ELSEVIER
DRUG DISCOVERY TODAY TECHNOLOGIES
Drug Discovery Today: Technologies
Vol. xxx, No. xx 2012

Epigenetics

Epigenetic drugs that do not target enzyme activity

Dafydd R. Owen*, John D. Trzupek

Pfizer Worldwide Research and Development, 200 Cambridgepark Drive, Cambridge, MA 02140, USA

While the installation and removal of epigenetic post-translational modifications or 'marks' on both DNA and histone proteins are the tangible outcome of enzymatically catalyzed processes, the role of the epigenetic reader proteins looks, at first, less obvious. As they do not catalyze a chemical transformation or process as such, their role is not enzymatic. However, this does not preclude them from being potential targets for drug discovery as their function is clearly correlated to transcriptional activity and as a class of proteins, they appear to have binding sites of sufficient definition and size to be inhibited by small molecules. This suggests that this third class of epigenetic proteins that are involved in the interpretation of post-translational marks (as opposed to the creation or deletion of marks) may represent attractive targets for drug discovery efforts. This review mainly summarizes selected publications, patent literature and company disclosures on these non-enzymatic epigenetic reader proteins from 2009 to the present.

Section editor:
Nessa Carey, Pfizer, UK.

Introduction

The definitions of epigenetics and the enzymes that mediate post-translational modifications (PTMs) of both DNA and selected amino acid residues in histone tails have been well explained and reviewed, both in this issue and elsewhere [1]. It is easy to visualize the role of a DNA methyltransferase (DNMT) 'writing' a methyl group onto cytosine at C-5 in a CpG dinucleotide [2] or the action of a histone deacetylase (HDAC) 'erasing' an acetyl group from the ε-NH functionality of a lysine residue found in a histone tail peptide [3]. These significant changes to both localized chemical structure and physicochemistry mediated by enzymatic activity, be it on the histone protein or DNA, clearly affect the overall tertiary structure of the modified chromatin. Each modification has some effect on the tightness with which the DNA-held genetic information is packaged by the surrounding protein. These variables either promote or limit accessibility to the DNA and control its availability for taking part in transcriptional activity [4].

Assuming the presence of druggable binding sites or ways to intercept enzyme function, these enzymatic targets naturally offer the opportunity for therapeutic intervention and the first examples of marketed drugs have already presented themselves in these classes [5]. This review focuses on the role of a third class of epigenetic proteins that do not catalyze a chemical transformation – the epigenetic 'reader' proteins [6,7]. More specifically it will highlight the role of the PTM readers of protein held methylation and acetylations. This review will not cover the reading of DNA held methylation. The interpretation of the information carried in the protein held epigenetic code of marks that sit above (epi) the DNA-held genome (genetics) necessitates this third class of epigenetic reader protein. These proteins recognize and bind to the various PTMs laid down or deleted by the epigenetic writers and erasers and effect changes in transcription, often through

*Corresponding author.: D.R. Owen (dafydd.owen@pfizer.com)

1740-6749/$ © 2012 Published by Elsevier Ltd. http://dx.doi.org/10.1016/j.ddtec.2012.10.008

a scaffolding role in the formation of large transcriptional complexes. The interpretation of ε-N-acetylated lysine marks by the bromodomain family of readers is a rapidly expanding field of interest and therapeutic potential. They interpret the transcriptional readiness of the chromatin through reading certain acetylated lysine marks. For example, acetylation of histone 3, lysine 9 (H3K9ac) is transcriptionally activating, as is H3K14ac. The acetylation of the lysine loosens the winding of the histone protein, improving access to the DNA ready for transcriptional activities. The formation of transcriptional complexes is thus mediated in part by the scaffolding role of bromodomain containing proteins which read the acetylation state of the histone.

Proteins performing an equivalent reader role for the post-translational modification of lysine at iterative levels of methylation (from mono through to tri) are also known. This role is performed by plant homeo domain (PHD), malignant brain tumor (MBT), Chromo, Agenet and Tudor domains as the lysine methyl readers. Subsets of these proteins are also capable of reading methylated arginines which also carry some of the multi-dimensional epigenetic histone code. The methyl based PTM reading process mirrors that of the acetyl based bromodomains as methylation of lysine marks are also associated with transcriptional activity control. For example, dimethylation of Histone 3 Lysine 4 (H3K4me2) is associated with activation of transcription while H3K9me2 is a transcriptionally repressive mark.

