Executive Summary

Epigenetics is one of the fastest-growing areas of the biological sciences, with the number of peer-reviewed research articles being published increasing practically exponentially. Biologists are recognizing that to understand human health and disease, they need to know more than the DNA sequence of any genes. Equally, if not more, important, they need to know how cells use the information encoded in the genome. That information is essentially stagnant if a gene lies dormant.

What turns genes on and off, and under what circumstances? That is what epigenetics is all about: how genomic information encoded in the DNA sequence is regulated by various nonDNA-sequence control factors. The science and technology of epigenetics are aimed at understanding and, ultimately, manipulating the various chemical and physical chromatin modifications that control gene expression.

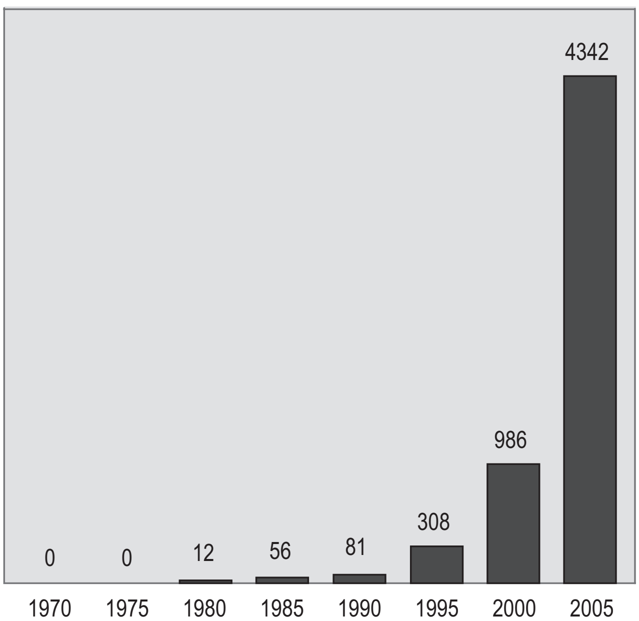
This report focuses on the 2 major types of epigenetic control factors:

- DNA methylation patterns formed by the presence of methyl molecules ($-CH_3$) attached to CpG dinucleotides along the entire length of the DNA double helix
- Various covalent modifications to the histone proteins around which the DNA helix is wound

Much more is known about the former, mostly because scientists have been studying DNA methylation much longer than they have any other type of epigenetic control mechanism. Recently, however, there has been a surge of interest and investment in the study of histone modifications. Scientists recognize various other types of epigenetic control factors as well, including other nonhistone proteins also involved in chromatin structure and noncoding RNA molecules. There hasn't been much interest, however—least of all commercial interest—in nonhistone proteins, and the small RNA world is generally considered a separate sector of the life sciences industry (mostly out of convention, although, as discussed in Chapter 2 of this report, some company epigenetic divisions are beginning to explore noncoding RNA applications). Researchers and companies are also beginning to appreciate and exploit the synergistic interactions that naturally occur among the different types of epigenetic control pathways.

While scientists have known about epigenetic phenomena for decades, interest in the field has exploded over the past decade—not just because it provides a new lens for analyzing and understanding the molecular etiology of human disease, but because the new knowledge, and the technologies stemming from that knowledge, could dramatically improve our ability to prevent and treat a wide range of human diseases.

The Rising Popularity of Epigenetics in the Scientific World



Source: Insight Pharma Reports, based on a survey of articles listed in PubMed

Concentration, to Now, in Oncology

Much, if not most, of the basic biomedical research in epigenetics conducted thus far, and almost all the clinical applications stemming from that research to date, are in the field of oncology. In fact, it was the connection between cancer and aberrant DNA methylation—a discovery made in the early 1980s—that served as one of the initial major drivers of the field, stirring both academic and pharmaceutical interest. Initially there was considerable skepticism about any possible epigenetic etiology to cancer, but a still-mounting body of evidence has washed away disbelief. Many cancers have been associated with hypermethylation of tumor suppressor genes; generally, the presence of too many methyl molecules (hypermethylation) results in gene silencing, and too few (hypomethylation) to gene activation.

Today, the notion that cancers are epigenetic diseases is so well established that the conventional mutational model of cancer—that cancer is caused by DNA mutations—has since been replaced with an epigenetic model. That cancer is an epigenetic disease doesn't mean that DNA mutations do not play a key role in pathogenesis. They do. It simply means that there are other components of the cellular machinery that must be considered. Not only do scientists today recognize the epigenetic etiology of cancer, they are increasingly discovering epigenetic etiologies underlying a wide range of human health disorders, from Alzheimer's disease to infertility.

