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Probing the Epigenome

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Epigenetic chemical probes are having a strong impact on biological discovery and target validation. Systematic coverage of emerging epigenetic target classes with these potent, selective, cell-active chemical tools will profoundly influence our understanding of the human biology and pathology of chromatin-templated mechanisms.

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Chemical probes are research-enablers

Advances in genomics and proteomics methodologies in recent years have made it possible to associate thousands of genes and proteins with specific diseases, biological processes, molecular networks and pathways. However, data from these large scale initiatives alone has not translated widely into new studies on these disease-associated proteins, and the biomedical research community still tends to focus on proteins that were already known before the sequencing of the human genome[1]. The human kinome for instance, a target class of direct relevance to cancer and other disease areas, is a telling example: based on the number of research articles indexed in pubmed in 2011, 75% of the research activity focused on only 10% of the 518 human kinases – largely the same kinases that were the focus of research before sequencing of the human genome - while 60% of the kinome, some 300 enzymes, was virtually ignored by the community[2].

We believe that the main reason for the resistance of the research community to work on new protein targets is the paucity of research tools to study the function and chemical tractability of previously uncharacterized proteins. Thus, the availability of a wider variety of tools such as antibodies and chemical probes (potent, selective, and cell-active compounds) could potentially transform biomedical research and enable development of new target areas. Indeed, chemical tools released, for instance, for nuclear hormone receptors about 20 years ago had a significant impact on this target area: of the 37 nuclear hormone receptors that have a known disease association, the eighteen most studied are those for which chemical probes are available[1]. Chemical probes are not only useful to investigate the cellular function of proteins, but also as preclinical target validation tools in disease-relevant assays[3]. Thus, evidence is mounting that unbiased chemical coverage of target classes strongly enables basic research and facilitates translation into drug discovery programs.

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Enzymes and effector proteins involved in epigenetic mechanisms represent a new frontier in drug discovery, and epigenetic related research has grown exponentially in recent years (**Supplementary Fig. 1**). Protein methyltransferases (PMTs) and lysine demethylases (KDMs) respectively deposit and remove methyl marks on histones, while lysine acetyltransferases (KATs) and histone deacetylases (HDACs) write and erase acetyl groups. These post-translational modifications can be read and interpreted by dedicated binding modules such as bromodomains (BRD) that bind target sequence motifs in an acetylation dependent way or a large diversity of methyl-lysine/arginine (Kme/Rme) dependent binding domains. Enzymes and effectors controlling DNA methylation also regulate chromatin mediated signaling. This set of 316 proteins (**Supplementary Table 1**) regulates gene expression programs and cell fate during development and in response to environmental cues. Dysregulation of these processes can be a driver in disease development, and epigenetic protein families are therefore emerging target classes in oncology and other disease areas[4]. Chromatin associated proteins are often composed of multiple domains, each carrying distinct functions. For instance, in addition to its catalytic domain, the histone methyltransferase MLL contains a bromodomain, four PHD finger domains that mediate a variety of protein-protein interactions, and a CXXC domain that binds un-methylated CpG dinucleotide sequences: precise chemical or genetic targeting of each individual domain with chemical probes or gene editing technologies such as CRISPR is necessary to predict domain function in disease. Here we provide an overview of the epigenetic target space and the impact of chemical tools on this biomedical research area.

Epigenetic target classes remain largely unexplored

A parallel can be made between the current state of epigenetic research and the kinase field of 30 years ago where great expectations in this target class were confounded by the lack of tools with which to prioritize and characterize potential therapeutic targets. In the 1980s even the feasibility of targeting any kinase was questioned due to the high cellular ATP concentration competing with inhibitor binding. Promiscuous natural products such as staurosporine mitigated these

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concerns and led to more selective inhibitors that were studied clinically and demonstrated that reasonable selectivity can be achieved by targeting the catalytic site. Approval of the first kinase inhibitors in the early 1990s opened the floodgates and moved this target area in the focus of pharmaceutical industry and intensified academic research. Thus, chemical tools not only enable research but also demonstrate druggability of novel binding sites and establish lead scaffolds for further exploitation.

As a consequence, systematic chemical biology approach towards the development of high quality chemical tools should also translate into more efficient exploration of novel drug discovery areas such as epigenetics. Given the strong and growing interest in epigenetic proteins, we analyzed recent research activity among these protein families. The number of articles indexed in Pubmed and the number of patents filed for a given protein were used as indicators of research activity. Genome-wide association studies (GWAS)[5] that link genetic variations in a protein with diseases, and susceptibility of cancer cell lines to the genetic knock-out of a protein by shRNA[6] served as metrics of relevance to translational research. In the light of these unbiased metrics, and as previously seen for human kinases[2], epigenetic target classes suffer a strong research bias toward previously well-studied targets. While the two metrics used here as indicators of disease association are not comprehensive across all diseases, the lack of correlation between these unbiased signals and the volume of research activity on each gene/protein is striking, as shown here for bromodomain containing proteins, protein methyltransferases, and other epigenetic target classes (**Fig. 1, Supplementary Fig. 2**, **Supplementary Table 1**).

For example, the number of articles indexed in Pubmed exceeds 9000 for the transcriptional activator EP300/p300 (which lights-up in shRNA studies) and 5000 for its close homologue CREBBP/CBP (a GWAS hit and a frequently mutated target in various diseases), but is only 36 for the arginine methyltransferase PRMT7, which

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has been associated with diseases in both shRNA and GWAS studies: silencing PRMT7 significantly decreased breast cancer cell invasion in vitro and metastasis in vivo[7, 8], and a SNP mapping at the *PRMT7* locus was associated with variations in magnesium concentration[9]. Thus, we believe that a potent, selective inhibitor of PRMT7 would enable mechanistic investigation of PRMT7 function in diverse cellular models, possibly with direct implications in drug discovery. Interestingly, the most studied genes seem enriched in disease-associated phenotypes based on the manually-curated Online Mendelian Inheritance in Man (OMIM – http://omim.org): the more research activity on a gene, the more chances to find links to a disease.

Profound impact of epigenetic chemical probes

Based on our hypothesis, the increasing availability of chemical probes during the past 5 years for both well- and under-studied epigenetic proteins should have significantly enabled biomedical research in this target area. Indeed, we find that, when available, these chemical tools have had a strong scientific impact. The research article describing the first chemical probe against a given epigenetic target is consistently the most cited article published that year on the targeted protein (**Supplementary Table 2**). Chemical probes are not only well cited, but also extensively used: in 2014 the majority of articles published on BET bromodomains and the methyltransferase G9a included experiments using BET and G9a inhibitors, respectively (**Fig. 2a-c)**.

An area of research where epigenetic chemical probes have had a profound impact is oncology drug discovery. For example, the panBET family bromodomain inhibitor JQ1 was first used to selectively kill NUT midline carcinoma (NMC) cells in which the nuclear protein NUT (nuclear protein in testis) is aberrantly fused to the bromodomains of either BRD4 or BRD3 (both members of the BET bromodomain family). These gene fusions are strong drivers of tumorigenesis giving rise to NUT midline carcinoma, an aggressive untreatable class of squamous cell carcinoma[10].

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While a related panBET inhibitor I-BET, developed by GSK revealed that selective targeting of BET bromodomains also modulates pro-inflammatory cytokine expression and offers protection against lipopolysaccharide-induced endotoxic shock and bacteria-induced sepsis in mouse models[11]. The now widespread availability of BET inhibitors strongly stimulated research activity demonstrating broad efficacy of BET inhibitors in a variety of cancer models[12]. Moreover, BET inhibitors have been found to modulate other diseases and biological processes that may give rise to the development of new drugs outside the cancer area. For instance, BET inhibition suppresses cardiomyocyte hypertrophy *in vitro* and pathologic cardiac remodeling *in vivo*, reactivates HIV from latency, and blocks the development of mature sperm cells suggesting potential applications as male contraceptive agents[12]. Remarkably, only a few years after their discovery, application of BET chemical probes has validated BET proteins as attractive therapeutic targets, and has led to 18 clinical trials currently underway for BET inhibitors in oncology.