Given the emerging nature of these targets, the prospect of approved drugs against these readers is some way off. However, in just a few short years many targets have gone from initial identification and characterization through knock-down/knockout studies and into a first generation of small molecule inhibitors. Publications on reader protein characterization in combination with a small number of research tools (antibodies and small molecule inhibitors) are on the increase, while the first generation of clinical candidates from the field are now entering early stage trials [8].

Bromodomains as targets for drug discovery

Bromodomains are protein interaction modules of around 110 amino acids in length that detect the presence of an acetyl group on the ε-NH_2 of specific lysine residues found within histone tails [9]. Bromodomains are designed to read the acetylation state of histone proteins exclusively. They are structurally conserved protein modules found within many larger chromatin-associated proteins and are frequently flanked by other reader domains such as PHDs or other multiple bromodomains. The bromodomain itself acts as an acetyl-lysine binding domain for the reading of post-translationally modified histones through a protein-protein interaction. The reading process may trigger further remodeling at epigenetically modifiable sites within the protein or DNA components of chromatin through the control of processes such as methyl or acetyl transfer, transcription coactivation and motor protein (helicase) activity. For example bromodomains are a protein recognition domain found within many histone acetyltransferases (HATs).

On recognition of certain acetyl lysine marks, the bromodomain has a key role in regulating further protein-protein interactions as part of chromatin remodeling and despite not affecting the presence or absence of post-translational marks directly, the function of the bromodomain ultimately manifests itself in transcriptional activity control [10]. According to an analysis of sequence databases in a recent publication by Filippakopoulos and Knapp, there are 61 bromodomains found within 46 diverse human proteins [11]. They further classified the bromodomains into eight subfamilies. X-ray crystal structures are available for around half of the bromodomains and this has revealed a conserved hydrophobic pocket across the target family that accepts the acetylated lysine side chain of the histone peptide. While it would be easy to dismiss the bromodomains as undruggable, as their function appears to depend on a low affinity protein-protein interaction spread across a large area, the compact and defined nature of these acetyl lysine pockets suggests that small molecule inhibitors may be identified. This raises the attractive chemotype possibility of eliciting net control of gene function with a small molecule, as opposed to having to achieve more direct gene silencing through oligonucleotide strategies. Because of the differences in electrostatics and shape at the entrance to the acetyl lysine pocket, the prospect for selective inhibitors of bromodomains exists – at least at the subfamily level. This is discussed in more detail later in the review.

The BET subfamily of the bromodomains

With this potential for small molecule chemical tractability, what is the therapeutic potential for blocking bromodomain binding sites with inhibitors? Taking the bromodomain and extra C-terminal domain (BET) family as an example (a subfamily of the bromdomains) [12,13], the discovery of multiple inhibitor chemotypes has allowed the first studies in small molecule mediated disease modulation to be carried out preclinically. This has highlighted BET family control of processes that mediate cancer [14], inflammation [15] and viral infection [16]. Other studies have associated BET family members with implications in CNS [17] and metabolic disorders [18].

While we are some way short of having approved 'epigenetic drugs that do not target enzyme activity', the BET family has seen the most activity in terms of chemotypes and clinical candidates. GlaxoSmithKline's (GSK) extensive efforts in the field represent an impressive example of target identification, medicinal chemistry lead optimization and clinical candidate identification [19]. Having started with a phenotypic screen looking for apolipoprotein A-1 (ApoA1) upregulators, hits

Please cite this article in press as: Owen, D.R. and Trzupek, J.D. Epigenetic drugs that do not target enzyme activity, Drug Discov Today: Technol (2012), http://dx.doi.org/10.1016/j.ddtec.2012.10.008

