Denise Myshko

NEW SCIENCE MEANS NEW WAYS TO TARGET DISEASE

Epigenetics — the study of changes in gene expression — is rapidly emerging as a field that presents tremendous opportunity for drug discovery.

We are on the edge of a new biology. It turns out that our genes are just part of the story about what makes us who we are. Much has been learned over the last decade about how the expression of genes can impact disease. Now researchers are studying how the environment impacts when genes are turned on or off. This science — epigenetics — is leading to a new understanding of biology and to new targets for new drugs.

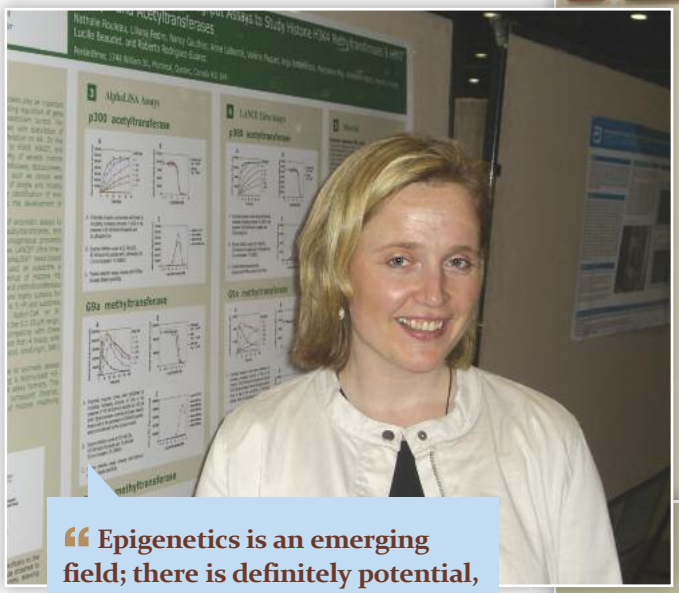
One source calls epigenetics a rapidly growing research field that investigates heritable alterations in gene expression caused by mechanisms other than changes in DNA sequence. The name epi-, which in Greek means over or above, and genetics sums up the approach scientists are taking to transform science.

"The concept around epigenetics is that cells respond to their environment and this changes the genes they express," says Kevin Lee, Ph.D., head of the Epinova discovery performance epigenetics unit at GlaxoSmithKline. "This happens in such a way that can be passed on to future cell generations and can become heritable."

While this discipline is still in its infancy, Dr. Lee says the field of epigenetics has the potential to be transformative and could change how patients are diagnosed and treated in the future.

"The mechanisms can profoundly change pivotal pathways in regulating cell function, and there is good evidence that these are the pathways that can go wrong in oncology and other diseases," he says.

Epigenetic mechanisms are involved in the development of cells and cell differentiation; when that regulation goes wrong, this can lead



> "Epigenetics is an emerging field; there is definitely potential, especially from a cancer perspective, to revolutionize the treatment of disease."
>
> **SARA HOWLAND** / PerkinElmer

> "The opportunity for epigenetics lies in making personalized therapeutics for genetically defined patients."
>
> **DR. ROBERT GOULD** / Epizyme

> "Epigenetics has the potential to address patient resistance to many of the drugs that are already on the market."
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> **DR. JOANNA HOROBIN** / Syndax

to disease, says Sara Howland, product portfolio director, drug discovery reagents within biodiscovery at PerkinElmer.

"Much of the research in the last 10 years has been focused on understanding how certain DNA or protein modifications are implicated in diseases, such as cancer," she says.

For the biopharmaceutical industry, the area of epigenetic research presents an opportunity within drug discovery, and experts say this research has the potential to open up a whole new set of drug targets implicated in many different diseases.

Joanna Horobin, M.D., president and CEO of Syndax Pharmaceuticals, says in oncology, epigenetic changes in cells are associated with many tumors.

"If tumor suppressor genes are silenced, those cells will grow in an uncontrolled way," she says. "One of the major causes of this type of silencing is the methylation of those genes. These are epigenetic changes."

Rajesh Chopra, Ph.D., VP, translational and early drug development at Celgene, says epigenetics is an exciting opportunity that will allow researchers to look at the fundamental pathways that lead to the development of cancers.

"If these changes can create a fundamental pathway, then targeting the different enzymes that alter how genes are expressed in cancer becomes very important," he says. "In addition, there is the potential to develop combination therapies, which is where the future in drug development for oncology lies."

Dr. Horobin says epigenetics presents a way of addressing resistance for many of the drugs that are already on the market.

"Our particular programs are looking to overcome epigenetic causes of drug resistance in breast and lung cancers," Dr. Horobin says. "We think there is a big opportunity to use this class of drugs to overcome resistance. We also believe there are specific other situations where epigenetic changes in tumors are the oncogenic drivers for those tumors. In these cases, this class of drugs can be used for specific indications. This is likely to be a major approach for oncology in the coming 10 years."