Another impactful use of epigenetic chemical probes has been for cases in which disease association had already been established for the protein target, and a chemical probe was used to test a 'therapeutic hypothesis' in which pharmacological inhibition of a catalytic activity, or of a specific protein-protein interaction, could replicate the effect of genetic deletions. Such examples include methyltransferase inhibitors with strong clinical potential such as DOT1L, EZH2, and PRMT5. Chemical probes for the catalytic activity of these enzymes phenocopy the therapeutic effect of shRNAs directed against these targets, were efficacious in xenograft models of mixed lineage leukemia, non-Hodgkins and mantel cell lymphomas, respectively, thereby further validating the chemical tractability of the methyltransferase target class[13, 14]. EZH2 chemical probes have also been used to demonstrate the addiction of SWI/SNF-mutated cells to the PRC2 complex, and consequent sensitivity of rhabdoid and ovarian tumors to EZH2 inhibition[14, 15]. Smilarly, ependymomas with a CpG island methylator phenotype were shown to be exquisitely sensitive to EZH2

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inhibitors[16]. Pharmacological activation of the histone deacetylase SIRT1 sensitized mixed lineage leukemia to a DOT1L chemical probe, raising the possibility of combination therapy[17], and resistance of metastatic breast cancer cells to the PI3K inhibitor GDC-0941 was overcome when combined with BET inhibitors [18]. As a final example, chemical probes targeting the interaction of Menin, (a component of the MLL complex) with its interaction partner, LEDGF, or the interaction of WDR5 with MLL, effectively disrupted the MLL complex, and demonstrated profound on-target activity in leukemia and prostate cancer models[19-22]. Interestingly, several of the recently reported epigenetic chemical probes target subunits of either wild-type or mutant MLL complexes – very large multiprotein complexes implicated in several types of leukemias and normal development (**Fig. 3a-d**). Thus, these tools can be used to further strengthen the therapeutic hypothesis of targeting the MLL complex in disease, and to dissect its role in developmental pathways.

Epigenetic chemical probes have also been used in more exploratory settings to discover novel biology. For example, a phenotypic screen of 2000 compounds revealed that BIX-01294, an inhibitor of the methyltransferases G9a and GLP, was able to reprogram mouse embryonic fibroblasts transduced with only two transcription factors into embryonic stem cells. The effect was further improved when the calcium channel agonist BayK8644 was combined with BIX-01294, while BIX-01294 alone could efficiently reprogram neural progenitor cells into induced pluripotent stem cells[23, 24]. These results suggest that G9a (and/or GLP) is an important regulator of cellular pluripotency. UNC0638, a second generation, less toxic G9a/GLP chemical probe, was also found to alter H3K9me2 patterning and chromatin structure at CpG islands in hematopoietic progenitor cells[25]. In another example, the G9a inhibitors BIX-01204 and UNC0638 protected hair cells from neomycin-induced damage *in vitro*, and from aminoglycoside-induced damage *in vivo,* suggesting a potential avenue for the treatment of sensorineural hearing loss [26]. Finally, prolonged exposure of lymphoma cells to an EZH2 chemical inhibitor

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revealed resistance mechanisms that should be addressed by next generation inhibitors[27].

Thus, when chemical probes are comprehensively validated[28] (target engagement is clearly established in cells at low concentration, and selectivity is evaluated on a diverse array of enzymes and receptors), and properly applied[3] (doses do not exceed 10 x cellular IC_{50} and inactive derivatives of the probe are used as "control" compounds), they can be profoundly influential for target discovery and broader understanding of human biology and pathology.

Outlook

The chemical probe coverage of BRDs and PMTs is now progressing rapidly (**Fig. 1**) and we anticipate that these novel chemical tools will be instrumental in probing target function and relevance for therapy. KDMs have so far proven more challenging due to the poor cell penetrance of metal-chelating inhibitors. Repeated efforts to develop chemical probes against KATs have been largely unsuccessful, and novel screening strategies, for instance incorporating other components of KAT chromatin complexes to increase druggability, target allosteric sites, or inhibit protein interactions, should be explored. Kme reader domains represent a barely touched landscape consisting of almost 200 proteins. The recently reported chemical probe for the MBT domain protein L3MBTL3[29] provides proof of principle that Kme-binding domains may be chemically tractable, yet further studies are required to reveal whether this target class is fertile ground for drug discovery. Chemical modification of RNA is emerging as an important factor in the epigenetic control of cell fate[30], and may represent the next frontier in the chemical biology of epigenetic mechanisms.

Beyond inhibitors that target epigenetic mechanisms there are a number of large 'chemically tractable' protein families with extensive disease links, but for which there remain insufficient chemical tools. These include also well explored target

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areas such as G-protein Coupled Receptors (GPCRs; 826 human proteins), serine/threonine protein kinases (> 500 proteins) and the Solute Carrier Protein (SLC) family of over 300 membrane transporters – all of which still harbor a high number of potential targets that are currently largely unexplored and functionally poorly annotated. We believe that systematic generation and wide dissemination of chemical probes for these potentially disease modifying targets will have tremendous impact on our understanding of the biology of these proteins and their therapeutic potential. A prerequisite of this will be the rigorous and comprehensive characterization of chemical tool compounds.

However, quality chemical probes are not trivial to develop, requiring multidisciplinary efforts including (ideally) biochemistry, structural biology, medicinal chemistry and cell biology. Traditionally this constellation of expertise has resided primarily in the drug discovery industry where the resulting chemical tools have remained proprietary and hidden from the wider research community. It is encouraging to see that, increasingly, industry is reaching out to collaborate with academia by providing chemical probes as well as expertise and reagents to discover new probes in these exciting areas. Examples of these collaborative efforts include the NIH Molecular Libraries Program, the Structural Genomics Consortium [http://thesgc.org], the GPCR consortium [http://gpcrconsortium.org/], a multi-pharma collaboration with NIH's National Center for Advancing Translational Sciences for drug repurposing, and the consortium to unlock the unknown kinome. Of note, these efforts aim to provide public domain knowledge and tools for the global research community and, in doing so, are changing the research landscape and culture of chemical biology. Early stage protein inhibitory compounds are no longer necessarily proprietary secrets on the path to new drugs, but instead, as shown above, they are being used as powerful tools by the wider community to 'crowd source' new therapeutic targets in more disease settings for more rapid and efficient translation.

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References:

1. Edwards, A.M. et al. Too many roads not taken. *Nature* **470**, 163-5 (2011).
2. Fedorov, O., Muller, S. & Knapp, S. The (un)targeted cancer kinome. *Nat Chem Biol* **6**, 166-169 (2010).
3. Bunnage, M.E., Chekler, E.L. & Jones, L.H. Target validation using chemical probes. *Nat Chem Biol* **9**, 195-9 (2013).
4. Arrowsmith, C.H., Bountra, C., Fish, P.V., Lee, K. & Schapira, M. Epigenetic protein families: a new frontier for drug discovery. *Nat Rev Drug Discov* **11**, 384-400 (2012).
5. Welter, D. et al. The NHGRI GWAS Catalog, a curated resource of SNP-trait associations. *Nucleic Acids Res* **42**, D1001-6 (2014).
6. Cheung, H.W. et al. Systematic investigation of genetic vulnerabilities across cancer cell lines reveals lineage-specific dependencies in ovarian cancer. *Proc Natl Acad Sci U S A* **108**, 12372-7 (2011).
7. Baldwin, R.M. et al. Protein arginine methyltransferase 7 promotes breast cancer cell invasion through the induction of MMP9 expression. *Oncotarget* **6**, 3013-32 (2015).
8. Yao, R. et al. PRMT7 induces epithelial-to-mesenchymal transition and promotes metastasis in breast cancer. *Cancer Res* **74**, 5656-67 (2014).
9. Meyer, T.E. et al. Genome-wide association studies of serum magnesium, potassium, and sodium concentrations identify six Loci influencing serum magnesium levels. *PLoS Genet* **6** (2010).
10. Filippakopoulos, P. et al. Selective inhibition of BET bromodomains. *Nature* **468**, 1067-73 (2010).
11. Nicodeme, E. et al. Suppression of inflammation by a synthetic histone mimic. *Nature* **468**, 1119-23 (2010).
12. Filippakopoulos, P. & Knapp, S. Targeting bromodomains: epigenetic readers of lysine acetylation. *Nat Rev Drug Discov* **13**, 337-56 (2014).
13. Chan-Penebre, E. et al. A selective inhibitor of PRMT5 with in vivo and in vitro potency in MCL models. *Nat Chem Biol* **11**, 432-7 (2015).
14. Copeland, R.A. Molecular pathways: protein methyltransferases in cancer. *Clin Cancer Res* **19**, 6344-50 (2013).
15. Bitler, B.G. et al. Synthetic lethality by targeting EZH2 methyltransferase activity in ARID1A-mutated cancers. *Nat Med* **21**, 231-8 (2015).
16. Mack, S.C. et al. Epigenomic alterations define lethal CIMP-positive ependymomas of infancy. *Nature* **506**, 445-50 (2014).
17. Chen, C.W. et al. DOT1L inhibits SIRT1-mediated epigenetic silencing to maintain leukemic gene expression in MLL-rearranged leukemia. *Nat Med* **21**, 335-43 (2015).
18. Stratikopoulos, E.E. et al. Kinase and BET Inhibitors Together Clamp Inhibition of PI3K Signaling and Overcome Resistance to Therapy. *Cancer Cell* **27**, 837-51 (2015).

