Epigenetics R&D Pipeline

Histone Deacetylases (HDACs) Offer the Most Promising Targets and Outnumber Other Classes of Epigenetic Targets
GBI Research Report Guidance

- Chapter three gives an insight into epigenetics, epigenetic enzymes, and the currently marketed drugs.
- Chapter four explains the therapeutic applications of epigenetics, with their role in cancers, Central Nervous System (CNS) disorders, aging, diabetes and obesity.
- Chapter five covers the epigenetic mechanisms or targets, and new druggable targets in addition to the existing validated targets.
- Chapter six discusses the marketed products, namely Vidaza, Dacogen, Istodax and Zolinza.
- Chapter seven analyzes the current epigenetic R&D product pipeline by stage of development, indication and mechanism of actions of the molecules under investigation.
- Chapter eight discusses the challenges, trends and opportunities in the field of epigenetics.
- Chapter nine covers the leading players in epigenetics research.
- Chapter 10 covers strategic consolidations and lists the M&A deals, licensing and co-development deals that have taken place in the last five years.
Executive Summary

Epigenetics refers to a regulatory system that selectively regulates gene expression in different cells without actually affecting the genomic makeup of the Deoxyribonucleic Acid (DNA) sequence. Epigenetics is emerging as a key determinant of cellular differentiation, and epigenetic regulation of gene expression has been seen to play a vital role in a number of human diseases.

The last a few years have seen a surge of research into epigenetic modification of the chromatin within a cell’s genome. Epigenetic changes appear to regulate differentiation of stem cells as well as giving rise to malignant cells. Much of the research has focused on enzymatic reactions involving deacetylation of histone, especially in Histone Deacetylases (HDAC). Toxicity and lack of selectivity are the most important issues with first-generation drugs, and resolving them is the main challenge in dealing with epigenetics.

The enormous potential of epigenetics, both from a therapeutic and business point of view, has attracted substantial interest from academia, investors, and pharmaceutical and biotechnology companies. The four marketed epigenetic-based drugs, Zolinza (vorinostat), Istodax (romidepsin), Dacogen (decitabine) and Vidaza (azacitidine), have shown therapeutic potential and paved the way for the development of second-generation epigenetic-based therapies. Epigenetics has been one of the most widely studied areas in recent years and has emerged as a promising focus in drug discovery. In addition to cancer, epigenetic changes play an important role in indications such as neurodegenerative diseases and metabolic disorders. Its therapeutic application in myriad disease conditions will make it a highly promising area of research in the future.

Histone Deacetylases Offers Strong Clinical Potential

Analysis of the product pipeline reveals that HDAC is the main area of interest in epigenetic research. In 2011, more clinical trials were being conducted for HDAC inhibitors than for any other epigenetic target. The following figure shows the proportion of R&D programs targeting HDAC, DNA Methyltransferase (DNMT), HMT (Histone Methyltransferase), a combination of DNMT and HDAC, and others.

Source: GBI Research
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2 Introduction

In a broad sense, epigenetics can be referred to as the study of pathways and/or mechanisms which initiate and maintain the heritable pattern of gene expression without altering Deoxyribonucleic Acid (DNA) sequence. Epigenetic information can pass from one cell to another, however, the epigenetic mark, by interacting with environmental factors, can change through life and are reversible.
The large pool of published data shows that epigenetic changes have the potential to target any disease area from cancer to CNS disorders, as well as many rare indications. Epigenetic enzymes have been successfully validated as druggable targets and there are approved epigenetic-based therapies available for the treatment of certain types of cancers.

Analysis of current R&D activities reveals that oncology is the main focus of epigenetic research. Of all R&D programs, XX% target various types of cancer, which was followed by hematological disorders (XX%) and CNS disorder (XX%). ‘Other’ accounts for XX% of R&D programs, comprising immunology, and infectious and musculoskeletal diseases.

Although cancer is the main area of interest, other therapy areas are also being studied extensively. Inhibitors of epigenetic enzymes have already shown beneficial therapeutic effects in in vivo and in vitro experiments and some of these small molecules such as EVP-XX from EnVivo Pharmaceuticals have reached clinical trials.
11 Epigenetics R&D Pipeline – Appendix

11.1 Market Definitions

Epigenetics: A branch of biology that studies the causal interactions between genes and their products which bring the phenotype into being.