Dr. Horobin says this also provides an opportunity to understand the patient populations for whom these strategies are going to be appropriate.

"We're at the tip of the iceberg in understanding exactly the best ways to use these epi-

> **“Understanding the key pathways and the way enzymes alter cancers and other diseases will transform therapies.”**
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> **DR. RAJESH CHOPRA** / Celgene

genetic agents,” she says. “In the next five to 10 years, we will see a true understanding of which drugs will work for which patients.”

Market Opportunities

Thus far, research in epigenetics has been focused in the area of cancer, but companies are now starting to look at other areas. GlaxoSmithKline, for example, has two epigenetic units, one in cancer and one in immunoinflammation.

Several products are already on the market that address epigenetic changes of cells: Dacogen (decitabine) from Eisai for MDS, a group of bone marrow diseases; Vidaza (azacitidine) and Istodax (romidepsin) for cutaneous T-cell lymphoma (CTCL), both from Celgene; and Zolinza (vorinostat) from Merck, for CTCL. These products fall into two categories that are thought to function by turning on certain genes: for example, tumor suppressor genes.

About 40 epigenetic drugs are under development by more than a dozen biotechnology companies, according to a June 2010 report by Insight Pharma Reports. These drugs focus mainly on the treatment of cancers and neurodegenerative and infectious diseases, although research is under way to explore the role of epigenetics in cardiovascular, metabolic, ocular, and other diseases.

Robert Gould, Ph.D., president and CEO of Epizyme, says epigenetics can create opportunities in rare genetically defined populations.

“A company such as Epizyme can target well-defined patient populations and have an opportunity to make a difference in these diseases,” he says. “Learning that we can inhibit epigenetic enzymes safely has been a great breakthrough. We’ve found that we can treat certain cancers in animals without affecting the animals themselves. One of the biggest uncertainties was knowing if inhibiting epigenetic enzymes would prove to be a safe mechanism.”

Dr. Lee says epigenetics is an exciting research area but its novelty is also extremely challenging.

“Our understanding of these pathways is growing exponentially, but we still have a fairly immature appreciation for these mechanisms,” Dr. Lee says. “At the moment, even in oncology, there is a whole area of biology that has been underexplored. That’s why I think it’s important that there be a great deal of collaboration between industry and academia.”

Dr. Lee says one example of this type of collaboration is the Structural Genomics Consortium, which is a public-private partnership where industry provides chemistry solutions and academia provides access to biology, biological reagents, and assays. GlaxoSmithKline, Pfizer, Merck, and Novartis have teamed up with the University of Oxford, the University of Toronto, and Karolinska Institutet in Stockholm to determine 3D structures of proteins of biomedical importance and proteins that represent potential drug targets. The collaboration is committed to open access and will place any results from the research in the public domain with no patent protection.

“Understanding the precise role of these complicated pathways in tumors is a big challenge,” Dr. Chopra says. “A target can be very tumor-specific. For example, the EZH2 gene, which has been shown to cause cancer in epithelial tumors, also has been shown to be a tumor suppressor in blood cancers.”

Dr. Chopra says the key challenge of the next five years will be defining which of the epigenetic targets are the major players in diseases.

“This a new and unknown area of research,” he says. “Histone deacetylases and DNA methyltranferase inhibitors are the first generation of epigenetic drugs. Although they have been around for decades, they were largely developed for this purpose over the last few years. Understanding the key pathways and the way these enzymes are altering cancers and other diseases will transform future therapies.” PV

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EXPERTS

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Selected EPIGENETIC Programs

Several companies are actively working in the epigenetics space. The following are selected samples of the work being done.

Celgene

Celgene has two of the four epigenetic drugs on the market: Vidaza (azacitidine) and Istodax (romidepsin) for the treatment of cutaneous T-cell lymphoma (CTCL). An oral form of Vidaza is in Phase II trials. Vidaza is currently given subcutaneously, a route of administration that can be uncomfortable for patients.

"In addition, the subcutaneous route can produce a level of toxicity, which can lead to interruption of the dosage," says Rajesh Chopra, Ph.D., VP of translational and early drug development at Celgene. "By having an oral formulation, we can make administration to patients much simpler. Also, an oral verison will allow the drug to be taken more continuously with fewer dose interruptions, and that increases the therapeutic value of the drug."

Dr. Chopra says the company anticipates filing registration for the oral version of Vidaza within two to three years.

Celgene is also studying about a dozen targets in preclinical research for oncology and inflammatory diseases.

"There is a lot of excitement in the field because a mutation in the metabolism pathway has been identified, this is called IDH1 and IDH2, or isocitrate dihydrogenase," he says. "These mutations are found in a large number of glioblastomas and leukemias. The exciting thing about this discovery is that mutations in IDH1 and IDH2 genes, as well as another gene called PEP2, actually alter methylation of DNA in both leukemia and glioblastoma. We now know there is a link between epigenetics and cancer mutations and this raises an opportunity to combine inhibitors of these enzymes, which are mutated, as well as epigenetic drugs to have a rational way of dealing with glioblastoma and leukemia."