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19. Borkin, D. et al. Pharmacologic inhibition of the Menin-MLL interaction blocks progression of MLL leukemia in vivo. *Cancer Cell* **27**, 589-602 (2015).
20. Cao, F. et al. Targeting MLL1 H3K4 methyltransferase activity in mixed-lineage leukemia. *Mol Cell* **53**, 247-61 (2014).
21. Malik, R. et al. Targeting the MLL complex in castration-resistant prostate cancer. *Nat Med* **21**, 344-52 (2015).
22. Grebien, F. Pharmacological targeting of the WDR5-MLL interaction in C/EBPα N-terminal leukemia. *Nature Chemical Biology* **in press** (2015).
23. Shi, Y. et al. Induction of pluripotent stem cells from mouse embryonic fibroblasts by Oct4 and Klf4 with small-molecule compounds. *Cell Stem Cell* **3**, 568-74 (2008).
24. Shi, Y. et al. A combined chemical and genetic approach for the generation of induced pluripotent stem cells. *Cell Stem Cell* **2**, 525-8 (2008).
25. Schones, D.E., Chen, X., Trac, C., Setten, R. & Paddison, P.J. G9a/GLP-dependent H3K9me2 patterning alters chromatin structure at CpG islands in hematopoietic progenitors. *Epigenetics Chromatin* **7**, 23 (2014).
26. Yu, H. et al. Inhibition of H3K9 methyltransferases G9a/GLP prevents ototoxicity and ongoing hair cell death. *Cell Death Dis* **4**, e506 (2013).
27. Gibaja, V. et al. Development of secondary mutations in wild-type and mutant EZH2 alleles cooperates to confer resistance to EZH2 inhibitors. *Oncogene* (2015).
28. Frye, S.V. The art of the chemical probe. *Nat Chem Biol* **6**, 159-161 (2010).
29. James, L.I. et al. Discovery of a chemical probe for the L3MBTL3 methyllysine reader domain. *Nat Chem Biol* **9**, 184-91 (2013).
30. Xhemalce, B., Robson, S.C. & Kouzarides, T. Human RNA methyltransferase BCDIN3D regulates microRNA processing. *Cell* **151**, 278-88 (2012).

Figure 1: Leveling the landscape of epigenetics research. Despite the exponential growth in epigenetics research activity, the majority of epigenetic targets are still largely unexplored: the number of patents filed and number of articles indexed in Pubmed are shown for each bromodomain containing protein (top) and protein methyltransferase (bottom). This biased research activity on a small subset of epigenetic targets is unjustified based on unbiased disease association assays such as susceptibility of cancer cell lines to shRNA knockdown studies, or GWAS disease association (black bars). The growing availability of chemical probes should enable research on underexplored protein targets. Data used to generate the figure is provided in Supplementary Table 1 and Supplementary Figure 1.

Figure 2: Epigenetic chemical probes are extensively used. (**a**) A surge in research activity followed the publication and wide availability of BET bromodomain (left) and G9a (right) inhibitors. (Red: articles in which chemical probes were used. Grey: articles in which chemical probes were not used. Black: all

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articles). Chemical probes were instrumental in revealing the clinical relevance of the BET bromodomains (**b**) and exploring the biology of the methyltransferases G9a/GLP (**c**).

Figure 3: Chemical biology tools for epigenetic drug discovery. Epigenetic transcriptional regulation is mediated by large multisubunit protein complexes which can be 'chemically interrogated' in both normal and disease models. **(a)** The MLL complex maintains homeostasis in haematopoietic cells. Oncogenic fusions of the MLL protein (**b**) or expression of the oncogenic p30 mutant of the C/EBPα transcription factor (**c**) are driver events in leukemia, while partial tandem duplication at the *MLL* gene is associated with poor treatment outcome (**d**).