11.2 Abbreviations

- AML: Acute Myeloid Leukemia
- BET: Bromodomain and Extra Terminal
- ChiP: Chromatin immunoprecipitation
- CHMP: Committee for Medicinal Products for Human Use
- CMML: Chronic Myelomonocytic Leukemia
- CNS: Central Nervous System
- COST: European Cooperation in Science and Technology
- COX-2: Cyclooxygenase 2
- CTCL: Cutaneous T-cell Lymphoma
- CUP: Cancer of Unknown Primary
- DAC: Deacetylase
- DNA: Deoxyribonucleic Acid
- DNMT: DNA Methyltransferase
- EC: European Commission
- EGFR: Epidermal Growth Factor Receptor
- EMA: European Medicines Agency
- EuGESMA: European Genomic and Epigenetic Study on MDS and AML
- EZH2: Enhancer of Zeste Homolog 2
- ESM: Esterase Sensitive Motif
- FAB: French-American-British
- FDA: Food and Drug Administration
- FL: Follicular Lymphoma
- FTO: Fat, Mass and Obesity-associated Protein
- fRNAL: functional RNA
- GR: Glucocorticoid Receptor
- HAT: Histone Acetyltransferase
- HCC: Hepatocellular Carcinoma
- HDAC: Histone Deacetylase
- HER2: Human Epidermal growth factor Receptor 2
- HMT: Histone Methyltransferase
- IL: Interleukin
- **IPSS:** International Prognostic Scoring System
- **KDAC:** Lysine Deacetylases
- **lincRNA:** Long, interdispersed, non-coding RNA
- **LLS:** Leukemia & Lymphoma Society
- **LSD:** Lysine-specific Demethylase
- **MAA:** Marketing Authorization Application
- **MCL:** Mantle Cell Lymphoma
- **MDS:** Myelodysplastic Syndrome
- **MHLW:** Ministry of Health, Labour and Welfare
- **MLL:** Mixed-lineage Leukemia
- **miRNA:** Micro Ribonucleic Acid
- **mTOR:** Mammalian Target of Rapamycin
- **NCCN:** National Comprehensive Cancer Network
- **NCI:** National Cancer Institute
- **ncRNA:** Non-coding Ribonucleic Acid
- **NHGRI:** National Human Genome Research Institute
- **NIMH:** National Institute of Mental Health
- **nmRNA:** Non-messenger Ribonucleic Acid
- **npcRNA:** Non-protein-coding Ribonucleic Acid
- **NSCLC:** Non-small-cell Lung Cancer
- **OTC:** Over-the-counter
- **PDGFRB:** Platelet-derived Growth Factor Receptor Beta
- **PTCL:** Peripheral T-cell Lymphoma
- **RA:** Refractory Anemia
- **RAEB:** Refractory Anemia with Excess Blasts
- **RAEB-T:** Refractory Anemia with Excess Blasts in Transformation
- **RARS:** Refractory Anemia with Ringed Sideroblasts
- **RNAi:** Ribonucleic Acid interference
- **RR:** Ribonucleotide Reductase
- **SAHA:** Suberoylanilide Hydroxamic Acid
- **sNDA:** Supplemental New Drug Application
- **STS:** Soft-tissue Sarcoma
- **TAP:** Therapy Acceleration Program
- **TGA:** Therapeutic Goods Administration
- **TNF:** Tumor Necrosis Factor
- **TS:** Thymidylate Synthase
- **VKOR:** Vitamin K Epoxide Reductase
11.3 Sources


- Vidaza prescribing information (2011), Celgene Corporation. Available From:
11.4 Research Methodology

GBI Research’s dedicated research and analysis teams consist of experienced professionals with marketing, market research and consulting backgrounds in the medical devices industry as well as advanced statistical expertise.

GBI Research adheres to the codes of practice of the Market Research Society (www.mrs.org.uk) and the Strategic and Competitive Intelligence Professionals (www.scip.org).

All GBI Research databases are continuously updated and revised.

11.4.1 Coverage

The objective of updating GBI Research coverage is to ensure that it represents the most up to date vision of the industry possible.

Changes to the industry taxonomy are built on the basis of extensive research of company, association and competitor sources.

Company coverage is based on three key factors: market capitalization, revenues and media attention/innovation/market potential.