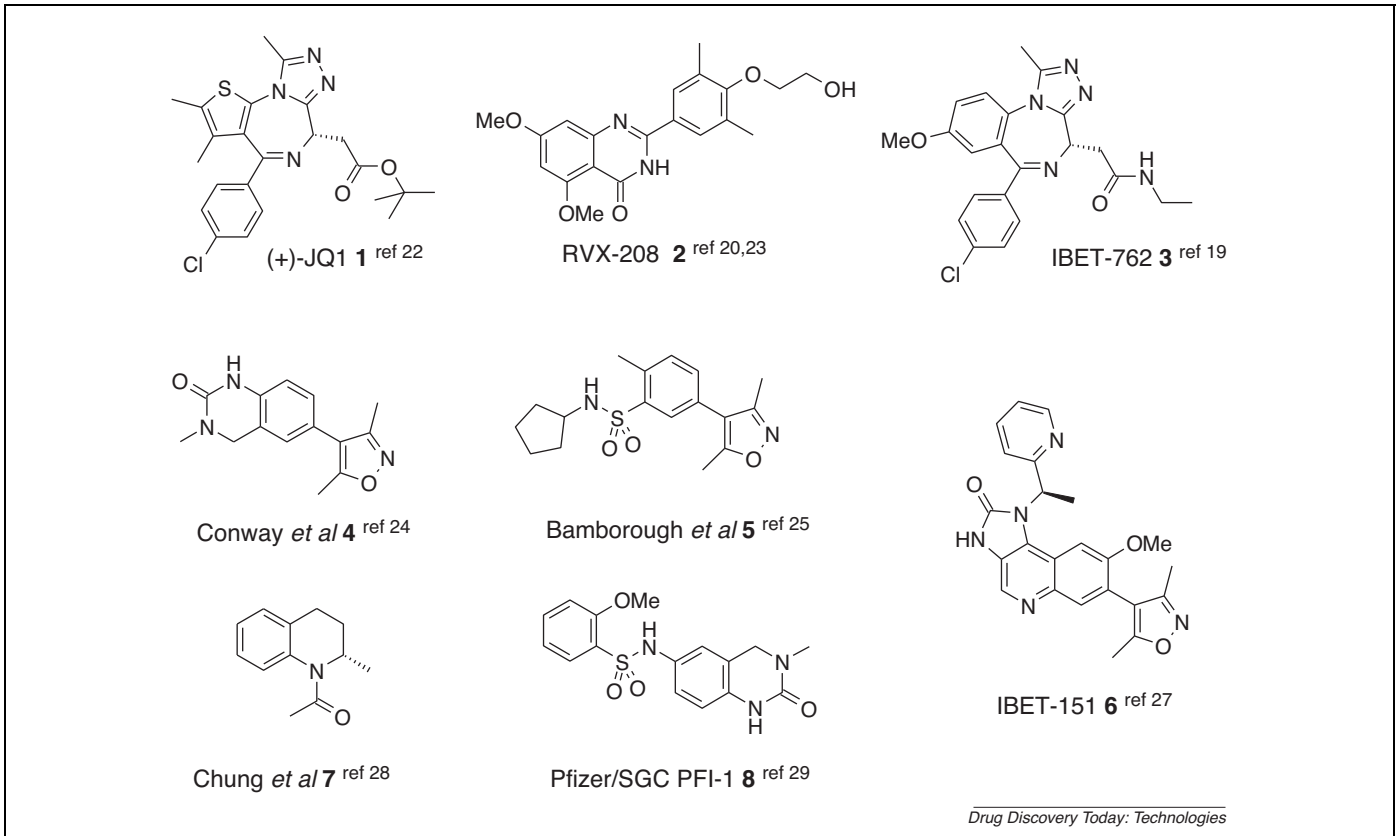


Figure 1. Disclosed small molecule BET family inhibitors.

were evaluated using chemoproteomic and siRNA techniques to identify the specific target responsible for the phenotypic effect. Using further biophysical assays and X-ray crystallography, the GSK team established that the BET proteins were in fact the molecular target responsible for the ApoA1 upregulation.

This same path was taken by the ResVerologix Corporation. Using a phenotypic screen looking for ApoA1 upregulation, they also identified what turned out to be a novel class of BET family binders [20]. Researchers at Mitsubishi Pharmaceuticals also employed an anti-inflammatory phenotypic screen to identify virtually the same chemotype as GSK in their ApoA1 work. This was explained by the fact that the cellular phenotype observed in their anti-inflammatory screen was also the outcome of BET protein binding and the each company had a similar screening file for the chemotype [21].