Fig 1

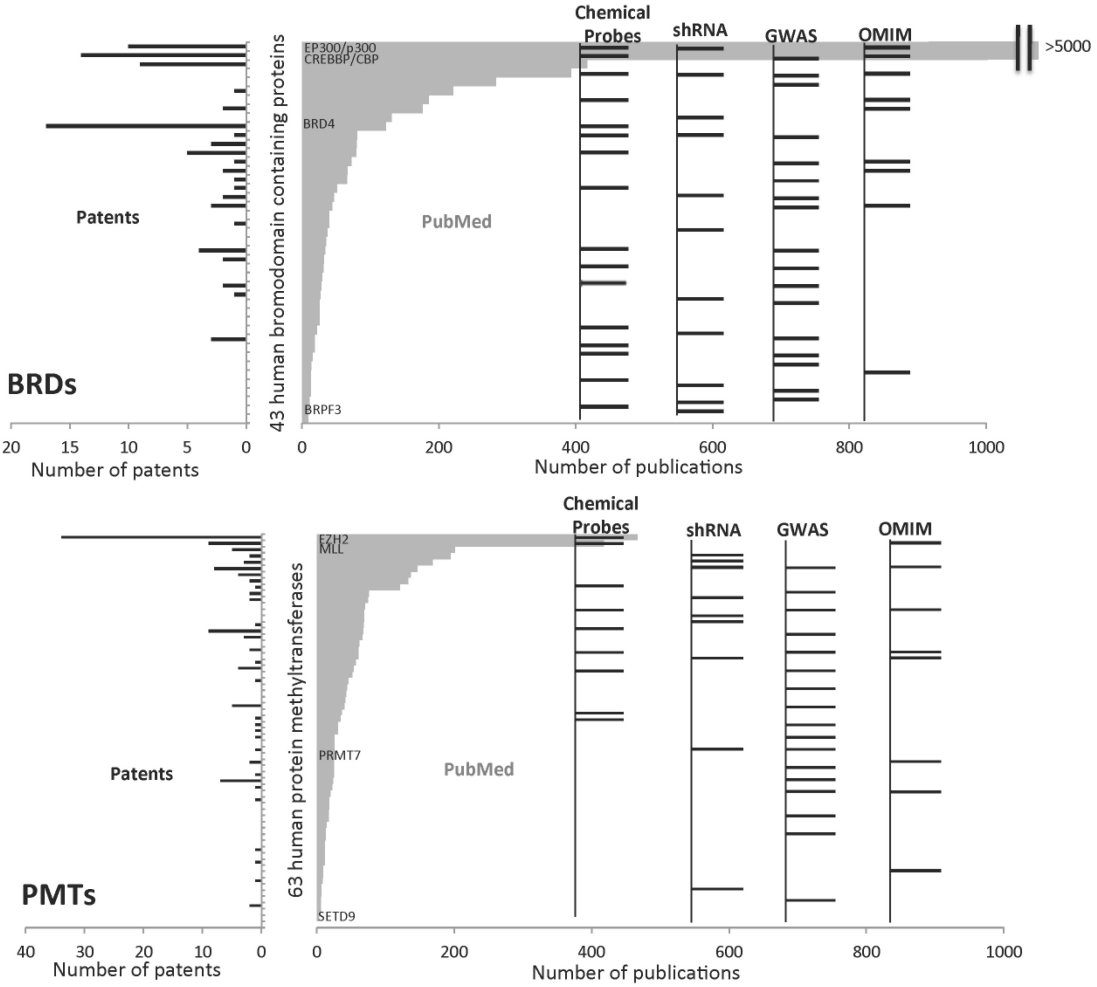


FIGURE 1

2a

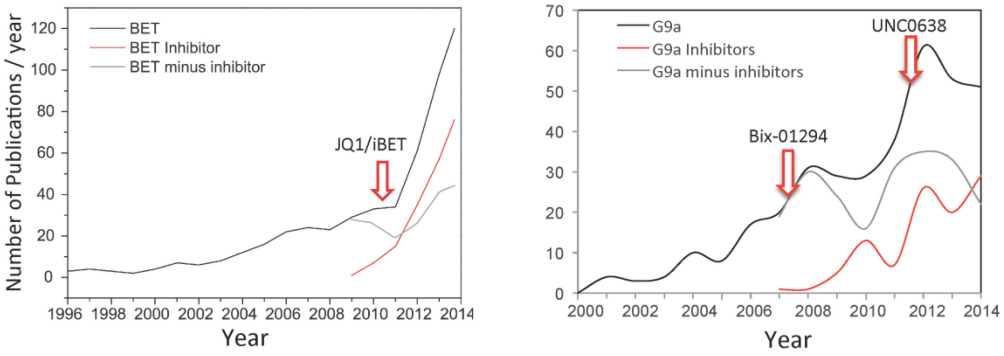
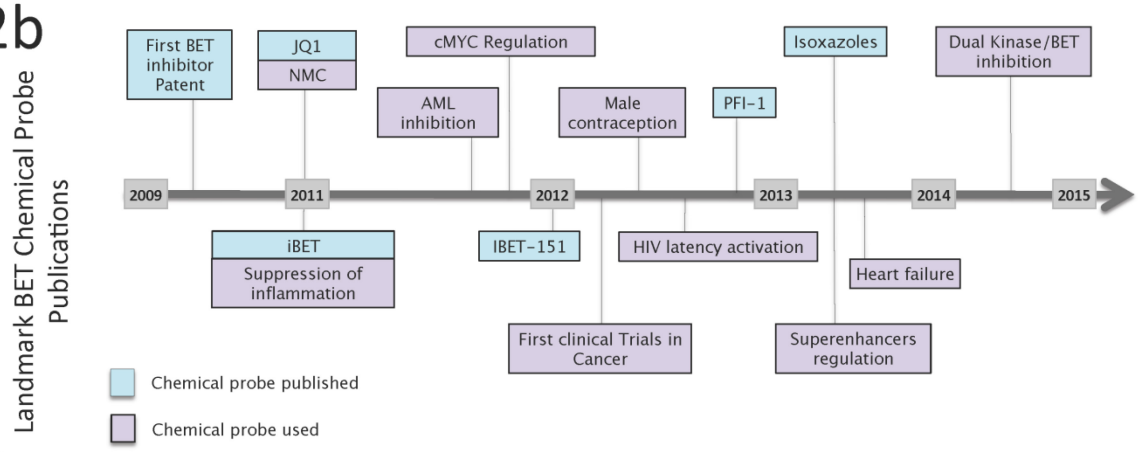
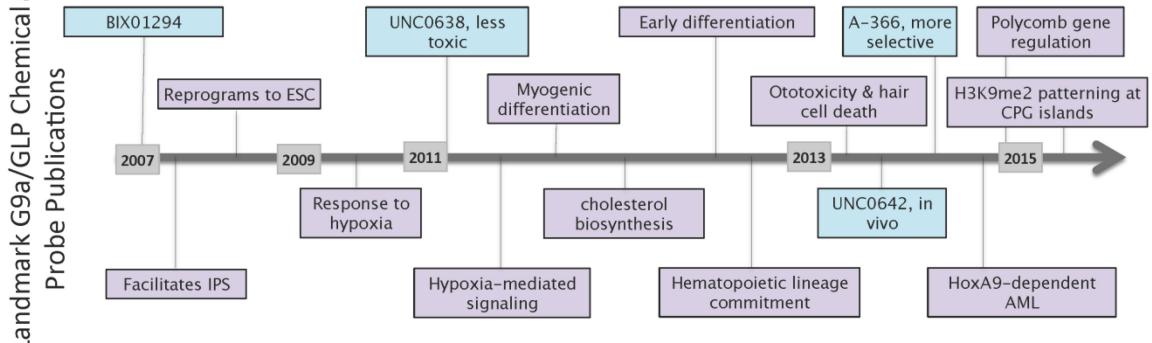

Number of Publications / year
BET
BET Inhibitor
BET minus inhibitor
JQ1/iBET
Year
G9a
G9a Inhibitors
G9a minus inhibitors
UNC0638
Bix-01294
Year

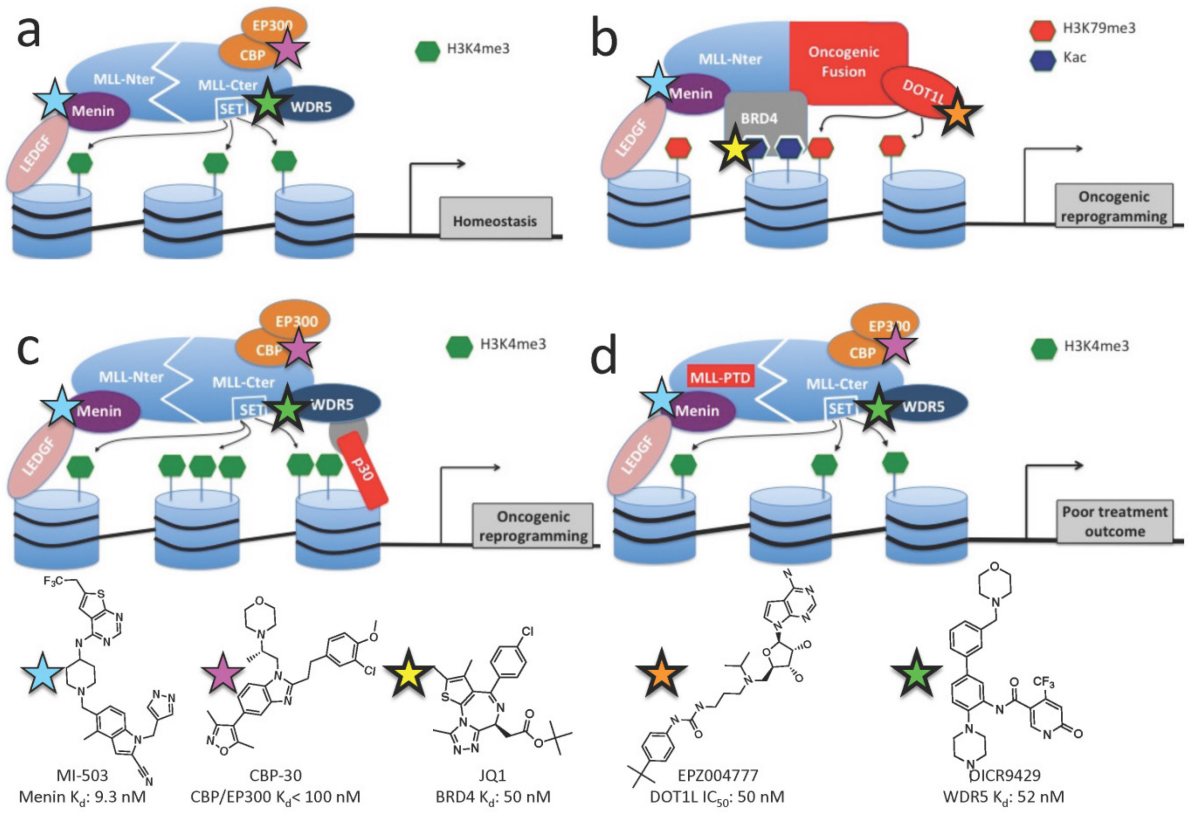
FIGURE 2a

2b


Landmark BET Chemical Probe Publications
First BET inhibitor Patent
JQ1
NMC
cMYC Regulation
AML inhibition
Male contraception
PFI-1
Isoxazoles
Dual Kinase/BET inhibition
2009
2011
2012
2013
2014
2015
iBET
Suppression of inflammation
IBET-151
HIV latency activation
Heart failure
First clinical Trials in Cancer
Superenhancers regulation
Chemical probe published
Chemical probe used

