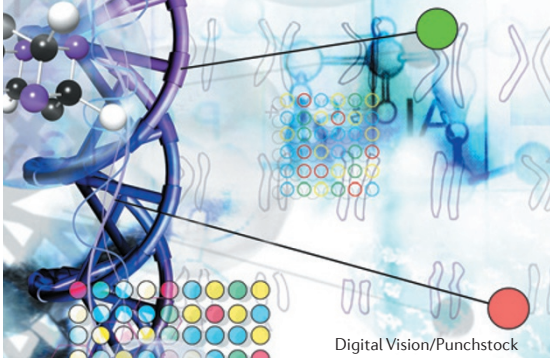
BIOBUSINESS BRIEFS

TARGET WATCH

Drugging the epigenome


Digital Vision/Punchstock

Epigenetic alterations — for example, changes in the way that the genome is packaged by surrounding histone proteins, causing genes to be switched on or off — are linked to diseases including cancers and immunoinflammatory disorders. Such evidence, coupled with recent progress in showing that enzymes involved in epigenetic processes can be modulated by drug-like small molecules, has fuelled interest in exploiting the therapeutic potential of epigenetic targets.

"Epigenetic targets are increasingly recognized as highly selective entry points for disease intervention rather than generic controllers of bulk gene expression," says James Audia, Chief Scientific Officer of Constellation Pharmaceuticals, an epigenetics-focused company based in Boston, Massachusetts, USA. "What makes epigenetic targets stand out in my mind is the potential to use them to reprogramme a cellular phenotype by altering the cellular transcriptional programme as a result of altering its epigenome," adds Cheryl Arrowsmith, Professor at the University of Toronto, Canada, and Chief Scientist at the Toronto laboratory of the Structural Genomics Consortium (SGC). "An example of this is the recent 'reprogramming' of drug-resistant leukaemia cells to become drug-sensitive by inhibition of the lysine-specific histone demethylase LSD1 (*Nature Med.* **18**, 605–611; 2012)."

Novel epigenetic targets such as histone demethylases are now rapidly joining established target classes such as histone deacetylases (HDACs). With the aim of illuminating trends in the field, a data mining-based analysis of ~380 proteins that make up the 'epigenome' defined in a recent review (*Nature Rev. Drug Discov.* **11**, 384–400; 2012) was conducted, which is highlighted in this article. The output of the analysis is designed to be explored through an interactive dashboard. Analysis details and guidance for using the dashboard are provided in Supplementary information S1 (box), and some example outputs are discussed here.

Analysis

Text-mining technology developed by Relay Technology Management, which is partly owned by Nature Publishing Group, was used to search over 3.7 million published documents indexed by Medline between 2001 and 2012 for information related to the set of epigenetic proteins, which fall into several families. A snapshot from the dashboard, with the parameters set to focus on two of these families — HDACs and histone methyltransferases — is shown in FIG. 1. Three further parameters (with values ranging from 0 to 1) are used to refine the output of the dashboard. The established index quantifies the degree to which epigenetics research has focused on each protein since 2001; the emerging index quantifies the degree to which the research has increasingly focused on each protein, relative to the historic level; and the targeting index quantifies the degree to which a protein has appeared in publications and grants in the context of molecular targeting applications or therapeutic concepts.

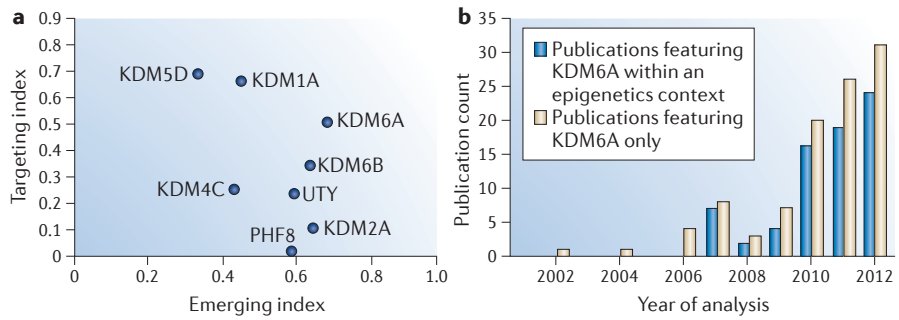
As expected, HDAC1, HDAC2 and HDAC3 — which are targeted by the approved anticancer drugs vorinostat and romidepsin, and have been researched extensively over the past decade — have both a high targeting index and a high established index. Among other proteins of interest in the two families, the histone methyltransferase EZH2 is an example of a protein for which the publication rate in the period analysed has been substantial overall and is also increasing, leading to high rankings in both the established index (FIG. 1) and the emerging index (not shown). Moreover, its activity has been implicated in various cancers and its small-molecule druggability has recently been demonstrated (*Nature Chem. Biol.* **8**, 890–896; 2012), which contributes to its relatively high targeting index. A discussion of data for some more recently emerging targets in the histone demethylase family is presented in BOX 1.

