

Executive Summary

Researchers have known for many years that inheritable changes can occur in cells that do not involve changes in the DNA sequence within those cells. These changes are referred to as epigenetic changes, as opposed to genetic changes in the DNA sequence of the cell. Epigenetics is now a rapidly emerging field. Diagnostic tests that detect epigenetic changes in a cell have reached the market, and four epigenetic drugs are now FDA-approved. In addition to the diagnostic companies in this field, over 40 pharmaceutical and biopharmaceutical companies are active in the field of epigenetics.

The first mechanism of epigenetics to be widely studied was DNA methylation. Two of the FDA-approved epigenetic drugs are demethylating agents, and most of the diagnostic activity to date in epigenetics has focused on methylation markers. A second major epigenetic mechanism is modification of histones. Many different enzymes can modify histones, including histone deacetylases (HDACs), histone methyltransferases, and others. Chapter 2 of this report presents an overview of epigenetics, its mechanisms, diagnostic methods to detect changes in DNA methylation, and epigenetic targets of pharmaceutical and biopharmaceutical companies.

Within the diagnostics segment of epigenetics, most of the focus has been on detection of changes in DNA methylation. The number of companies developing methods to detect methylation changes has not changed significantly in recent years. Three companies (Epigenomics, OncoMethylome Sciences, and Orion Genomics) are now active in this field. They are being joined by reference laboratories that have licensed their technology to develop Laboratory-Developed Tests (LDTs) and by certain diagnostic companies that are entering the field through agreements with epigenetic diagnostic companies. In addition, one early-stage company is focusing on histone modification patterns. The activities of these diagnostic companies are discussed in Chapter 3. Considerable progress has been made. Two CE-marked tests for colorectal cancer screening are available in Europe (and one of these tests is also available in Asia). Both tests detect the *Septin9* DNA methylation biomarker, which was developed by Epigenomics. Epigenomics has completed a large prospective clinical study validating this biomarker. Within the United States, in terms of LDTs, LabCorp and Quest Diagnostics offer competing tests for colorectal cancer screening. These are LabCorp's ColoSure (which utilizes OncoMethylome's DNA methylation detection technology) and Quest Diagnostics' ColoVantage, which uses technology licensed from Epigenomics. LabCorp has two additional tests that are available today. ARUP Laboratories has entered this market more recently.

Considerable activity and interest is focused on the therapeutic segment of the epigenetic field. The first epigenetic drugs to reach the market target hematological cancers. Within the hematological market, the currently approved indications for these epigenetic drugs represent fairly small markets. The two DNA hypomethylation agents [Celgene's Vidaza (azacitidine) and Eisai's Dacogen (decitabine)] are both FDA-approved for treatment of myelodysplastic syndromes (MDS), while the two FDA-approved HDAC inhibitors [Merck's Zolinza (vorinostat) and Celgene's Istodax (romidepsin)] are indicated for treatment of cutaneous T-cell lymphoma (CTCL). Istodax, which was approved in late 2009, was launched onto the US market in 2010. However, it is expected that epigenetic drugs may prove to be useful for treatment of a wide range of diseases including hematological cancers, solid tumors, and other non-cancer indications. Major disease indications that are being targeted by companies developing epigenetic-based drugs are discussed in Chapter 4.

The potential therapeutic applications of epigenetics have attracted a large and growing number of pharmaceutical and biopharmaceutical companies. Over 40 companies that are now active in this field are included in this report. These include large pharmaceutical companies, emerging new companies, and a range of companies that fall in between. Despite the current challenging economic conditions, some of the companies in the epigenetics field have been able to attract venture capital investments. Examples of epigenetic therapeutic companies that received venture capital investments in 2009 or 2010 include Acetylon Pharmaceuticals, Chroma Therapeutics, and Epizyme. Other venture capital-funded companies in epigenetics include Constellation Pharmaceuticals and Syndax Pharmaceuticals. Some epigenetic companies have also been able to raise money by entering into partnerships with other companies. These and other companies are included in the more than 40 companies discussed in Chapter 5. The first epigenetic drugs focused on inhibiting DNA methylation (*e.g.*, Celgene's Vidaza and Eisai's Dacogen). Johnson & Johnson has marketing rights for Dacogen outside of North America. Both these agents are analogs of the pyrimidine nucleoside cytosine and must be incorporated into the DNA in order to inhibit the DNA methyltransferase enzyme. Much of the current activity in epigenetic therapy is focused on HDAC inhibitors (such as Merck's Zolinza and Celgene's Istodax). Many companies are developing novel HDAC inhibitors, as discussed in Chapter 5. Table 5.2 presents over 30 companies developing almost 40 HDAC inhibitor compounds or programs. Thus, HDAC inhibitors have become a crowded, competitive field. As a result, a number of companies that are interested in epigenetics are now developing potential new therapies targeted against novel epigenetic targets.

Chapter 6 discusses business considerations for diagnostic and therapeutic companies working within the field of epigenetics. Since these are relatively new commercial fields, the current markets are small but there is significant opportunity. As with all emerging and rapidly changing fields, companies participating in epigenetics face a number of strategic issues. Diagnostic companies face challenges such as identification and validation of biomarkers, strategic issues relating to delivery of tests to the market, and various issues that affect market penetration. Therapeutic companies face issues related to concerns that epigenetic drugs may have broad activities that could result in safety issues, competition in the crowded HDAC inhibitor field, development of therapies that are directed against completely novel targets, and others. The epigenetics market is evolving and these changes, in addition to many of the corporate agreements that have been made within the therapeutic epigenetic field, are also examined.

The final chapter, Chapter 7, consists of interviews with experts at ten therapeutic companies and three diagnostic companies that are active in the field of epigenetics. These experts discuss their own companies' activities, the overall field of epigenetics, and many of the challenges and issues that companies in this field are facing.