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Diagnostics and Therapeutics

While the potential medium- to long-term commercial applications of epigenetic knowledge and technology are varied, with one of the more exciting distant applications being stem cell medicine, there are 2 major immediate applications already on the market or expected to be on the market within the next 1 to 5 years:

- *Diagnostic:* Since most disease-associated epigenetic changes appear to occur early during the progression of disease, the strength of epigenetic biomarkers lies partly in their capacity to serve as *early* indications of disease, when prognosis is good.

- *Therapeutics:* The strength of epigenetic therapy is in its targeted approach. By intervening more discreetly with molecular pathways instead of going for the whole-cell kill, as conventional chemotherapy does, epigenetic drugs promise a safer, more effective way to manage cancer.

Both the diagnostic and therapeutic markets are in their infancy. In fact, profits from the diagnostic market are practically negligible to date. While many labs worldwide offer homebrew DNA methylation diagnostic services for a few rare diseases, there is not a single regulated test on the market. The first regulated tests will be introduced into US or European reference laboratories sometime during 2008. They include OncoMethylome's tissue-based and urine-based early diagnostic tests for prostate cancer (in partnership with Veridex) and stool-based colorectal screening test (in partnership with EXACT) and Epigenomics' blood-based early detection colorectal test (in partnership with Abbott) and tissue-based prostate molecular classification assay.

Once launched, the diagnostic sector of the industry is expected to experience a dramatic growth phase over the next 1 to 5 years, driven in part by continuing advances in epigenetic science (e.g., biomarker discovery) and technology (e.g., the development of better, clinically useful biomarker assays).

With 3 epigenetic-based FDA-approved drugs already on the market—2 demethylating agents and 1 HDAC inhibitor—the therapeutic sector of epigenetics dominates the market landscape with approximately $300 million in annual global sales and a compound annual growth rate of about 60%. Most of the buzz today is around the recent US Food and Drug Administration (FDA) approval of the first histone deacetylase (HDAC) inhibitor, Merck's Zolinza (vorinostat), in October 2006, for the treatment of cutaneous T-cell lymphoma. Several companies have additional lead HDAC inhibitors in pivotal clinical trials.

Not surprisingly, all epigenetic products currently on the market and almost all late-stage epigenetic products in development are cancer-related.

This report provides an overview of the scientific and technological landscape from which both the diagnostic and therapeutic sectors of the nascent "epigenetics industry" are emerging, plus a qualitative analysis of the scientific, technological, and commercial achievements and challenges facing both sectors. Although both sectors hold forth tremendous hope for the future of cancer care as well as other types of human health care, both are faced with serious challenges. Key among these is the malleable nature of epigenetic phenomena. For example, one of the reasons demethylating agents are effective is the reversible nature of DNA methylation. Methyl molecules come and go over time, as the cell demands, disease sets in or, as is the case here, demethylating agents intervene. But what happens when the demethylating agent is removed? Will those tumor suppressor genes, which had been reactivated through drug therapy, become suppressed again?

A key, related challenge for the diagnostic sector is clinical validation. In December 2006 Roche ended a 4-year collaboration with Epigenomics for the commercialization of one of the latter company's lead diagnostic biomarker assays, because clinical test results were not up to par. Epigenomics has since optimized the assay and secured a new commercialization partnership with Abbott Laboratories.

Research Tools for Epigenetics

Although the focus of the report is on diagnostics and therapeutics, sections of the report also touch on the research tools sector of the epigenetic marketplace. It would be naïve not to do so, given that the industry is so young and that there is so much concentrated activity around discovery. Currently, with estimated annual global sales of about $100 million, the research tools sector of the epigenetics market space is obviously much more profitable than the diagnostic sector today. But again, when the diagnostic sector emerges, sometime within the next 1 to 5 years, its growth and profits will rapidly outpace the steady but moderate growth of the research tools market.

Much of the current excitement in the research tools area is with the recently introduced high-throughput sequencing platforms and their combined use with chromatin immunoprecipitation (ChIP), in a process known as ChIP-Seq. ChIP-Seq is designed for genomewide analysis of histones and other chromatin proteins. The excitement that ChIP-Seq has elicited in the epigenetics R&D realm is another indication of an expanding industry, less focused on DNA methylation and more interested and *capable* of exploiting other types of epigenetic control factors.