A derivative of the Mitsubishi chemotype was studied and disclosed as the first fully characterized small molecule BET family inhibitor by Filippakopoulos, Knapp and Bradner *et al.* [22]. Named (+)-JQ1 (**1**, Fig. 1), the compound showed cell differentiation and growth arrest in an *in vivo* model of the rare cancer NUT Midline Carcinoma (NMC). All three of these molecular discoveries have led to compounds in clinical trials or advanced pre-clinical research. The ResVerlogix compound RVX-208 (**2**) has seen Phase 2B cardiovascular clinical trials [23] while GSK's IBET-762 (**3**) is also in the clinic for NMC [8,19]. While (+)-JQ1 and IBET-762 are both potent (<100 nM) binders to the BET family readers, it would seem that RVX-208 is somewhat weaker from oral disclosures by ResVerlogix. It also displayed an interesting asymmetric inhibition of the first and second domains of BRD4 (>10-fold selective for the second domain over the first) and in other BET family members – a property not observed in other disclosed chemotypes thus far. The significance of this is as yet not fully understood. However, given the similarity in the BET family binding sites among BRD2, 3, 4 and T [11], first and second domain selectivity may be an area for exploitation in terms of BET inhibition profile.

A small number of orthogonal chemotypes have also been disclosed. All compounds contain some form of acetyl lysine mimetic. Whereas the triazole of the GSK/(+)-JQ1 chemotype accepts a hydrogen bond from the Asn 140 in the BRD4 (**1**) crystal structure, Conway (Compound **4**) [24] and Bamborough (Compound **5**) [25] have independently described 3,5-dimethylisoxazole as a viable acetyl lysine mimetic. Conway and Brennan (of the Structural Genomics Consortium (SGC)) have collaborated to further expand the chemical space around isoxazole variants [26]. Seal *et al.* have developed Bamborough's fragment hits into an optimized dimethylisoxazole series for GSK in the discovery of IBET-151 (**6**) [27].

Please cite this article in press as: Owen, D.R. and Trzupek, J.D. Epigenetic drugs that do not target enzyme activity, Drug Discov Today: Technol (2012), http://dx.doi.org/10.1016/j.ddtec.2012.10.008

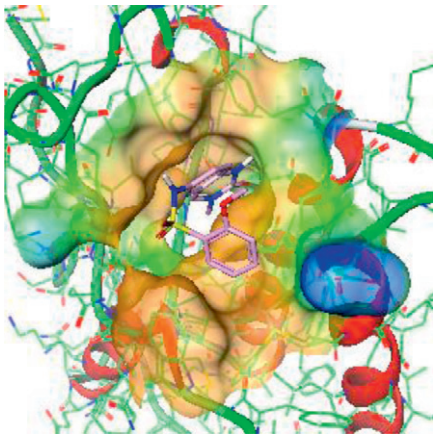


Figure 2. Pfizer/SGCs PFI-1 (**8**) bound in BRD4 (**1**).

Chung has also described a fragment-based approach to identifying novel chemotypes for GSK (**7**) [28]. A designed selection of fragments with the potential to be N-acetyl lysine mimetics yielded novel, yet weak hits of moderate efficiency in this proof of principle study. Pfizer in collaboration with the SGC has disclosed the BET family chemical probe (PFI-1) both online and in oral presentations (**8**) [29]. This was discovered through fragment screening to identify a nonselective bromodomain binding pharmacophore (a bicyclic urea) followed by installation of extra functionality to secure BET subfamily selectivity guided by protein X-ray co-crystal structures (Fig. 2).

Other non-BET bromdomains

Outside of the BET family very little optimized chemical matter exists with weak hits known for cAMP-response element-binding protein binding protein (CREBBP) [30] and P300/CBP-associated factor (PCAF) [31]. In the absence of chemical matter, only the reader protein structures/models are available for druggability assessment. Building on the large scale structural analysis of the bromodomains by Filippakopoulos and Knapp, which clearly showed that each bromodomain protein contains a small and defined binding site for acetyl lysine recognition [11], Knapp has collaborated further with Hoelder *et al.* to provide a comprehensive scoring analysis of the bromodomain family binding sites for druggability [32]. Overall bromodomain sequence homology was not a useful technique for inter-protein druggability comparison. Using the SiteMap product from Schrodinger, SiteScore and *D*-scoring protocols on just the acetyl lysine binding sites were assessed for definition, volume and polarity, all factors that govern the likelihood of efficient inhibition by small molecules. Grooves, pockets and shelves are among the features that vary considerably around the binding site entrance. This suggested that there will be a spectrum of druggability within the bromodomain family. However, because of the defined acetyl lysine binding pockets available, any of the bromodomain subfamilies score better than most standard protein–protein interactions which normally span large, open, featureless surfaces. Among the most druggable subfamilies within bromodomains by this predictive computational method was the BET family. This is supported by the small molecule solutions that have already been identified [19–22,24–30]. Poorer relative druggability scores were obtained for the likes of the BAZ2B, SMARCA and PB1 bromodomains, but in relative terms this target class does not score much worse than kinases by this predictive method. Given that this is a protein–protein interaction under consideration, it seems remarkably amenable to small molecule intervention and therefore make the family an attractive set of drug targets.