2c


Landmark G9a/GLP Chemical Probe Publications
BIX01294
UNC0638, less toxic
Early differentiation
A-366, more selective
Polycomb gene regulation
Reprograms to ESC
Myogenic differentiation
Ototoxicity & hair cell death
H3K9me2 patterning at CPG islands
2007
2009
2011
2013
2015
Response to hypoxia
cholesterol biosynthesis
UNC0642, in vivo
Facilitates IPS
Hypoxia-mediated signaling
Hematopoietic lineage commitment
HoxA9-dependent AML


a
EP300
CBP
MLL-Nter
MLL-Cter
Menin
SET
WDR5
LEDGF
H3K4me3
Homeostasis
b
MLL-Nter
Oncogenic Fusion
Menin
DOT1L
BRD4
LEDGF
H3K79me3
Kac
Oncogenic reprogramming
c
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Oncogenic reprogramming
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MLL-PTD
MLL-Cter
Menin
SET
WDR5
LEDGF
H3K4me3
Poor treatment outcome
MI-503
Menin Kd: 9.3 nM
CBP-30
CBP/EP300 Kd< 100 nM
JQ1
BRD4 Kd: 50 nM
EPZ004777
DOT1L IC50: 50 nM
DICR9429
WDR5 Kd: 52 nM

Figure 3 a-d

Probing the Epigenome

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Supplementary Table 2. Chemical probes are highly cited. The paper presenting the first chemical probe for a given target systematically ranks in the top 3 of the most cited papers of that year on this target. Citation numbers were taken from Google Scholar. The number of papers published on a target in the year the chemical probe paper was published is taken from Pubmed and indicated in parenthesis next to the citation rank.

Target	Probe	Date Published	Citations	Citation rank	Pubmed ID
BET Bromo-domains	JQ1	Sep 2010	641	1(22)	20871596
	I-BET	Nov 2010	371	2(22)	21068722
	GW841819X	May 2011	112	4(34)	21568322
	I-BET151	Oct 2011	343	3(34)	21964340
	PFI-1	Nov 2012	45	14(52)	23095041
DOT1L	EPZ004777	Jul 2011	278	1(20)	21741596
	SGC0946	Dec 2012	46	2(20)	23250418
EP300/P300	C646	May 2010	149	3(609)	20534345
EZH2	EPZ005687	Sep 2012	192	3(268)	23023262
	GSK126	Oct 2012	349	1(268)	23051747
	GSK343	Oct 2012	46	21(268)	24900432
	EI1	Dec 2012	140	5(268)	23236167
G9a/EHMT2	BIX-01294	Feb 2007	406	1(49)	17289593
	UNC0638	Jul 2011	142	1(76)	21743462
JMJD3	GSK-J1	Jul 2012	147	1(28)	22842901
SMYD2	AZ505	Jul 2011	67	2(8)	21782458

	HIST	ADD	BAH	BROMO	CHROMO	DNMT
AIRE						
ARID4A					YES	
ARID4B					YES	
ASH1L			YES	YES		
ASH2L						
ASXL1						
ASXL2						
ASXL3						
ATAD2				YES		
ATAD2B				YES		
ATAT1						
ATRX		YES				
BAHCC1			YES			
BAHD1			YES			
BAZ1B				YES		
BAZ2A				YES		
BAZ2B				YES		
BRD1				YES		
BRD2				YES		
BRD3				YES		
BRD4				YES		
BRD7				YES		
BRD9				YES		
BRDT				YES		
BRPF1				YES		
BRPF3				YES		
BRWD1				YES		
BRWD3				YES		
CAMKMT						
CARM1						
CBX1					YES	
CBX2					YES	
CBX3					YES	
CBX4					YES	
CBX5					YES	
CBX6					YES	
CBX7					YES	
CBX8					YES	
CDY1					YES	
CDY1B					YES	
CDY2A					YES	
CDY2B					YES	
CDYL					YES	
CDYL2					YES	
CECR2				YES		
CHD6					YES	
CHD7					YES	
CHD8					YES	

CHD9				YES	
CLOCK					
CREBBP			YES		
CXXC1					
DIDO1					
DNMT1		YES			YES
DNMT3A	YES				YES
DNMT3B	YES				YES
DNMT3L	YES				YES
DOT1L					
DPF1					
DPF2					
DPF3					
EHMT1					
EHMT2					
ELP3					
EP300			YES		
EZH1					
EZH2					
GLYR1					
GTF3C4					
HAT1					
HDAC10					
HDAC11					
HDAC3					
HDAC4					
HDAC5					
HDAC6					
HDAC7					
HDAC8					
HDAC9					
HDGF					
HDGFL1					
HDGFRP2					
HDGFRP2					
ING1					
ING2					
ING4					
ING5					
INTS12					
JARID2					
JHDM1D					
JMJD1C					
JMJD5					
KAT2A			YES		
KAT2B			YES		
KDM1A					
KDM1B					
KDM2A					

KDM2B		
KDM3A		
KDM3B		
KDM4A		
KDM4B		
KDM4C		
KDM4D		
KDM4DL		
KDM5A		
KDM5B		
KDM5C		
KDM5D		
KDM6A		
KDM6B		
KIAA1045		
KIAA2026	YES	
L3MBTL		
L3MBTL2		
L3MBTL3		
L3MBTL4		
MBD1		
MBD2		
MBD4		
MBD5		
MBD6		
MBTD1		
MECOM		
MECP2		
METTL21D		
MINA		
MLL	YES	
MLL2		
MLL3		
MLL4		
MLL5		
MLLT10		
MLLT6		
MPHOSPH8		YES
MSH6		
MSL3L1		YES
MTF2		
MUM1		
MYST1		YES
MYST2		
MYST3		
MYST4		
NCOA1		
NCOA3		
NO66		

NSD1		
ORC1	YES	
PHF1		
PHF10		
PHF11		
PHF12		
PHF13		
PHF14		
PHF15		
PHF16		
PHF17		
PHF19		
PHF2		
PHF20		
PHF20L1		
PHF21A		
PHF21B		
PHF23		
PHF3		
PHF6		
PHF7		
PHF8		
PHIP		YES
PHRF1		
PRDM1		
PRDM10		
PRDM11		
PRDM12		
PRDM13		
PRDM14		
PRDM15		
PRDM16		
PRDM2		
PRDM4		
PRDM5		
PRDM6		
PRDM7		
PRDM8		
PRDM9		
PRMT1		
PRMT2		
PRMT3		
PRMT5		
PRMT6		
PRMT7		
PRMT8		
PSIP1		
PWWP2B		
PYGO1		

PYGO2			
Q6ZW69			
RAG2			
RAI1			
RERE	YES		
RSF1			
SCMH1			
SCML2			
SETD1A			
SETD1B			
SETD2			
SETD3			
SETD4			
SETD5			
SETD6			
SETD7			
SETD8			
SETDB1			
SETDB2			
SETMAR			
SFMBT1			
SFMBT2			
SHPRH			
SIRT1			
SIRT2			
SIRT3			
SIRT4			
SIRT5			
SIRT6			
SIRT7			
SMYD1			
SMYD2			
SMYD3			
SMYD4			
SMYD5			
SP100		YES	
SP110		YES	
SP140		YES	
SP140L		YES	
SPIN1			
SPIN2A			
SPIN2B			
SPIN3			
SPIN4			
SUV39H1			YES
SUV39H2			YES
SUV420H1			
SUV420H2			
TAF1		YES	