- An exhaustive search of 56 member exchanges is conducted and companies are prioritized on the basis of their market capitalization;
- The estimated revenues of all major companies, including private and governmental, are gathered and used to prioritize coverage; and
- Companies which are making the news, or which are of particular interest due to their innovative approach are prioritized.

GBI Research aims to cover all major news events and deals in the medical industry, updated on a daily basis.

The coverage is further streamlined and strengthened with additional inputs from GBI Research’s expert panel (see below).

11.4.2 Secondary Research

The research process begins with exhaustive secondary research on internal and external sources being carried out to source qualitative and quantitative information relating to each market.

The secondary research sources that are typically referred to include, but are not limited to:

- Company websites, annual reports, financial reports, broker reports, investor presentations and SEC Filings;
- Industry trade journals, scientific journals and other technical literature;
- Internal and external proprietary databases;
- Relevant patent and regulatory databases;
- National government documents, statistical databases and market reports;
- Procedure registries; and
- News articles, press releases and web-casts specific to the companies operating in the market.

11.4.3 Primary Research

GBI Research conducts hundreds of primary interviews a year with industry participants and commentators in order to validate its data and analysis. A typical research interview fulfills the following functions:

- It provides first-hand information on the market size, market trends, growth trends, competitive landscape and future outlook;
- It helps in validating and strengthening the secondary research findings; and
- It further develops the analysis team’s expertise and market understanding.
Primary research involves email interactions and telephone interviews as well as face-to-face interviews for each market, category, segment and sub-segment across geographies. The participants who typically take part in such a process include, but are not limited to:

- Industry participants: CEOs, VPs, marketing/product managers, market intelligence managers and national sales managers
- Hospital stores, laboratories, pharmacies, distributors and paramedics
- Outside experts: Investment bankers, valuation experts, research analysts specializing in specific medical equipment markets
- Key Opinion Leaders: Physicians and surgeons specializing in different therapeutic areas corresponding to different kinds of medical equipment.

The report consists of the following four major sections

- Therapeutic Landscape
- Geographic Landscape
- Pipeline Analysis
- Competitive Analysis

11.4.4 Therapeutic Landscape

- Revenues for each indication, geography-wise is arrived at by utilizing the GBI Research market forecasting model. The global revenue for each indication is the sum value of revenues of all seven regions.
- The annual cost of therapy for each indication is arrived at by considering the cost of the drugs, dosage of the drugs and the duration of the therapy.
- The generic share of the market for each indication is obtained by calculating the prescription share for generic drugs and the respective cost of treatment.
- The treatment usage pattern which includes quantitative data on the diseased population, treatment-seeking population, diagnosed population and treated population for an indication, is arrived at by referring to various sources as mentioned below.
- The marketed drugs section contains an overview of the drugs, their mechanism of action, efficacy and safety issues related to the drugs. The drugs profiled in this section are chosen based on estimated revenues and their mechanism of action.

GBI Research uses the epidemiology-based treatment flow model to forecast market size for therapeutic indications.

11.4.4.1 Epidemiology-based Forecasting

The forecasting model used at GBI Research makes use of epidemiology data gathered from research publications and primary interviews with physicians to represent the treatment flow patterns for individual diseases and therapies. The market for any disease segment is directly proportional to the volume of units sold and the price per unit.

\[
\text{Sales} = \text{Volume of Units sold} \times \text{Price per Unit}
\]

The volume of units sold is calculated on the average dosage regimen for that disease, duration of treatment and number of patients who are prescribed drug treatment (prescription population). Prescription population is calculated as the percentage of population diagnosed with a disease (diagnosis population). Diagnosis population is the population diagnosed with a disease expressed as a percentage of the population that is seeking treatment (treatment-seeking population). Prevalence of a disease (diseased population) is the percentage of the total population who suffer from a disease/condition.

Data on treatment seeking rate, diagnosis rate and prescription rate, if unavailable from research publications, are gathered from interviews with physicians and are used to estimate the patient volumes for the disease under consideration. Therapy uptake and compliance data are fitted in the forecasting model to account for patient switching and compliance behavior.
To account for differences in patient affordability of drugs across various geographies, macroeconomic data such as inflation and GDP; and healthcare indicators such as healthcare spending, insurance coverage and average income per individual are used.

Annual cost of treatment is calculated using product purchase frequency and the average price of the therapy. Product purchase frequency is calculated from the dosage data available for the therapies and drug prices are gathered from public sources.

