Beyond PARP Inhibitors: Agents in Pipelines Target DNA Repair Mechanisms

By Amy Maxmen

For decades, scientists have looked for ways to prevent cancer cells from mending damage inflicted by chemotherapy and radiation treatments. Now, drugs that obstruct repair pathways have begun to enter clinical trials, and more reside in laboratories at earlier stages of development.

The best known and furthest along of these are targeting DNA repair mechanisms in breast cancer. In 2009, BSI-201, or iniparib, became the first such inhibitor to reach a phase III clinical trial. Developed by BiPar Sciences, a wholly owned subsidiary of Sanofi-Aventis, iniparib blocks a signaling enzyme called poly(ADP-ribose) polymerase (PARP1). The PARP1 enzyme recognizes and eliminates oxidized DNA bases, which would otherwise accumulate and kill cells.

Normally, another repair pathway involving the tumor suppressor genes BRCA1 and BRCA2 mends these breaks—a second line of defense. But an estimated 5%–10% of all breast cancer patients carry BRCA1 and BRCA2 mutations that disable this backup mechanism. When both the PARP and the BRCA repair pathways are disabled—a situation known as synthetic lethality—the damaged and unrepaired DNA kills the cell.

Last year, phase II trials with another PARP inhibitor, AstraZeneca’s olaparib, supported the idea that synthetic lethality could indeed be lethal to cancer cells. Tested in BRCA1 and BRCA2 mutation carriers, the drug produced response rates that many impartial observers said were impressive.

However, clinical trials are also testing PARP inhibitors in patients who do not necessarily have BRCA mutations. For instance, BiPar’s phase III trial, which has completed enrollment, is assessing the efficacy of iniparib in combination with the chemotherapy drugs gemcitabine and carboplatin in more than 420 patients with triple-negative breast cancer (those who underexpress the HER2, estrogen, and progesterone receptors). Here the strategy is to use the PARP inhibitor to prevent the tumor from repairing the chemotherapy-caused damage. In an earlier phase II trial with 116 patients, tumors shrank in approximately 62% of those receiving iniparib and gemcitabine, compared with 21% in the group receiving gemcitabine alone.

Other Cancers and Other Agents

BiPar is also testing iniparib in phase II trials in squamous-cell lung cancer and ovarian and endometrial cancers. A phase Ib trial is under way in pancreatic cancer, as well as a phase I–II trial in glioblastoma. Other pharmaceutical companies, including Pfizer, Abbott, Merck, and AstraZeneca, have PARP inhibitors in early-phase trials.

Alan Ashworth, Ph.D., director of the Breakthrough Breast Cancer Research Center in London and a well-known BRCA researcher, speculates that these mutations represent the tip of the iceberg of repair defects associated with cancers. For instance, tumors with a defect in the tumor suppressor gene PTEN have been linked to many cancers, including 25%–40% of glioblastomas. These may also be sensitive to PARP inhibitors, Ashworth said. “So we are really thinking about a broad range of cancers, including prostate, colorectal, and endometrial cancers, that also have dysfunction in DNA repair pathways.”

PARP enzymes are not the only players in the DNA repair arena. Checkpoint proteins also help protect DNA, putting the cell replication cycle on hold until mistakes are fixed. Defects in checkpoint proteins, such as p53 and Chk2, have been linked to cancer. The defective proteins appear to help cancer cells evade checkpoints and prolif-
erate despite mistakes in their DNA. But if these mistakes accumulate—with radiation, for instance, and the help of drugs targeted at checkpoint proteins—damage builds up and can kill the cell.

In a 2006 *Nature* study, Shideng Bao, Ph.D., of Duke University Medical Center in Durham, N.C., and colleagues reported that inhibiting Chk1 and Chk2—protein kinases involved in checkpoint control following DNA damage—sensitized brain cancer cells to radiotherapy in cell culture. In other studies, Chk1 inhibitors increased cancer cell death in the presence of p53 mutations.

