At the Flick of a Switch: Epigenetic Drugs

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Leukemia and lymphoma, so-called "blood-based" cancers, share many firsts in the history of cancer research. They were the first cancers to be treated with radiation therapy (around 1900), the first to be clinically tested and treated with chemotherapy (nitrogen mustard in the 1940s), and, more recently, the first to be treated with a novel type of therapy called epigenetic therapy. While companies have reported impressive earnings for the first three (and only) epigenetic drugs approved by the U.S. Food and Drug Administration (FDA), all intended for single agent use in the treatment of either cutaneous T cell lymphoma (CTCL; a rare form of non-Hodgkin's lymphoma) or myelodysplastic syndrome (MDS; a precursor to a type of leukemia known as acute myelogenous leukemia, or AML), the hope and expectation is that, once again, blood is just the beginning. "We have been aware of epigenetic defects in cancer for almost two decades, but it hasn't been thought of as a great therapeutic direction to go, despite these agents," says William G. Nelson, an oncology researcher at Johns Hopkins University School of Medicine. "That's changing very quickly."

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Targeting the Epigenome

Unlike the genome, which is kept static across time, the epigenome is a decidedly dynamic component of the cell, over time and among different cell types. The epigenome encompasses cellular non-DNA-sequence-based regulatory elements that control gene expression and are transmitted from one cellular generation to the next. Those elements include methyl modifications of the genome, covalent modifications of the histone proteins, which are closely associated with genomic DNA allowing its tight packaging into chromosomes, and assorted other chemical changes and entities. The dynamic nature of the epigenome makes biological sense. Utilizing its epigenome to turn genes on and off in response to what is happening in its environment, a cell is able to adapt readily to change by removing DNA methylation marks or altering the histone protein in the necessary way. But that same readiness is a risk, too. It means that things can go wrong just as quickly as they can go right—a tumor suppressor gene, for example, turned off by a misguided cue could mark the beginning of cancer.

The first evidence that epigenetic abnormalities play a role in cancer etiology was reported by Andy Feinberg and Bert Vogelstein (Feinberg and Vogelstein, 1983). Prior to that, most biologists were skeptical of this connection. Today, biologists are so certain that there is a connection that they speak of the "epigenetic model of cancer," not necessarily in lieu of but in addition to the mutational model of cancer (Feinberg et al., 2006), and a growing number of researchers and companies are becoming involved in epigenetic drug research and development. The epigenetic etiology of disease allows for a new way to treat disease. Instead of killing damaged cells (i.e., cancer cells), as conventional chemotherapy does, epigenetically active drugs are designed to reverse the (epigenetic) damage while keeping cells alive. The goal is to restore normal states of gene expression by turning aberrantly silenced genes back on. There are two main types of epigenetic drugs: DNA methylation inhibitors and histone deacetylation inhibitors. Both are designed to inhibit enzymes that play key roles in installation of specific epigenetic modifications, i.e., epigenetic programming.

DNA Methyltransferase Inhibitors: Silence Is Death

The DNA methyltransferases (DNMTs) are enzymes that transfer methyl groups ($-CH_3$) to cytosines in DNA during cell division. Too many enzymes causes too much methylation, which usually means too much gene silencing (e.g., silencing of tumor suppressor genes) and disease development. DNMT inhibitors, also known as demethylating agents, act as substitutes for cytidine residues during cell division: they get incorporated into the DNA in lieu of cytosines, thereby binding to and blocking DNMTs and depleting the cell of overly active methylating enzymes. There are two FDA-approved demethylating agents: 5-azacytidine (Vidaza), a derivative of the nucleoside cytidine; and 5-aza-2′-deoxycytidine, or decitabine (Dacogen), the deoxyribose analog of 5-azacytidine.

When patients with MDS are administered either decitabine or azacytidine, they gain about an extra year of life. AML patients appear to live longer lives as well, when administered either drug, although that finding is not as well established. As Jean-Pierra Issa, a researcher at the M.D. Anderson Cancer Center (Houston, TX), notes, "Other drugs like classical chemotherapy cytotoxic agents do not prolong life. I think that this observation has two very important and very gratifying implications. One is that we are affecting people's lives—not just quality of life but length of life. But also, these drugs are different from classical cytotoxics, and it is clear that we have introduced a different way of treating cancer." DNMT inhibitors don't kill. They simply inflict targeted damage or, rather, reverse epigenetic damage already done.

Several additional DNMT inhibitor compounds are in development, including the well-known zebularine (e.g., Marquez et al., 2005), another derivative of 5-azacytidine, and some lesser known compounds like procainamide, an already marketed antiarrythmia drug. Hopkins' Nelson and colleagues have been

investigating procainamide for its recently discovered capacity to reverse epigenetic silencing. "There's a little shyness about the drug in general," says Nelson, "because most antiarrythmia drugs have some proarrythmia risk. It's not as great a risk as people think, but it is a worry." Nelson's team is screening analogs of procainaimide in search of one (or more) that would exhibit methyltransferase inhibition and the propensity for lower proarrythmia risk.