The epidemiology-based forecasting model uses a bottom-up methodology and it makes use of estimations in the absence of data from research publications. Such estimations may result in a final market value which is different from the actual value. To correct this ‘gap’ the forecasting model uses ‘triangulation’ with the help of base year sales data (from company annual reports, internal and external databases) and sales estimations.

11.4.4.1 Analogous Forecasting Methodology

Analogous forecasting methodology is used to account for the introduction of new products, patent expiries of branded products and subsequent introduction of generics. Historic data for new product launches and generics penetration are used to arrive at robust forecasts. Increase or decrease of prevalence rates, treatment seeking rate, diagnosis rate and prescription rate are fitted into the forecasting model to estimate market growth rate.

The proprietary model enables GBI Research to account for the impact of individual drivers and restraints in the growth of the market. The year of impact and the extent of impact are quantified in the forecasting model to provide close-to-accurate data sets.

11.4.4.1.1 Disease Population

The diseased population for any indication is the prevalence. The prevalence rates are usually obtained from various journals, online publications, sources such as the American Heart Association (AHA), World Health Organization (WHO), and so on.

11.4.4.1.2 Treatment Seeking Population

The treatment seeking population is always calculated as a percentage of prevalence. The number denotes the actual number of patients who are going to hospitals to get diagnosis reports for any disease. The treatment seeking population is primarily driven by the onset of symptoms, patient awareness and the severity of the disease.

11.4.4.1.3 Diagnosis Population

Out of the patients who undergo diagnostic tests to confirm a disease, only a few people get diagnosed with the disease. This number as a percentage of the treatment seeking population is the diagnosis rate. The diagnosis population is primarily driven by the sensitivity of the diagnostic tests, state-of-the-art technology, patient access to these diagnostic tests and cost of the diagnostic tests.

11.4.4.1.4 Prescription Population

For any disease, multiple treatment options exist. For example, in dyslipidemia various treatment options such as, lifestyle modification and drug therapy are available. Prescription population is defined as the number of patients who are prescribed drug therapy. This is calculated as a percentage of the diagnosis population. The prescription population is primarily driven by the age at which the disease is diagnosed, the disease stage, patient health and cost of drug treatment.

11.4.4.2 Market Size by Geography

The treatment usage pattern and annual cost of treatment in each country has been factored in while deriving the individual country market size.

Forecasting Model for Therapeutic Areas
The above figure represents a typical forecasting model followed in GBI Research. As discussed previously, the model is built on the treatment flow patterns. The model starts with the general population, then diseased population as a percentage of the general population and then follows the treatment seeking population as a percentage of the diseased population and diagnosed population as a percentage of the treatment seeking population. Finally, the total volume of units sold is calculated by multiplying the treated population by the average dosage per year per patient.

Articles from research journals and agency publications such as the British Medical Journal, the New England Journal of Medicine, and sources such as the American Heart Association (AHA), World Health Organization (WHO) and clinicaltrials.gov have been referred. The marketed drugs section is taken from company websites and internal databases.
11.4.5 Geographical Landscape
GBI Research analyzes only seven major geographies: the US, the top five countries in Europe (the UK, Germany, France, Spain, and Italy) and Japan. The total market size for each country is provided which is the sum value of the market sizes of all the indications for that particular country.

11.4.6 Pipeline Analysis
This section provides a list of molecules at various stages in the pipeline for various indications. The list is sourced from internal database and validated for the accuracy of phase and mechanism of action at clinicaltrials.gov and company websites. The section also includes a list of promising molecules which is narrowed down based on the results of the clinical trials at various stages and the novelty of mechanism of action.

11.4.7 Competitive Landscape
Profiles of leading players are provided along with an overview of key products marketed by the companies for various indications. An analysis of strengths, weaknesses, opportunities and threats of each company with respect to various indications is also listed.

GBI Research aims to cover all major M&A, licensing deals and co-development deals related to the market. This section is sourced from the companies' websites and internal databases.

11.5 Expert Panel Validation
GBI Research uses a panel of experts to cross verify its databases and forecasts.

GBI Research expert panel comprises marketing managers, product specialists, international sales managers from medical device companies; academics from research universities and key opinion leaders from hospitals.

Historic data and forecasts are relayed to GBI Research’s expert panel for feedback and are adjusted in accordance with their feedback.

11.7 Disclaimer
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