TAF1L		YES		
TAF3				
TCF19				
TCF20				
TET1				
TET2				
TET3				
TNRC18	YES			
TRDMT1				YES
TRIM24		YES		
TRIM28		YES		
TRIM33		YES		
TRIM66		YES		
UBR7				
UHRF1				
UHRF2				
UTY				
WHSC1				
WHSC1L1				
ZCWPW1				
ZCWPW2				
ZMYND11		YES		
ZMYND8		YES		
BAZ1A		YES		
BPTF		YES		
BRD8		YES		
CHD1			YES	
CHD2			YES	
CHD3			YES	
CHD4			YES	
CHD5			YES	
HDAC1				
HDAC2				
ING3				
KAT5			YES	
MBD3				
MORF4L1			YES	
MTA1	YES			
MTA2	YES			
MTA3	YES			
PBRM1	YES	YES		
SMARCA2		YES		
SMARCA4		YES		
SMARCC1			YES	
SMARCC2			YES	
IDH1				
IDH2				
SETD9				
AKAP1				

CCDC101
FMR1
FXR1
FXR2
LBR
LOC100129278
RNF17
SMN1
SMN2
SMNDC1
SND1
STK31
TDRD1
TDRD10
TDRD12
TDRD3
TDRD5
TDRD6
TDRD7
TDRD9
TDRKH
TP53BP1
ZGPAT

HAT	HDAC_SIRT	PMT	KDM	MBD	MBT	PHD
						YES
		YES				YES
						YES
						YES
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PWWP	SPINDLIN	TET	TUDOR	IDH
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	PubMed	Patents	GWAS	OMIM	Chemical Probes	shRNA
KIAA2026	9	0	0	0	0	YES
BRPF3	10	0	0	0	YES	YES
TRIM66	11	0	YES	0	0	0
ATAD2B	13	0	YES	0	0	YES
BRD9	13	0	0	0	YES	0
BRWD3	13	0	0	YES	0	0
SP140L	14	0	YES	0	0	0
BAZ2B	15	0	YES	0	YES	0
CECR2	19	0	0	0	YES	0
SP140	19	3	YES	0	0	YES
BRPF1	21	0	0	0	YES	0
ASH1L	26	0	0	0	0	0
BRDT	26	0	0	0	0	0
BRWD1	26	0	YES	0	0	YES
PHIP	27	1	0	0	0	0
BRD1	28	2	YES	0	YES	0
TAF1L	29	0	0	0	0	0
BAZ2A	31	0	YES	0	YES	0
ATAD2	32	2	0	0	0	0
BRD3	34	4	YES	0	YES	0
ZMYND8	35	0	0	0	0	0
ZMYND11	37	0	0	0	0	YES
BAZ1A	40	1	0	0	0	0
BRD8	40	0	0	0	0	0
SP110	44	3	YES	YES	0	0
BPTF	47	2	YES	0	0	YES
BRD7	51	1	0	0	YES	0
BAZ1B	66	1	YES	0	0	0
TRIM33	67	2	0	YES	0	0
TRIM24	72	1	YES	YES	0	0
BRD2	79	5	0	0	YES	0
SP100	80	3	0	0	0	0
PBRM1	81	1	YES	0	YES	YES
BRD4	122	17	0	0	YES	0
KAT2A	131	0	0	0	0	YES
TAF1	176	2	0	YES	0	0
SMARCA2	185	0	0	YES	YES	0
TRIM28	221	1	0	0	0	0
KAT2B	283	0	YES	0	0	0
SMARCA4	393	0	YES	YES	YES	YES
MLL	417	9	0	0	0	0
CREBBP/CBP	5481	14	YES	YES	YES	0
EP300/p300	9389	10	0	YES	YES	YES

	PubMed	Patents	GWAS	OMIM	Chemical Probes	shRNA
ATAT1	17	0	0	0	0	0
TAF1L	29	0	0	0	0	0
GTF3C4	37	0	0	0	0	YES
ELP3	41	2	0	0	0	YES
MYST4	43	1	0	0	0	0
HAT1	56	1	0	0	0	YES
MYST3	58	0	0	0	0	0
MYST1	59	0	0	0	0	0
MYST2	60	0	0	0	0	0
KAT2A	131	0	0	0	0	YES
TAF1	176	2	0	YES	0	0
KAT5	195	0	0	0	0	YES
NCOA1	239	0	0	0	0	0
KAT2B	283	0	YES	0	0	0
CLOCK	335	8	YES	0	0	0
NCOA3	342	1	YES	0	0	0
CREBBP/CBP	5481	14	YES	YES	0	0
EP300/p300	9389	10	0	YES	YES	YES

	PubMed	Patents	GWAS	OMIM	Chemical Probes	shRNA
SIRT7	31	4	0	0	0	0
HDAC10	32	6	0	0	0	0
SIRT4	32	6	0	0	0	0
HDAC11	36	2	0	0	0	0
SIRT5	47	7	0	0	0	0
HDAC8	63	12	0	YES	YES	0
SIRT6	79	9	0	0	0	0
HDAC7	110	4	YES	0	YES	0
SIRT2	112	11	0	0	YES	0
HDAC9	121	8	YES	0	YES	0
SIRT3	121	13	0	0	YES	0
HDAC5	167	6	YES	0	YES	0
HDAC4	240	16	YES	YES	YES	0
HDAC6	245	26	0	YES	YES	0
HDAC3	361	17	0	0	YES	0
HDAC2	537	18	0	0	YES	0
SIRT1	755	23	0	0	YES	0
HDAC1	929	15	0	0	YES	0

	PubMed	Patents	GWAS	OMIM	Chemical Probes	shRNA
Q6ZW69	0	0	0	0	0	0
SETD9	3	0	0	0	0	0
METTL21D	6	0	0	0	0	0
PRDM11	6	2	YES	0	0	0
PRDM6	6	0	0	0	0	0
PRDM12	7	0	0	0	0	YES
PRDM13	7	0	0	0	0	0
PRDM7	8	1	0	0	0	0
SETD5	9	0	0	YES	0	0
SMYD5	9	0	0	0	0	0
PRDM10	12	1	0	0	0	0
PRDM8	12	0	0	0	0	0
SETD4	12	1	0	0	0	0
SETDB2	12	0	0	0	0	0
PRDM15	13	0	YES	0	0	0
SETD6	13	0	0	0	0	0
SMYD4	14	0	0	0	0	0
CAMKMT	17	0	YES	0	0	0
PRDM4	17	0	0	0	0	0
SETD1B	18	0	0	0	0	0
SETD3	18	1	0	0	0	0
PRDM5	20	0	YES	YES	0	0
SUV420H2	22	1	0	0	0	0
PRDM14	24	7	YES	0	0	0
PRDM9	25	1	0	0	0	0
SMYD1	25	0	YES	0	0	0
WHSC1L1	25	2	0	YES	0	0
ASH1L	26	0	0	0	0	0
PRMT7	26	1	YES	0	0	YES
PRMT8	26	0	0	0	0	0
SUV420H1	26	1	YES	0	0	0
MLL5	31	1	0	0	0	0
SMYD2	31	1	YES	0	YES	0
EZH1	34	1	0	0	YES	0
SETMAR	36	0	0	0	0	0
SUV39H2	40	5	YES	0	0	0
SETD1A	41	0	0	0	0	0
PRMT2	43	0	0	0	0	0
SETD2	44	0	YES	0	0	0
MLL4	46	1	0	0	0	0
PRMT3	52	0	0	0	YES	0
SMYD3	53	4	YES	0	0	0
PRMT6	57	1	0	0	0	0
EHMT1	60	0	0	YES	YES	YES
PRDM16	60	2	YES	YES	0	0
SETD8	62	0	0	0	0	0
MLL3	66	3	0	0	0	0

DOT1L	67	9	YES	0	YES	0
WHSC1	68	1	0	0	0	0
PRDM2	69	0	0	0	0	YES
SETD7	69	0	0	0	YES	YES
NSD1	70	0	YES	YES	0	0
SETDB1	74	2	0	0	0	0
MLL2	76	2	0	0	0	YES
EHMT2	121	1	YES	0	YES	0
SUV39H1	133	2	0	0	0	0
CARM1	137	4	0	0	0	0
PRMT5	146	8	0	0	0	0
MECOM	169	3	YES	YES	0	YES
PRDM1	195	2	0	0	0	YES
PRMT1	201	5	0	0	0	YES
MLL	417	9	0	0	YES	0
EZH2	467	34	0	YES	YES	0

