Epizyme: Plying the Epigenome's Enzymes

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Since the human genome was published 10 years ago, the hunt has been on in industry and academia to find the genetic basis for human disease. The genome includes the DNA sequence, the strings of nucleic acids coding our genetic inheritance. But over the years, researchers started looking at another layer of heritable influence, the epigenome that acts by controlling pathways involved turning genes on and off. And a small company based in Cambridge, MA, is hoping they'll be the one—or at least one of the companies—to find commercial success in developing new drugs for cancer based on new targets of the epigenome.

Epizyme got its start in mid 2008 and is among the first biotechnology companies with its sole focus on exploiting epigenetic discoveries to develop new medicines. Broadly, epigenetics involves a series of changes involving chemical modifications to the cell's chromatin, the DNA and related proteins found in the nucleus of each cell. These modifications do not alter the underlying DNA sequence. Instead, they act on controlling gene transcription, or the process of whether a gene is activated or suppressed. Epizyme's goal is to find ways that influence gene transcription control.

In 2007, Epizyme's founders, Nobel Laureate Robert Horvitz of MIT and Yi Zhang of the University of North Carolina, advised Epizyme's potential investors into taking the new epigenetic biology forward into a company focused on epigenetic enzymes. In particular, Zhang's academic work was instrumental in identifying specific chromatin-modifying enzymes that appeared to be playing driving roles in human diseases.

Today, Epizyme employs about 30 people in R&D, including five medicinal chemists. Their total headcount stands at 36 and is expected to reach 45–50 by year's end.

Targeting Histone Methytransferases

In a 2009 review article, Epizyme researchers summarized the universe of enzymatic epigenetic modifiers to include DNA methyltransferases (DNMTs), which methylate the carbon atom at the 5-position of cytosine in the CpG dinucleotide sites of the genome; protein methyltransferases (PMTs), which methylate lysine or arginine residues on histones and other proteins; protein demethylases, which remove methyl groups from the lysine or arginine residues of proteins; histone acetyltransferases, which acetylate lysine residues on histones and other proteins; histone deacetylases (HDACs), which remove acetyl groups from lysine residues on histones and other proteins; ubiquitin ligases, which add ubiquitin to lysine residues on histones and other proteins; and specific kinases that phosphorylate serine residues on histones (Copeland et al., 2009).

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Other companies are already out in front developing and marketing small-molecule inhibitors against HDACs (vorinostat, romidepsin) and DNMTs (azacitadine, decitabine). Epizyme's strategy is to focus on the "HMTome"—the collection of the body's histone methytransferase (HMT) enzymes. "We believe that the epigenetic enzymes, in particular the HMTs, afford a valuable pharmacological basis for intervening in aberrant gene transcription," explains Robert Copeland, Ph.D., Epizyme's chief scientific officer.

For those individuals in the future found to have disease involving abnormal methylation, targeted HMT inhibition might provide a highly effective route to correcting abnormal gene function. "Targeting HMTs is a way to develop personally targeted medicines that are defined by specific genetic alterations," adds Copeland.

HMTs are a very large family of enzymes with an estimated 96 individual types found in the human genome. Epizyme has chosen to begin its HMT mining starting with HMTs that are genetically altered in specific patient populations, like cancer.

Using publicly available genomic databases, including the Cancer Genome Atlas database, and the insight of academic collaborators, Epizyme is looking for genetic alterations in HMTs, such as gene amplification, specific point mutations, or mutations in associated proteins or pathways. "We are looking for situations in which a specific cancer is being driven by a genetic alteration in a specific HMT or in the pathway that is impacted by an HMT," says Copeland. "We are doing this so that we can identify patients that we know are likely to benefit from a specific therapy and then develop a small molecules to address that need."