Dash Dhanak, who leads the epigenetics research programme at GlaxoSmithKline, believes that the recently demonstrated druggability of several proteins, including EZH2 and DOT1 (another histone methyltransferase), is encouraging for the next generation of epigenetic drugs. However, understanding the biology associated with

Box 1 | **Demethylases as emerging targets**

Over the past decade, researchers have begun to uncover the importance of the methylation status of lysine and arginine residues on the histones that package DNA (*Nature Rev. Drug Discov.* **11**, 384–400; 2012). These methyl marks — which are made by methyltransferases and removed by demethylases — act as binding sites for other proteins and can be associated with either transcriptional repression or activation.

As shown in panel **a** of the figure, no demethylases have target index values as high as the established histone deacetylases (HDACs) in FIG. 1, but some do have a comparatively high emerging index, reflecting their relatively recent discovery and subsequent growth in literature reports focusing on them, as shown in panel **b** for lysine-specific demethylase 6A (KDM6A; also known as UTX), a Jumonji domain-containing lysine-specific demethylase. Moreover, some members of the family, including lysine-specific demethylase 1 (LSD1; also known as KDM1A) and KDM6A, have been associated with cancer and inflammation, and small-molecule inhibitors have been reported (for example: *Nature* **488**, 404–408; 2012).



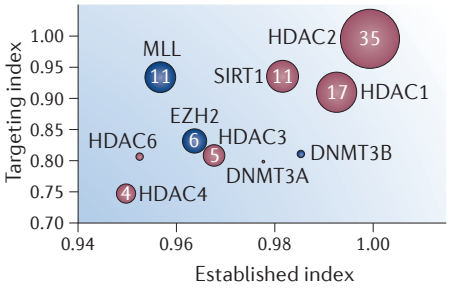


Figure 1 | **Epigenetics dashboard snapshot.** Selected members of the histone deacetylase (HDAC)–sirtuin (SIRT) family (red) and methyltransferase family (blue) that have both a high established index and a high target index are shown. The circle size indicates the number of issued US patents related to the target, shown within the circles; see Supplementary information S1 (box) for details. DNMT, DNA methyltransferase; MLL, mixed lineage leukaemia protein.

modulating each target is a major challenge. "The target landscape is broad and the extent of validated (and valid) chemical matter is limited (and limiting), often requiring risky investment to develop the chemical tools necessary to conduct the translational experiments. We are elucidating the fundamental science in the course of doing drug discovery," says Audia.

"What the community really needs is a set of tool compounds that can be used to explore the biology of each target and for target validation in disease models," says Arrowsmith. "Traditionally, such compounds (potent, selective, cell-active and not cytotoxic) have not been widely available to academics who publish the majority of the literature that is used to make decisions on the therapeutic potential of a target." With this in mind, the SGC has an ongoing project to develop and disseminate 'open-access' epigenetic chemical probes, especially for community-wide use to validate targets, explore target biology and also to identify potentially negative effects of target inhibition (see the SGC website). "The field is too large and the potential too vast for any single company or sector to be able to explore all the possibilities," concludes Arrowsmith.

Samia Burridge

FURTHER INFORMATION

Epigenetics dashboard: http://public.tableausoftware.com/views/NRDD_Epigenetics_Explorer/EpigeneticsDataExplorer
Relay Technology Management: http://www.relaytm.com
SGC — Chemical Probes: http://www.thesgc.org/scientists/chemical_probes
SGC — The ChromoHub Project: http://apps.thesgc.org/resources/phylogenetic_trees/index.php

SUPPLEMENTARY INFORMATION

See online article: S1 (box)

ALL LINKS ARE ACTIVE IN THE ONLINE PDF