Chemical Probe Polyspecificity:
-EHMT1, EHMT2

	PubMed	Patents	GWAS	OMIM	Chemical Probes	shRNA
NO66	9	1	0	0	0	0
JHDM1D	13	0	0	0	0	0
PHF2	16	2	0	0	0	0
KDM4D	17	0	0	0	0	0
KDM4DL	17	0	0	0	0	0
JMJD5	18	0	0	0	0	0
KDM1B	18	0	0	0	0	0
UTY	21	0	0	0	0	0
KDM3B	35	0	YES	0	0	0
KDM6B	35	1	0	0	0	0
MINA	35	1	0	0	0	0
KDM2B	36	0	YES	0	0	0
JMJD1C	38	1	YES	0	0	YES
KDM3A	39	0	0	0	0	YES
KDM4B	40	0	YES	0	0	0
KDM4C	41	0	YES	0	0	0
KDM5D	44	0	0	0	0	YES
KDM2A	45	1	0	0	0	YES
PHF8	46	0	YES	YES	0	0
KDM5A	51	0	0	0	0	YES
KDM6A	53	1	0	YES	0	0
KDM4A	56	0	YES	0	0	0
KDM5C	60	0	0	YES	0	0
JARID2	61	5	0	0	0	0
KDM5B	68	0	0	0	0	0
KDM1A	165	40	0	0	YES	0

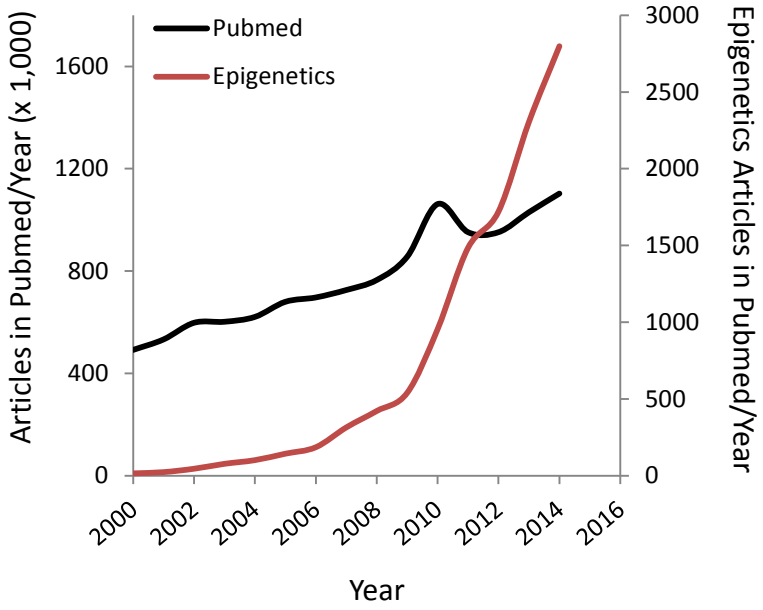
	PubMed	Patents	GWAS	OMIM	Chemical Probes	shRNA
LOC100129278	2	0	0	0	0	0
KIAA1045	3	0	0	0	0	0
HDGFL1	4	0	0	0	0	0
ZCWPW2	5	0	0	0	0	0
BAHCC1	6	0	0	0	0	0
TDRD10	6	0	0	0	0	0
TDRD12	6	0	0	0	0	0
PWWP2B	7	0	0	0	0	0
SPIN4	7	0	0	0	0	0
PHF21B	9	0	0	0	0	0
SPIN3	9	0	0	0	0	0
ZCWPW1	9	0	YES	0	0	0
BRPF3	10	0	0	0	0	YES
PHF13	10	0	0	0	0	0
SPIN2B	10	0	0	0	0	0
ASXL3	11	0	YES	YES	0	0
MBTD1	11	0	0	0	0	0
PHF23	11	0	YES	0	0	0
RNF17	11	1	0	0	0	YES
STK31	11	1	0	0	0	0
TRIM66	11	0	YES	0	0	0
L3MBTL4	12	0	YES	0	0	YES
TDRD5	12	0	0	0	0	0
CDY2B	13	0	0	0	0	0
JHDM1D	13	0	0	0	0	0
TDRD6	13	0	0	0	0	0
TDRKH	13	0	0	0	0	0
BAHD1	14	0	0	0	0	0
DPF1	14	0	0	0	0	0
PHF15	14	0	0	0	0	0
SFMBT2	14	0	0	0	0	0
SP140L	14	0	YES	0	0	0
SPIN2A	14	0	0	0	0	0
BAZ2B	15	0	YES	0	0	0
DPF3	15	0	0	0	0	0
PYGO1	15	0	0	0	0	0
TNRC18	15	0	0	0	0	0
CDY2A	16	0	0	0	0	0
CDYL2	16	0	YES	0	0	0
PHF2	16	2	0	0	0	0
CDY1B	17	0	0	0	0	0
PHF20L1	17	0	0	0	0	0
SCML2	17	0	0	0	0	YES
CHD9	18	0	YES	0	0	0
INTS12	18	0	YES	0	0	YES
PHF16	18	0	0	0	0	YES
PHF19	18	0	YES	0	0	0

UBR7	18	0	0	0	0	0
MBD5	19	0	0	YES	0	0
MLLT6	19	0	0	0	0	0
PHF14	19	1	0	0	0	0
PHF7	19	0	0	0	0	YES
SP140	19	3	YES	0	0	YES
CCDC101	20	0	0	0	0	0
HDGFRP2	20	0	0	0	0	0
MUM1	20	1	0	0	0	0
SHPRH	20	1	0	0	0	YES
BRPF1	21	0	0	0	0	0
L3MBTL3	21	0	YES	0	YES	0
MPHOSPH8	21	0	0	0	0	0
MSL3L1	21	0	0	0	0	0
PHF12	21	0	0	0	0	0
SFMBT1	21	0	0	0	0	0
TDRD7	21	0	0	YES	0	0
CDY1	22	1	0	0	0	0
PHF3	22	1	0	0	0	0
TDRD3	22	0	YES	0	0	YES
CBX6	23	0	0	0	0	0
GLYR1	24	0	0	0	0	YES
PHF21A	24	0	YES	0	0	0
CHD6	25	2	YES	0	0	0
TCF19	25	0	YES	0	0	0
WHSC1L1	25	2	0	YES	0	0
ASH1L	26	0	0	0	0	0
ASXL2	26	0	0	0	0	0
ZGPAT	26	0	YES	0	0	0
CHD2	27	2	YES	YES	0	YES
BRD1	28	2	YES	0	0	0
ING3	28	0	0	0	0	0
SCMH1	28	0	YES	0	0	0
SMNDC1	28	0	0	0	0	0
ARID4B	29	0	0	0	0	0
PHF17	30	0	0	0	0	0
PHF20	30	1	YES	0	0	0
PHRF1	30	0	YES	0	0	0
BAZ2A	31	0	YES	0	0	0
CBX7	31	1	YES	0	0	0
CDYL	31	0	YES	0	0	0
MLL5	31	1	0	0	0	0
PHF11	31	0	YES	YES	0	0
TDRD1	31	0	0	0	0	0
PHF10	32	1	YES	0	0	0
ING5	33	2	0	0	0	0
PYGO2	33	0	0	0	0	0
ARID4A	34	0	0	0	0	YES
L3MBTL	34	1	0	0	0	0