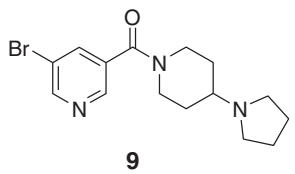
Two other factors remain that may change any potential analysis of the bromodomain binding sites for druggability. First, further small molecule probes for this class of protein may reveal the possibility for ligand-induced binding pockets that are impossible to observe or predict from the apo structures currently available. Second there is a possibility to occupy a deeper pocket, beyond the conserved asparagines placed for acetyl group recognition, which appears to be fully occupied by five as yet non-displaceable water molecules. No published small molecule inhibitor has accessed this pocket, however should this prove possible, the impact on both potency and selectivity for the bromodomains would be significant.

The methyl-lysine readers as drug targets

Much like the bromodomains, the readers of methylated lysine and arginine residues in histones play an important role in epigenetic control of transcription. The methylated histone protein residues contain extra degrees of dimensionality, as unlike the single variable of acetylation read by bromodomains, lysine residues may be methylated iteratively up to three times for a more complex, protein-held level of the epigenetic code. The differing levels of methylation change the steric environment and the ability of the nitrogen atom of the amino acid residue to hydrogen bond during protein–protein interactions. This subtle variable is enough to have profound effects on recruitment to chromatin related complexes responsible for transcriptional activity control.

The druggability of the methyl-lysine binders is predicted to be less than the equivalent bromodomain acetyl-lysine reading proteins [33]. This prediction is once again made in the absence of any significant number of small molecule probe publications. One exception is the work of Frye where some small molecule ligands for targets within the MBT family have been identified [34,35]. These are part of the large 'Royal Family' of methyl-lysine readers. (Other members include, Chromo, Tudor and PHD domains) [36]. Frye has also authored a comprehensive review on the potential of

Please cite this article in press as: Owen, D.R. and Trzupek, J.D. Epigenetic drugs that do not target enzyme activity, Drug Discov Today: Technol (2012), http://dx.doi.org/10.1016/j.ddtec.2012.10.008



9

Drug Discovery Today: Technologies

Figure 3. Frye's L3MBTL1 antagonist.

methyl-lysine and arginine binders as targets for drug discovery [37].

Frye's small molecule research work has identified the first MBT antagonists based on mimicking the lower methylation states of the endogenous histone peptide. Frye selected the second MBT domain of lethal (**3**) malignant brain tumor-like protein 1 as a model protein for antagonist design given the structural information available for the protein and its confirmed role in binding methylated lysine. A strategy of employing aromatic anchors attached through a linker to pyrrolidine as an ε-lysine nitrogen functionality mimetic yielded weak micromolar hits of reasonable efficiency. Conformational constraint of the aliphatic linker into a piperidine established a 5 μM nicotinamide based inhibitor 9 (Fig. 3) for the L3MBTL1 methyl-lysine-binding site. As designed, the co-crystal structure proved that the pyrrolidine picked up the expected hydrophobic cage and π-cation interactions normally afforded the methylated histone peptide substrate.

Schapira *et al*. have published a druggability score (*D*-score) assessment of the methyl-lysine binders [33]. Using the SiteMap application (from Schrodinger) to assign a *D*-score through scoring parameters for and against suitability of the pocket for accommodating small molecules, a druggability prediction for the family was established. Interestingly, given the knowledge that the BET bromodomains are druggable as small molecule probes exist, Schapira used the *D*-score of this family as a benchmark for his methyl-lysine reader predictions. The analysis spanned MBT, Tudor, Chromo, PHD, WDR and PWWP (Pro-Trp-Trp-Pro) domains. All of the bromodomain 'control' pockets were assigned as druggable by the method. The performance within the individual fold families for the methyl-lysine readers was less consistent. Some of the highlighted conclusions was the highly druggable nature of the WDR family and the difficulties apparent for the MBT and Tudor fold families. This is not to say the Royal Family of methyl-lysine readers is undruggable. Selected targets within families do score well such as CBX2 (Chromo), PHF8 (PHD) and WDR5 (WDR). This could mean a lower number of viable targets for exploration, but with a higher potential for selectivity. The analysis acknowledges that this can only be a prediction and highlights some caveats to the methods, however perhaps the most useful conclusion is that much needed chemical probe-seeking programs could be prioritized using this ranking analysis for the binding sites [38].

