in the clinic, though there are vaccines in development. By binding to telomerase, it directly inhibits the enzyme’s activity.

A short-chain lipidated oligonucleotide that binds to the catalytic site of telomerase, GRN-163L is currently in six early-stage trials. Four Phase I and I/II trials finished in 2009 and four randomized Phase II trials will begin shortly in lung and breast cancers, myeloma, and chronic leukemia. The compound also is in Phase II in acute myelogenous leukemia, and will be tested in breast cancer with bevacizumab and paclitaxel.

“As this is the first and only telomerase-based drug, there is no playbook for how to test it,” said Okarma. “But we’ve learned a lot so far about the pharmacodynamics and pharmacokinetics of the drug as a single and combination treatment in solid and liquid tumors from our Phase I trials,” he said. These studies show that the drug is hitting the target – telomerase in cancer stem cells, Okarma added. Other cancers imetelstat inhibits in vivo and in vitro include pancreatic, neuroblastoma, and pediatric glioma.

Geron is funding its work by a series of private financings $40 million in December 2006, $51 million in September 2005, $46.2 million in February 2009, and a private placement of $39.5 million in November 2004. Licensing deals, such as those made with Procter & Gamble and Xcellsyz, both for its hTERT technology in July 2004, have yet to demonstrate results, but a July 2005 alliance with Merck for $21.5 million helped to put Geron on firm financial footing. When Merck filed its IND for its telomerase-based vaccine in December 2007, Geron received a $4 million milestone payment. The company ended the first quarter with $166.5 million in cash and investments.
Immunotherapy Vaccines Offer Another Option

Along with imetelstat, Geron is also immersed in telomerase-targeting vaccines. It is developing an autologous vaccine, GRNVAC1, and recently reported Phase II results with 20 patients with AML. The intradermally administered vaccine employs dendritic cells transfected ex vivo with the whole coding sequence of hTERT RNA.

A number of high-risk patients in clinical and molecular remission from 4 months to 2 years have begun an extended boost phase, and analyses show that the 14 in complete remission are negative for a gene associated with AML proliferation.

Okarma acknowledges that long-term, autologous vaccines are not a cost-effective strategy, so it is developing a second, allogenic product using embryonic stem-cell-developed dendritic cells, GRNVAC2. With technology licensed from Geron, Merck is also working on a non-dendritic cell vaccine.

Geron isn’t the only company working on telomerase-based vaccines. The South Korean company Kael GemVax is furthest ahead, in Phase III trials with GV-1001, an hTERT peptide fragment directed to the active site of telomerase, which elicits both cytotoxic T-cell and helper T-cell responses.

Developed by Gustav Gaudernack, chair of immunology at Oslo University Hospital, GV-1001 has produced good results in nine Phase I/II trials, alone and in combination with chemotherapy in a range of cancers, with a response rate of 50-80 percent. These trials were sponsored by a Norwegian start-up, GemVax.

The vaccine has had a rocky development road due to funding issues and resulting ownership changes, Gaudernack said. Due to a lack of funding, after the initial trials run by GemVax, it was sold to a Danish company, Pharmexa, before being acquired by Kael GemVax. Now it is being tested in 1,100 pancreatic cancer patients in a Phase III trial program in the U.K. called TeloVac. Patients receive gemcitabine and capecitabine, and then the vaccine with either sequential or concurrent granulocyte-macrophage colony-stimulating factor, GM-CSF. Another trial, in chronic lymphocytic leukemia, has just begun at the Karolinska Hospital in Stockholm.

A previous Phase III trial, called PrimoVax, conducted by Pharmexa before Kael GemVax acquired the vaccine, was halted because of poor design, and provides an object lesson in how immunotherapeutic cancer vaccines should and shouldn’t be used, said Gaudernack. In PrimoVax, the vaccine was given before chemotherapy, which is “counterintuitive,” he said. “It is difficult to get the immune system to mount a defense while it is deteriorating with a large tumor inside,” Gaudernack said.

Real Evidence Still To Come

Despite the early trial results for some agents, the true potential of the disparate field of cancer stem cell therapeutics remains largely unknown at this point.

The late-stage trial likely to finish first is GemVax’s in pancreatic cancer, and there is reason for optimism. Phase II trials of Geron’s drug will also be telling. Results from this trial are likely to inform the subsequent development of earlier-stage therapeutics. Whether the universal cancer stem cell target, telomerase, or certain pathways active in particular cancers will turn out to be effective is unknown now.

The safety profile of targeting cancer stem cells also looms as an unknown, and could prove to be an impediment. Robert Vonderheide, a professor at the University of Pennsylvania and telomerase expert, noted recently that other actions of telomerase have been discovered in normal cells, and the safety of telomerase-targeting therapies must be firmly established. Targeting other pathways, such as Wnt and Notch, must also be shown to be safe.
Part of the danger inherent in novel fields that target emerging science is the evolving knowledge of the mechanisms involved. But the possibility of a double-hit against cancer – by combining cancer stem cell therapies with chemotherapy to kill tumor cells and the cancer stem cells left behind – will continue to draw significant research attention.