Last year, AstraZeneca began enrolling patients in trials to determine the proper dosage of the Chk1 kinase inhibitor AZD7762 in combination with gemcitabine in patients with solid tumors. And in March, Eli Lilly began trials evaluating a Chk1 kinase inhibitor, designated LY2606368, in patients with non–small cell lung cancer, colorectal cancer, and ovarian cancer. Both groups are slated to complete the studies in 2012.

Drug developers are also targeting enzymes that regulate Chk1 and Chk2. In response to DNA damage, the ataxia telangiectasia mutated (ATM) kinase and another effector kinase, ATR, initiate a cascade leading to DNA repair; ATM inhibitors could allow the damage to go unrepaired. Last year in *Molecular Cancer Therapeutics*, a team lead by Kristoffer Valerie, Ph.D., at Virginia Commonwealth University reported that glioma cells become more sensitive to radiation after treatment with the ATM inhibitor KU-60019. KuDOS Pharmaceuticals, now a wholly owned subsidiary of AstraZeneca, is developing the agent.

Members of the cyclin-dependent kinase (CDK) family also halt the cell cycle for repair. Geoffrey Shapiro, M.D., Ph.D., director of the early drug development center at Dana–Farber Cancer Institute in Boston, helped discover that cancer cells become more sensitive to chemotherapy when certain CDKs are inhibited. He suggests that selectively blocking certain CDKs prevents BRCA from repairing mistakes.

Piramal Life Sciences has a CDK1–CDK4 inhibitor, called P276-00, in multiple early trials in combination with chemotherapy drugs to treat advanced malignant melanoma, pancreatic cancer, multiple myeloma, and head and neck cancer. However, other members of the CDK family play key roles in normal cells, so showing that the drug is specific to CDK1 and CDK4 and does not inhibit other members of the family is important, Shapiro said.

**Specificity**

By exploiting defects that only cancer cells carry, repair inhibitors should leave normal cells unscathed. Yet sometimes their degree of specificity isn’t apparent until trials have begun. For example, one drug that looked promising in preclinical studies disrupted the repair enzyme MGMT. MGMT repairs damage by removing harmful alkylations, such as those that the DNA-damaging drug temozolomide causes. But a trial evaluating MGMT inhibitors in combination with temozolomide was stopped early because the combined treatments harmed bone marrow as well as malignant tissue.

“The difficult part of DNA repair inhibitors is that they increase toxicity of a DNA damaging drug, so the real issue is how to get cancer specificity.”

“...and then choose their therapy, we improve outcomes.”

Likewise, the DNA-damaging drug methotrexate harms tumors with defects in the DNA mismatch repair gene MSH, a mutation that 40% of cancer patients with hereditary nonpolyposis colon cancer carry. Methotrexate has been used to treat cancer since the 1940s, but because of various rates of success, more reliable treatments have replaced it. However, if patients can be efficiently screened for MSH defects, those who are likely to respond best to methotrexate can be selected.

“It may be that we have a lot of the right drugs to treat cancer, but we are giving them to the wrong patients,” says Ashworth. “There’s often a disconnect between genetic testing and treatment, but if we can test people rapidly andchoose their therapy, we improve outcomes.”

Although PARP inhibitors may prove to be effective on their own in patients with BRCA defects, Shapiro predicts that repair inhibitors will be most powerful in combination with other drugs. Testing drug cocktails has never been easy, however. “The problem with the checkpoint and DNA repair inhibitors is that they are very difficult to develop alone,” he says. “We want to use them with a DNA-damaging agent, so we not only have to demonstrate that they’re safe on their own but you must quickly get them into combination trials and do randomized studies with chemotherapy drugs to show these augment DNA damage.”

It may be worth the wait, according to commissioned researchers in this field. “The future for DNA repair inhibitors is phenomenal, and we’re working hard to identify new potential targets,” Helleday said. “It’s been a little slow going, but it’s only the very beginning.”

Dr. Ashworth is a named coinventor on several patents held by AstraZeneca relating to the use of PARP inhibitors. Dr. Helleday is named on patents related to DNA repair and has reported receiving remuneration from KuDOS Pharmaceuticals.