Conclusions

Although the title of this review perhaps seems a little premature given the dearth of chemical matter known, the target space for 'epigenetic drugs that do not target enzyme activity' certainly holds some considerable potential. The fact that the actions of epigenetic readers do influence transcriptional control means that they may offer a subtle and potentially safe intervention point in epigenetic therapies of the future.

The fundamental nature to the control exerted on many vital genetic, developmental and maintenance processes is promising for efficacy, but challenging for safety. In fact, the whole safety aspect to epigenetics remains to be fully understood. With early promise in cancer therapies in HDACs with acceptable toleration profiles, the more stringent safety profiles for chronic use in non-oncology indications clearly remains untested. The epigenetic associations to disease is now undoubted and the battery of drug discovery strategies available to academia and industry are poised to deliver several small molecule solutions given the apparently druggable nature of these epigenetic reader protein targets [38].

Conflict of interests statement

Some of the authors' own science is reviewed within the text. The authors are employees of Pfizer and declare no other conflict of interests.

References

1 Arrowsmith, C.H. *et al.* (2012) Epigenetic protein families: a new frontier for drug discovery. *Nat. Rev. Drug Discov.* 11, 384–400
2 Hermanna, A. *et al.* (2004) Biochemistry and biology of mammalian DNA methyltransferases. *Cell. Mol. Life Sci.* 61, 2571–2587
3 (a) Kouzarides, T. (2000) Acetylation: a regulatory modification to rival phosphorylation? *EMBO J.* 19, 1176–1179;
(b) Choudhary, C. *et al.* (2009) Lysine acetylation targets protein complexes and co-regulates major cellular functions. *Science* 325, 834–840
4 Jenuwein, T. and Allis, C.D. (2001) Translating the histone code. *Science* 293, 1074–1080
5 Grant, S. *et al.* (2007) Vorinostat. *Nat. Rev. Drug Discov.* 6, 21–22
6 Chung, C.-w. and Witherington, J. (2011) Progress in the discovery of small-molecule inhibitors bromodomain-histone interactions. *J. Biomol. Screen.* 16, 1170–1185
7 Hewings, D.S. *et al.* Progress in the development and application of small molecule inhibitors of bromodomain-acetyl-lysine interactions. *J. Med. Chem.*, in press
8 A Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics, and Clinical Activity of GSK525762 in Subjects with NUT Midline Carcinoma (NMC). ClinicalTrials.gov identifier NCT01587703
9 Chung, C.-w. and Tough, D.F. (2012) Bromodomains: a new target class for small molecule drug discovery. *Drug Discov. Today: Ther. Strateg.* http://dx.doi.org/10.1016/j.ddstr.2011.12.002
10 Taverna, S.D. *et al.* (2007) How chromatin-binding modules interpret histone modifications: lessons from professional pocket pickers. *Nat. Struct. Mol. Biol.* 14, 1025–1040
11 Filippakopoulos, P. *et al.* (2012) Histone recognition and large scale structural analysis of the human bromodomain family. *Cell* 149, 214–231
12 Prinjha, R.K. *et al.* (2012) Place your BETs: the therapeutic potential of bromodomains. *Trends Pharmacol. Sci.* 33, 146–152

Please cite this article in press as: Owen, D.R. and Trzupek, J.D. Epigenetic drugs that do not target enzyme activity, Drug Discov Today: Technol (2012), http://dx.doi.org/10.1016/j.ddtec.2012.10.008