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### Clinical Trials Moving Forward

If Geron is the best known of the companies working on telomerase, others are also moving ahead – and could get to market first.

Kael-GemVax is teaming up with Lytix Biopharma of Tromso, Norway to test GX-001 and Lytix' synthetic lytic peptide LTX-315 (or Oncopore) in combination to treat certain solid cancers. Both drugs recently began a Phase I trial in up to 40 patients with transdermally accessible solid tumors. Lytic peptides destroy cell membranes by lysis in response to invading bacteria, viruses and fungi.

Oncopore is a lytic peptide that also has an anti-tumor effect that causes necrotic degradation and releases danger signals from the tumor, leading to an induction of anti-tumor responses. The ongoing trial, which combines two immunotherapies, a vaccine and a peptide drug, will test for tumor necrosis after local injection and induction of an anti-tumor immune response. It also represents a new approach to studying multiple novel drugs in combination in early-stage trials, which is gaining steam ("The Pink Sheet," June 14, 2010).

A full-length hTERT peptide vaccine is being developed by researchers at the University of Pennsylvania School of Medicine. Like Geron CEO Tom Okarma, Robert Vonderheide, a professor at the university, views telomerase as a universal tumor antigen and therefore applicable to all cancers.

Now in Phase I testing, the full-length hTERT vaccine is being given to patients after the anti-CD25 monoclonal antibody daclizumab, Biogen's Zenapax, in order to strengthen CD4 and CD8 cell responses. “The problem with giving immunotherapies to cancer patients is that they are immune-suppressed,” Vonderheide said. Daclizumab given before the vaccine should amplify patients’ immune responses, he said. Such an approach to treating cancer by teaming anti-cancer drugs and vaccines with immunostimulatory molecules given before or with cancer therapies is being adopted by numerous companies, as reported at ASCO in June.

At ASCO’s 2010 annual meeting in Chicago, Vonderheide presented Phase I data from a trial with the vaccine and daclizumab in metastatic breast cancer patients showing that one infusion of the anti-CD26 monoclonal antibody dacluzimab given a week before receiving the vaccine produced rapid loss of regulatory T cells, which tumors secrete to dampen the body’s immune response. The drug did not cause toxicity and together with the vaccine produced disease stabilization in 6 of 10 patients. “For this group of patients, an extended period of stable disease represents an encouraging result,” Vonderheide said.

Many of these women have been previously treated with several chemotherapy regimens, which failed, but using this approach, they could receive multiple doses of the vaccine without experiencing any of the toxicities that often accompany chemotherapy. Data for overall survival is not yet available, but Penn researchers say the results represent significant promise for treating the patient population that does not respond to standard therapies.

Vonderheide and team plan to begin much larger studies in the near future, and ultimately, to expand the new combined approach to women who are currently in remission but at very high risk of relapse.

Vonderheide thinks that the best use of this vaccine in the future could be preventing cancer in high-risk populations, such as women at risk of breast cancer. Ultimately, the goal for this and other immunotherapy vaccines would be to produce as safe and strong an immune response as that generated by vaccines against viruses. If that is possible, this telomerase-based vaccine could be used in high-risk populations like the HPV vaccines are now used.
To date, Vonderheide has received $2 million in funding for the vaccine over 4 years from an ROI from the National Institutes of Cancer and the Breast Cancer Research Foundation.

Vaxon Biotech in Paris has a vaccine about to begin Phase III testing in locally advanced and metastatic NSCLC. VX-001 uses two cryptic peptides, rather than dominant hTERT peptides, with low HLA-1 affinity. That means they are non-immunogenic and produce strong immune responses in advanced cancer patients. Vaxon’s Phase I/II trial in NSCLC was extended to hepatocellular, breast, pancreatic, and prostate cancers. These studies showed that the vaccine was safe and well-tolerated and elicited an immune response in 70 percent of patients; responses have lasted for four years with VX-001 vaccine boosts. This response is quite unusual in patients with advanced cancer, who are immunocompromised due to both the disease and previous treatment with chemotherapy.

In the first group of 33 NSCLC patients, survival was 18.8 months vs. 10 months in matched controls, and in the extension trial of 83 more patients, 33 had disease stabilization for over 6 months, with three partial and one complete response. The VX-001 vaccine has been granted orphan drug status from FDA and the European Medicines Agency for HLA-A2+ patients with TERT-positive tumors.

On May 19, Vaxon announced that it has concluded its Phase I/II trial with a total of 116 patients. Survival of vaccinated patients correlated with immune response, with four objective responses and 33 with disease stabilization for over 6 months. Analysis of the 33 NSCLC patients demonstrated that VX-001 produced objective responses in more than 42 percent of patients, Vaxon will launch the first Phase III trial in NSCLC first, to be followed by hepatocellular carcinoma and breast cancer in 2012 and 2013.

To date, Vaxon has raised over €16 million, including seed funding from INSERM-Transfer, INSERM’s technology transfer arm. It is open to partnering its Phase III in NSCLC or earlier-stage trials.