Epigenetics: Moving Beyond the Early Promise  By Paul Watson

When the U.S. Food and Drug Administration (FDA) approved the DNA methyltransferase (DNMT) inhibitors Vidaza [azacitidine; Celgene] in 2004 and Dacogen [decitabine; SuperGen] in 2006 for the treatment of myelodysplastic syndromes (MDS), it signaled the vast potential of epigenetics for the oncology industry. This was further reinforced in 2006 with the FDA approval of Zolinza [vorinostat; Merck], the first histone deacetylase (HDAC) inhibitor indicated for the treatment of refractory cutaneous T-cell lymphoma.

Epigenetics, which literally translates as “above the genome,” researches the molecular mechanisms that result in heritable alterations to the genome without changing the DNA sequence itself. These molecular mechanisms include DNA methylation and histone modifications, both of which typically result in inappropriate gene silencing or activation. During DNA methylation, enzymes attach methyl groups onto genes, inhibiting their functioning ability. During the covalent modification of histones, enzymes promote chemical modifications such as acetylation, methylation, and ubiquitination, which can disrupt chromatin stability and transcriptional regulation, resulting in the loss of expression of tumor suppressor genes or inappropriate upregulation of genes that may act as oncogenes.

A common analogy compares the genome with a computer and the epigenome with the software that tells the computer how to operate. Manipulating this epigenetic software may result in the development of novel, targeted oncology agents, with perhaps the best known validation of this approach being the creation of HDAC inhibitors.

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Complex, but Promising

Targeting an epigenetic process as opposed to a specific gene may appear exceedingly complex, but there is vast potential in such an approach. According to Mark Goldsmith, MD, PhD, president and chief executive officer of Constellation Pharmaceuticals, a biopharmaceutical company specializing in epigenetics, “There is an opportunity, through manipulating chromatin modulations, to modulate programs of genes, not just a single gene or a single pathway. While that introduces complexity from a drug discovery point of view, it’s an attractive option.”

Epigenetics may be doubly attractive to the industry because epigenome functions are driven by enzymes. “Chemists can make enzyme inhibitors really efficiently, and can quickly achieve a drug candidate,” said Mohammad Azab, MD, chief medical officer of SuperGen, a pharmaceutical company based in Dublin, California.

Dr. Azab posited that epigenetics would likely supplant other methods of gene therapy, since the latter attempts to switch on cancer suppressor genes via gene delivery or switch off cancer promoting genes via antisense or small interfering RNA (siRNA) therapies, all of which suffer from issues regarding effective systemic drug delivery.

Another reason that targeting an epigenetic process rather than a specific gene may be preferable is the willingness of cancer itself. “Targeting a program is more attractive than targeting a single gene, because cancer cells seem to find so many ways to get around single gene targeting,” said Joseph F. Costello, PhD, a professor of Neurosurgery and director of the Epigenetics Division of the Cell Cycle and Signaling Program at the University of California, San Francisco.

Much of the promise in this field currently revolves around DNMTs and HDAC inhibitors. According
to Robert Gould PhD, the president and CEO of Epizyme Inc., both treatments demonstrated that epigenetic pathways could be used to achieve therapeutic impact. “The explosion in understanding of the histone methyltransferases and histone demethyltransferases developed a momentum with good business opportunities,” he said. At Epizyme, researchers are developing first-in-class inhibitors of histone methyltransferases (HMTs)—epigenetic enzymes that are thought to promote cancer pathogenesis.

According to SuperGen’s Azab, the validation for epigenetics occurred with the FDA approvals of Vidaza and Dacogen. It is in his opinion, that with these approvals, the field of gene therapy was supplanted by epigenetics. “In certain diseases, we no longer had to do gene therapy to switch on cancer suppressor genes,” he said. “We could actually switch on genes by altering the epigenome with small molecules.”

**The Next Class**

Currently, much of the excitement in the epigenetics field surrounds DNMT inhibitors and HMT inhibitors. Research has revealed that when DNA methyltransferase enzymes become corrupt, they can switch off tumor suppressor genes. As a result, many researchers are studying the process of gene silencing by DNA methylation.

At SuperGen, following the clinical development of Dacogen, researchers developed and are bringing to the clinic SGI-110 a novel DNMT inhibitor that may prove efficacious in MDS, acute myeloid leukemia (AML), and solid tumors.