Of the 96 known human HMTs, Epizyme's lead drug discovery efforts target DOT1L and EZH2. In a recent report, Epizyme researchers described an EZH2 point mutations among a subset of NHL patients (Sneeringer et al., 2010). They found that patients with disease had a combination of mutant enzyme and wild-type enzyme that led to disease. "The two in concert is what causes the disease," says Copeland. "We believe this is the first example of a human disease in which there is a required coupling of a wild-type and mutant enzyme. We have been able to translate that finding into an EZH2 drug discovery effort." Similarly, in cancer, DOT1L activity has been identified in a certain type of leukemia called mixed lineage leukemia.

But the company is not solely investigating DOT1L and EZH2. Their platform technology includes a universal mechanism for assaying HMT targets. "With

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that knowledge, we have been able to put in place a cross-screening panel where today we have 14 of the 96 human HMTs in a panel with robust biochemical pathways," explains Copeland. "That allows us to take every compound we create and test it against every enzyme." Using this technique, the company claims to have discovered potent and selective inhibitors for 12 of the 14 enzymes so far.

New Biology, New Challenges, Lots of Anticipation

Epizyme will face the common hurdles of translating inhibitors of a target into therapeutically valuable entities, including pharmacokinetic properties and all of the things that make a compound usable as a medicine in people. Before that, they face the additional burden of proving in vivo efficacy in animal models for an unprecedented target. Though not yet published, the company does claim to have in vivo proof of concept data backing up its approach.

"Targeting the epigenome has already been done successfully," explains Jean-Pierre Issa, Co-Director of the Center for Cancer Epigenetics, Professor in the Department of Leukemia, and Chief of Translational Research at MD Anderson Cancer Center, who has conducted clinical trials of the HDACs and DNMTs. "I would be excited about clinical trials of the next generation of those drugs."

But he cautions against haste. "In general, people have some concerns regarding the specificity of epigenetic targeting. The next-generation drugs are looking at a narrow target, like a particular HMT. Even this may be nonspecific since HMTs may have a lot of downstream effects we are not always aware of," he says. "It is theoretically possible that it's not a good idea to reactivate those genes. This has been the issue that has plagued epigenetics for a while."

Issa adds that recent history with epigenetic agents has been mixed. "Those in the field have been very worried because much of the drugs that have been available so far really target the whole genome and don't do anything specifically for cancer," he says. "Although this approach really has worked and many drugs are FDA approved, there are concerns that the nonspecificity may perhaps in some cases promote tumors and limit how long we can give these drugs in cancer prevention, and so on." He hopes this concern will be allayed by the next generation of drugs.

Perhaps the real promise in epigenetics has been afforded by discoveries fueled by next-generation DNA sequencing, which has greatly increased the availability of genomic information. "We have known for a while that mutant genes, particularly active mutating genes, are great targets for drug development—they indicate Achilles heels of tumors and provide markers for who to treat and so on," adds Issa. "With our understanding from next-gen sequencing, it turns out there are more mutations in epigenetic regulators than any other class of proteins in cancer. This has really heightened interest in these targeted drugs."

Partners with Big Pharma

Big pharma has certainly noticed the promise of epigenetics and Epizyme, in particular. In January 2011, GlaxoSmithKline (GSK) formed a partnership with Epizyme worth potentially up to $630 million. The deal charges Epizyme with identifying an unstated number of specific targets, excluding DOT1L and EZH2, and identifying small-molecule HMT inhibitors that are pharmacologically tractable for clinical use. "This is obviously a significant opportunity for Epizyme," says Copeland, who is a former vice president in the cancer biology program at GSK.

In March 2011, Epizyme made an alliance with Japanese health care products company Eisai Co., Ltd, focusing solely on the EZH2 target for cancer therapeutics. Eisai will provide up to $200 million to Epizyme based on progress in developing new treatments for lymphoma and other cancers in genetically defined patients.

Epizyme's small molecule collection numbers > 6,000—its first steps toward its vision of translating epigenetic science into the next generation of personalized medicine.

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