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Web Exclusive: Searching for New Targets

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Over the past two decades, more than a dozen cancer drugs have been approved that target a specific protein or cellular pathway unique to cancer cells, with many more being investigated in clinical trials. When a potential target has been identified, a new class of agents may emerge, such as antiangiogenic drugs, EGFR inhibitors, and mTOR inhibitors. (Read about these and other drug classes in [“Cancer Therapies”](#) from the *CURE 2009 Cancer Resource Guide*). There are many more novel agents in preclinical and early phase trials. Here are just a few of the newer classes of drugs making their mark in the oncology pipeline.

PARP Inhibitors

One class of drugs garnering attention after recent positive data were announced from two phase II studies in breast cancer is PARP inhibitors. Poly (ADP-ribose) polymerase is a protein that looks for breaks in DNA and helps to repair those breaks. Unfortunately, PARP can also help cancer cells resist chemotherapy that targets the DNA of cancer cells. Researchers have looked at using PARP inhibitors as a single agent in cancers that have a single DNA-repair defect, as is the case for breast cancer patients with a BRCA mutation, as well as in combination with other drugs that target DNA repair pathways. Two drugs highlighted at this year’s American Society of Clinical Oncology meeting, BSI-201 and olaparib, will continue to be studied in larger trials in triple-negative and BRCA-associated breast cancer. PARP inhibitors are also in early clinical testing for ovarian and brain cancers. Read more about about BSI-201 and olaparib in [“PARP Inhibitors Successful Against Hard-to-Treat Breast Cancer”](#) from *CURE*’s 2009 coverage of ASCO.

Disrupting the Vascular Environment

Similar to antiangiogenic agents, such as Avastin (bevacizumab) and Sutent (sunitinib), which block the tumor’s ability to receive nutrients and oxygen via the

bloodstream, vascular disrupting agents (VDAs) also impede the tumor's blood supply. But unlike antiangiogenic drugs, which prevent the binding of vascular endothelial growth factor (VEGF), a protein that signals blood vessel growth to the tumor, to its receptor, VDAs actually attack the blood vessels that are already formed near the tumor. Because of the method of action, researchers believe this may be a prime drug for a combination regimen with other targeted agents. Scientists are investigating one such VDA, cilengitide, in a phase III study in glioblastoma multiforme, an aggressive form of brain cancer. (See how cilengitide works against brain tumors in "[A Better Way to the Brain](#)"). Other forms of cancer being explored include lung and head and neck cancers.

Blocking Insulin-Like Growth Factor

The hormone insulin-like growth factor (IGF-1), a cousin of insulin, is thought to have a role in many types of cancer, including breast, colorectal, and lung cancers, as well as some types of sarcoma. Researchers believe that by inhibiting the IGF-1R pathway, cancer cells lose their ability to multiply and spread. Although no IGF-1R inhibitors have been approved in cancer, there are several in ongoing clinical trials alone or in combination with chemotherapeutic and biological agents.

The Extended HER Family

The HER family consists of four types of epidermal growth factor receptors, including the epidermal growth factor receptor 1 (HER1) and HER2. In 1998, Herceptin (trastuzumab) became the first approved drug to target a member of the HER family—HER2 (read more about HER2 in "[Herceptin in the Spotlight](#)" from the Spring 2006 issue). Nearly a decade later, Tykerb (lapatinib) went one step further, targeting both HER2 and HER1. Approvals for other drugs that target EGFR have been approved for lung, breast, and colorectal cancers. Now, researchers are examining other novel therapies that target more than one HER receptor. XL-647, a drug being tested in a phase II non-small cell lung cancer trial, targets HER1, HER2, and HER4 as well as other targets.