13 Conway, S.J. Bromodomains: are readers right for epigenetic therapy? *ACS Med. Chem. Lett.*, in press
14 You, J. *et al.* (2009) Regulation of aurora B expression by the bromodomain protein BRD4. *Mol. Cell. Biol.* 29, 5094–5103
15 Bo Huang, B. *et al.* (2009) BRD4 coactivates transcriptional activation of NF-κB via specific binding to acetylated RelA. *Mol. Cell. Biol.* 29, 1375–1387
16 Wu, S-Y. *et al.* (2006) BRD4 links chromatin targeting to HPV transcriptional silencing. *Genes Dev.* 20, 2383–2396
17 Muller, S. *et al.* (2011) Bromodomains as therapeutic targets. *Expert Rev. Mol. Med.* 13 e29/1–e29/9
18 Denis, G.V. *et al.* (2010) An emerging role for bromodomain-containing proteins in chromatin regulation and transcriptional control of adipogenesis. *FEBS Lett.* 584, 3260–3268
19 Chung, C.-w. *et al.* (2011) Discovery and characterization of small molecule inhibitors of the BET family bromodomains. *J. Med. Chem.* 54, 3827–3838
20 Young, P. (2012) RVX-208 is a BET inhibitor currently in phase II human clinical trials for the treatment of atherosclerosis. *Resverlogix Corporate Presentation, 2nd Epigenetics in Drug Discovery*, Boston, MA, May 30–31
21 Adachi, K. Thienotriazlodiazepine compound and a medicinal use thereof. *PCT/JP2006-310709-WO/2006/129623*
22 Filippakopoulos, P. *et al.* (2010) Selective inhibition of BET bromodomains. *Nature* 468, 1067–1073
23 ApoA-I Synthesis Stimulation and Intravascular Ultrasound for Coronary Atheroma Regression Evaluation (ASSURE I). ClinicalTrials.gov identifier NCT01067820
24 Hewings, D.S. *et al.* (2011) 3,5-Dimethylisoxazoles act as acetyl-lysine-mimetic bromodomain ligands. *J. Med. Chem.* 54, 6761–6770
25 Bamborough, P. *et al.* (2012) Fragment-based discovery of bromodomain inhibitors. Part 2: Optimization of phenylisoxazole sulfonamides. *J. Med. Chem.* 55, 587–596
26 Hay, D. *et al.* The design and synthesis of 5- and 6-isoxazolylbenzimidazoles as selective inhibitors of the BET bromodomains. *Med. Chem. Commun*, in press
27 Seal, J. *et al.* (2012) Identification of a novel series of BET family bromodomain inhibitors: binding mode and profile of I-BET151 (GSK1210151A). *Bioorg. Med. Chem. Lett.* 22, 2968–2972
28 Chung, C.-w. *et al.* (2012) Fragment-based discovery of bromodomain inhibitors. Part 1: Inhibitor binding modes and implications for lead discovery. *J. Med. Chem.* 55, 576–586
29 Owen, D.R. (2012) Chemical probes for epigenetics. *Pfizer Corporate Presentation, 2nd Epigenetics in Drug Discovery*, Boston, MA, May 30–31 http://www.thesgc.org/scientists/chemical_probes/PFI-1/
30 Sachchidanand, *et al.* (2006) Target structure-based discovery of small molecules that block human p53 and CREB binding protein association. *Chem. Biol.* 13, 81–90
31 Zeng, L. *et al.* (2005) Selective small molecules blocking HIV-1 Tat and coactivator PCAF association. *J. Am. Chem. Soc.* 127, 2376–2377
32 Vidler, L.R. *et al.* Druggability analysis and structural classification of bromodomain acetyl-lysine binding sites. *J. Med. Chem.*, in press
33 Santiago, C. *et al.* (2011) Druggability of methyl-lysine binding sites. *J. Comput. Aided Mol. Des.* 25, 1171–1178
34 Herold, J.M. *et al.* (2011) Small-molecule ligands of methyl-lysine binding proteins. *J. Med. Chem.* 54, 2504–2511
35 Herold, J.M. *et al.* (2012) Structure–activity relationships of methyl-lysine reader antagonists. *Med. Chem. Commun.* 3, 45–51
36 Mallette, F.A. and Richard, S. (2012) The fight of the Tudor domain 'Royal family' for a broken DNA throne. *Cell Cycle* 11, 1483–1484
37 Herold, J.M. *et al.* (2011) Drug discovery towards antagonists of methyl-lysine binding proteins. *Curr. Chem. Genomics* 5, 51–61
38 Phylogenetic trees for all target classes reviewed can be found at: http://apps.thesgc.org/resources/phylogenetic_trees/

Please cite this article in press as: Owen, D.R. and Trzupek, J.D. Epigenetic drugs that do not target enzyme activity, Drug Discov Today: Technol (2012), http://dx.doi.org/10.1016/j.ddtec.2012.10.008