HDAC Inhibition: Turn It Up!

Ever since it received FDA approval in October of 2006, Merck's Zolinza (vorinostat), the first and only FDA-approved histone deacetylase (HDAC) inhibitor, has generated considerable industry buzz, boosting interest and investment in HDAC inhibitor R&D. The HDACs are a family of 11 enzymes that play a very important role in regulating gene expression by removing acetyl groups (CH_3CO–) from histone proteins and shutting down gene expression. Biologically, deacetylation of histones causes chromosomal DNA to wrap more tightly around histones, which prevents easy access of the transcription machinery to the genetic information that needs to be transcribed. Researchers have reported abnormal HDAC overexpression in many different types of cancer cells. The rationale behind HDAC inhibition as a cancer therapy is that tumor suppressor genes that have been shut down by too much HDAC activity will be turned back on and normal cell function will be restored. While HDAC inhibitors clearly inhibit HDAC enzymes, they also inhibit other aceylation signaling events, making it difficult to know if the clinical effects seen with vorinostat or other HDAC inhibitors are due to HDAC inhibition, as planned, or incidental interference with off-target pathways.

It might be still somewhat of a mystery why HDAC inhibitors work in the clinic, but they do work. Vorinostat's FDA approval is testament to that. So are some of the clinical trial results reported for the other HDAC inhibitors, like panobinostat and romidepsin. Miles Prince, head of the Haemotology Unit at Peter MacCallum Cancer Centre (Melbourne, Australia), is involved with clinical trials with both compounds. Some of the more exciting results he has seen lately include responses to single-agent panobinostat (Novartis' LBH589) among patients with Hodgkin's lymphoma, AML, and MDS and responses among patients with myeloma who have been refractory to bortezomib (Millenium's Velcade, a proteasome inhibitor), when bortezomib is used in combination with romidepsin. Romidepsin is also in phase II development for treatment of CTCL and peripheral T cell lymphomas (PTCL). Both Gloucester Pharmaceuticals (Gloucester, MA) and the National Cancer Institute (NCI) are running trials. According to Prince, the compound has demonstrated definite efficacy in these trials, with some patients entering prolonged remissions of 60 months or more. According to Elizabeth Faust, vice president of Medical Affairs at Gloucester, the company plans to file a new drug application (NDA) for CTCL by the end of 2008.

Other companies with HDAC inhibitors in development include MethylGene (Montreal, Quebec), CuraGen (Branford, CT), Ortho Biotech (a unit of Johnson & Johnson, Raritan, NJ), Pharmacyclics (Sunnyvale, CA), and Syndax (Waltham, MA). Each is taking its own approach. For example, according to MethylGene's CEO, Donald Corcoran, one of the key ways that MethylGene differentiates itself from the competition is that its lead HDAC inhibitor compound (MGCD0103) was rationally designed to target four specific HDACs involved in specific cancers. Vorinostat is a paninhibitor and therefore does not have that same selectivity; neither does Gloucester's romidepsin.

From Blood to Body

As to why the focus with DNMT inhibitors has been on blood-based cancers, says Issa: "When the drugs were developed 40 years ago, they were developed as analogs of the most active leukemia drug, cytarabine, or ara C. So even before we knew the mechanism of action of the drug, people were interested in testing it in leukemia. So almost all of the early clinical experience with the drug was with leukemias, and that's where the responses were seen at the time."

HDAC inhibitors don't have the same history, but their focus has been on hematology as well. Again, it is where responses have been seen. "People have really tried with solid tumors, including us," says MethylGene's Corcoran. "But at least as a single agent, hematology is where the data have been really good." Faust agrees: "With romidepsin, it really was an empiric observation. In the cancers that were tested, that's where it had the most activity." She points out, however, that most of those tests were with single agents. The scenario is likely to be different when results emerge from the growing number of clinical trials combining epigenetic drugs with conventional chemotherapies.

As to whether or not there are any real biological or chemical differences between blood-based and solid tissue cancers, Issa noted just one with demethylating agents: demethylating agents work only in replicating cells, and the rate of active cell division is higher in leukemias than in solid tumors. "So there are some pharmacological barriers with solid tumors," he says. But there aren't enough to dissuade experts from believing that a day will come when the results from combination trials for solid tumors catch up with some of the positive responses being seen for the hematological malignancies. "We will be at a point in a few years," says Issa, "where epigenetic therapy is incorporated into curative regimens for many different cancers."

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