Celgene has an agreement with Agios in this area.

Epizyme

Epizyme is researching small molecule histone methyltransferase (HMT) inhibitors, a new class of personalized therapeutics for the treatment of genetically defined cancer patients based on breakthroughs in the field of epigenetics. Genetic alterations in the HMTs are strongly associated with the underlying causes of multiple human diseases, including cancer.

"When it comes to cancer, there are often environmental effects that lead to a change in cell growth," says Robert Gould, Ph.D., president and CEO of Epizyme. "Some of these changes are in a family of enzymes called histone methyltransferases (HMTs), and the changes are enough to make the subset of cells that have had this change grow uncontrollably, which might lead to leukemia or lymphoma." He says one of Epizyme's programs, called DOT1L, addresses an acute form of leukemia. DOT1L is associated with a form of leukemia called MLL-rearranged leukemia. This results in the increased expression of specific genes that are known to drive leukemia cell proliferation. The company's DOT1L small molecule inhibitors selectively kill MLL cells, while sparing cells that do not contain this chromosomal alteration.

"This disease comes in infant, childhood, and adult forms, all of which can be devastating because these patients, including children under 5 years of age, usually die within a year or two of getting leukemia," Dr. Gould says. "There are few effective therapies, but sometimes an entire bone marrow stem cell transplant can help."

In March 2011, Epizyme partnered with Eisai to discover, develop, and commercialize therapeutics targeting EZH2, an epigenetic enzyme, for the treatment of lymphoma and other cancers in genetically defined patients.

"There is a change in the enzyme EZH2 that causes a subset of lymphoma," Mr. Gould says. "We think by inhibiting the enzyme that caused the uncontrolled growth of these enzymes, there is a real opportunity to make a difference in people's lives."

Epizyme also has a partnership with GlaxoSmithKline to discover, develop, and market novel small molecule therapeutics targeting HMTs.

GlaxoSmithKline

GlaxoSmithKline has two epigenetic units, one in cancer and one in immuno-inflammation.

"Several years ago, we did an extensive analysis to identify new areas of research that would be attractive and potentially transformative," says Kevin Lee, Ph.D., head of the Epinova discovery performance epigenetics unit (DPU) at GlaxoSmithKline. "This led to the formation of two discovery performance units, or DPUs. We have a DPU focused solely on oncology epigenetics. My group, which we call Epinova, is focused primarily on immuno-inflammation, and we will collaboratively explore other areas depending on where the science makes sense."

"One of the fundamental principles within our group is partnership and collaboration," Dr. Lee adds. "We have a range of academic and commercial collaborations. We have one with Rockefeller University, for example."

The company is looking at the role of bromodomains in macrophage function, control of the immune response, and the particular molecules that would have applicability for the spectrum of autoimmune diseases.

A paper last year in Nature published results that showed the first demonstration that this family of proteins could be impacted by a drug.

"From a scientific perspective, that is novel," Dr. Lee says. "The impact on immune response is significant, and these molecules don't block macrophage production. They only target a specific gene set that is in a specific epigenetic state. In a macrophage, it's well-known that certain genes are primary response genes and are rapidly switched on when encountered with a foreign object. We are now

beginning to understand how this happens, and we can also identify the actual epigenetic marks that define these gene sets."

GlaxoSmithKline is also working on histone demethylases, which may have a role in immune function.

Syndax Pharmaceuticals

Syndax is employing epigenetics to overcome the problem of resistance with oncology treatments. The company's lead program is entinostat, an oral histone deacetylase (HDAC) inhibitor.

Entinostat is being studied in advanced breast cancer in combination with aromatase inhibitors. The company recently completed a randomized, placebo-controlled Phase II trial for this indication.

Entinostat also is being studied in various cancers, including advanced non-small-cell lung cancer and advanced colorectal cancer in combination with azacitidine. Syndax has several studies ongoing under a cooperative research and development agreement with the National Cancer Institute.

Research has shown that HDACs are involved in the expression of various genes, such as the estrogen receptor, that regulate cell growth, differentiation, and apoptosis.

Such genes are frequently silenced in cancer cells through the overexpression of enzymes including HDACs. Studies have demonstrated that HDAC inhibition can significantly enhance anticancer activity when used in combination with a broad range of anticancer agents.

"We are using entinostat to take advantage of the fundamental science of epigenetics," says Joanna Horobin, M.D., president and CEO of Syndax. "Epigenetic changes in tumors are the cause of drug resistance against many of the classes of agents we already use. What's exciting is how this technology could reverse resistance."

She says the company expects to begin a Phase III program in breast cancer early next year, with a filing date in 2015. PV