During the symposium, Dr. Azab noted that there were three main enzymes involved in de novo methylation—the impetus behind methylation and switching off of cancer suppressor genes—DNMT1, DNMT3A, and DNMT3B. DNMT inhibitors that can re-express tumor suppressor genes dysregulated by these enzymes may prove advantageous in numerous cancer types.

For example, lung cancer may be actively promoted by DNMTs. Dr. Azab cited recent data demonstrating that tumor genesis in smokers seemed to occur with the increased activity of DNMT that seem to be associated with smoking. “The DNA methyltransferases have been switching off some of the lung’s tumor suppressor genes,” he said.

Such rapidly mounting evidence of the role DNMTs play in the promotion of cancer makes the epigenetic approach an attractive option for researchers looking for an alternative route for attacking cancer. “There really isn’t another mechanism for therapeutically reactivating tumor suppressors without going after the transcription regulation machinery or the epigenetics that support that,” said Dr. Goldsmith. “It’s a different way of modulating cancer and I’m not really sure how one would go about doing that without taking an epigenetic approach.”

Azab thought that the DNMT inhibitors are very effective at re-expressing immune complexes and making the tumor more susceptible to the immune response. “So in combination with other immune therapies or with chemotherapy this could have huge potential.”
“There are human tumor cell lines that are critically dependent on the activity of one of these enzymes,” said Gould. “In forms of leukemia, chromosomal translocations result in a very specific methylation pattern that gives you leukemia. By inhibiting that enzyme, you can then selectively kill those leukemic cells.”

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Epigenome Mapping

Another promising avenue revolving around epigenetics is mapping the DNA methylation and histone modification patterns that comprise the epigenome itself, a process that has been likened to the Human Genome Project. Professor Costello has recently embarked on this publicly-accessible mapping project, which is sponsored by the NIH Roadmap Epigenomics Mapping Consortium.

HDACs Disappoint

Despite the allure of epigenetics, researchers have been disappointed with the early results attained by many of the HDAC inhibitors in clinical trials. HDAC inhibitors have been associated with tolerability issues and efficacy limitations owing to their lack of specificity. As Gould pointed out, the original HDAC inhibitors relied on a very nonspecific warhead on the molecule to achieve their inhibition. “What we’ve learned over the last few years is that you can make exquisitely selective inhibitors for the histone methyltransferases,” he said.

Gould also believed that the safety and efficacy issues associated with the HDACs were due to the lack of early genomic evidence linking HDACs to cancer. “The bounty of information currently available on HMTs renders this point moot,” he said.

Advantages of HMTs

One of the advantages, as presented by Gould, is that “there’s clear genomic evidence which show that translocations, point mutations, overexpression, and gene duplications of HMT family members really are drivers of many cancers.” Being as “we know that these enzymes are driving many cancers, we can specifically target these diseases,” he said.

Furthermore, histone methyltransferases are an extensive family. According to Gould, there are 96 proteins within the human genome that may potentially be histone methyltransferases. In comparison, the human genome only encodes 18 HDACs. Such a large family gives researchers the ability to create extremely specific inhibitors.

The project focuses on cells from the blood, brain, breast, and human embryonic stem cells that may be relevant to complex disease states such as cancer. “The information that is coming from the epigenome mapping and it’s linkage to certain disease states immediately presents us with the candidate biomarkers to use,” said Costello. “We can then move our capital to the projects that are most likely to succeed.” By better understanding the molecular underpinning driving the cancer, researchers can then develop novel therapeutics based on relevant data.

**The Holy Grail**

Gould believes that epigenetics, in general, and the epigenome mapping project, in particular, will facilitate patient recruitment and stratification, thereby preventing researchers and companies from expending capital on treatments that will likely fail during clinical trials.

“The Holy Grail in epigenetics is to pursue very specific targets for which we already have a clear pharmacodynamic linkage, a clear cellular effect, and a clear way of measuring that effect,” said Gould. This will have both benefits and drawbacks for the oncology industry. Spending extra time searching for a viable target through preclinical research will inevitably slow down the drug development process.

“The good news from an investment perspective is that the probability of success in the clinic should be higher,” said Costello. “I think the success of this field will depend on how well it chooses the targets.”

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