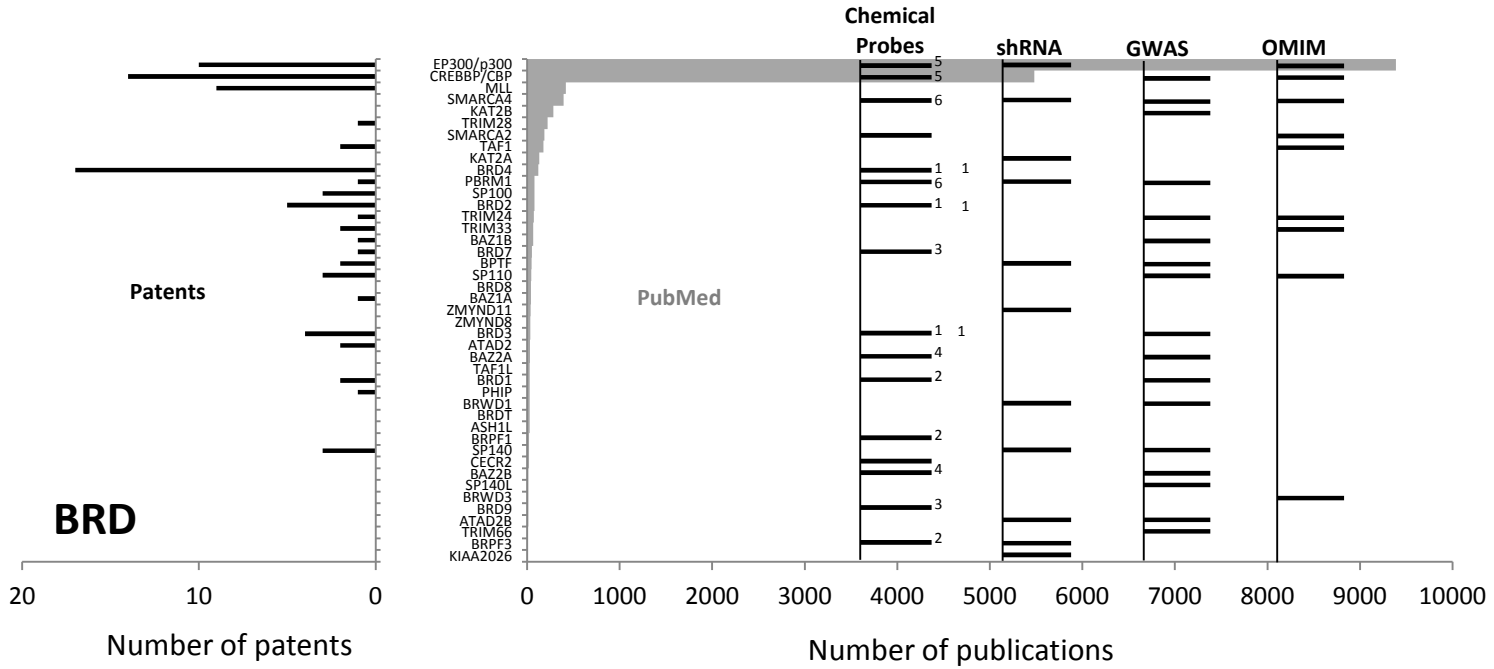
L3MBTL2	34	0	0	0	0	YES
RERE	35	0	YES	0	0	0
ZMYND8	35	0	0	0	0	0
KDM2B	36	0	YES	0	0	0
ZMYND11	37	0	0	0	0	YES
BAZ1A	40	1	0	0	0	0
CHD5	40	3	0	0	0	0
KDM4B	40	0	YES	0	0	0
SPIN1	40	0	0	0	0	0
SUV39H2	40	5	YES	0	0	0
TCF20	40	0	0	0	0	0
KDM4C	41	0	YES	0	0	0
MLLT10	41	0	YES	0	0	0
PHF6	41	0	0	YES	0	0
TAF3	41	0	YES	0	0	YES
UHRF2	41	0	YES	0	0	0
CBX8	42	0	0	0	0	0
CXXC1	42	0	0	0	0	0
MYST4	43	1	0	0	0	0
DIDO1	44	0	0	0	0	YES
KDM5D	44	0	0	0	0	YES
MTF2	44	0	0	0	0	0
SP110	44	3	YES	YES	0	0
DPF2	45	0	0	0	0	0
KDM2A	45	1	0	0	0	YES
CHD1	46	2	0	0	0	YES
MLL4	46	1	0	0	0	0
PHF1	46	1	0	0	0	YES
PHF8	46	0	YES	YES	0	0
BPTF	47	2	YES	0	0	YES
MTA3	49	0	YES	0	0	YES
RAI1	49	1	0	YES	0	0
CHD8	50	0	0	YES	0	0
KDM5A	51	0	0	0	0	YES
ING2	54	1	0	0	0	0
KDM4A	56	0	YES	0	0	0
RSF1	56	0	0	0	0	0
FXR2	57	1	YES	0	0	0
MYST3	58	0	0	0	0	0
MYST1	59	0	0	0	0	0
ORC1	59	1	0	YES	0	0
KDM5C	60	0	0	YES	0	0
CBX2	63	3	0	YES	0	0
BAZ1B	66	1	YES	0	0	0
MLL3	66	3	0	0	0	0
MORF4L1	66	0	0	0	0	0
TRIM33	67	2	0	YES	0	0
KDM5B	68	0	0	0	0	0
WHSC1	68	1	0	0	0	0

AKAP1	69	1	0	0	0	0
NSD1	70	0	YES	YES	0	0
TDRD9	71	0	YES	0	0	0
TRIM24	72	1	YES	YES	0	0
CBX4	73	0	0	0	0	0
FXR1	74	2	0	0	0	0
SETDB1	74	2	0	0	0	0
MLL2	76	2	0	0	0	YES
ING4	77	6	0	0	0	0
SP100	80	3	0	0	0	0
ASH2L	81	3	YES	0	0	YES
PBRM1	81	1	YES	0	0	YES
HDGF	85	9	0	0	0	0
CHD3	86	1	0	0	0	0
ASXL1	89	2	0	YES	0	0
DNMT3L	89	3	0	0	0	0
LBR	90	0	YES	YES	0	0
SND1	93	2	0	0	0	0
CHD7	98	2	0	YES	0	0
ING1	102	8	0	YES	0	0
MTA2	102	0	0	0	0	0
CBX1	104	0	0	0	0	0
SMARCC2	104	0	0	0	0	YES
UHRF1	116	4	0	0	0	0
CHD4	129	0	0	0	0	YES
SUV39H1	133	2	0	0	0	0
CBX3	145	0	0	0	0	0
SMARCC1	152	0	0	0	0	YES
MTA1	166	13	0	0	0	0
ATRX	173	4	0	YES	0	0
KAT5	195	0	0	0	0	YES
CBX5	196	0	0	0	0	0
PSIP1	218	0	0	0	0	0
TRIM28	221	1	0	0	0	0
TP53BP1	226	2	0	0	0	0
AIRE	229	3	YES	YES	0	0
SMN2	281	20	0	YES	0	0
DNMT3A	302	8	YES	YES	0	0
DNMT3B	331	9	YES	YES	0	0
MSH6	337	5	0	YES	0	YES
SMN1	359	8	0	YES	0	0
MLL	417	9	0	0	0	0
DNMT1	516	14	0	YES	0	0
FMR1	636	20	0	YES	0	0
RAG2	671	5	0	YES	0	0

	PubMed	Patents	GWAS	OMIM	Chemical Probes	shRNA
SETDB2	12	0	0	0	0	0
MBD6	13	0	0	0	0	0
BAZ2B	15	0	YES	0	0	0
MBD5	19	0	0	YES	0	0
TET3	20	1	YES	0	0	0
BAZ2A	31	0	YES	0	0	0
TET1	36	2	0	0	0	0
TRDMT1	42	0	YES	0	0	0
MBD1	61	1	0	0	0	0
MBD4	67	0	0	0	0	0
MBD3	71	0	0	0	0	0
SETDB1	74	2	0	0	0	0
DNMT3L	89	3	0	0	0	0
MBD2	95	7	0	0	0	0
TET2	121	3	YES	YES	0	0
IDH2	179	10	0	YES	0	0
DNMT3A	302	8	YES	YES	0	0
DNMT3B	331	9	YES	YES	0	0
IDH1	337	20	0	YES	YES	0
MECP2	436	16	0	YES	0	0
DNMT1	516	14	0	YES	YES	0



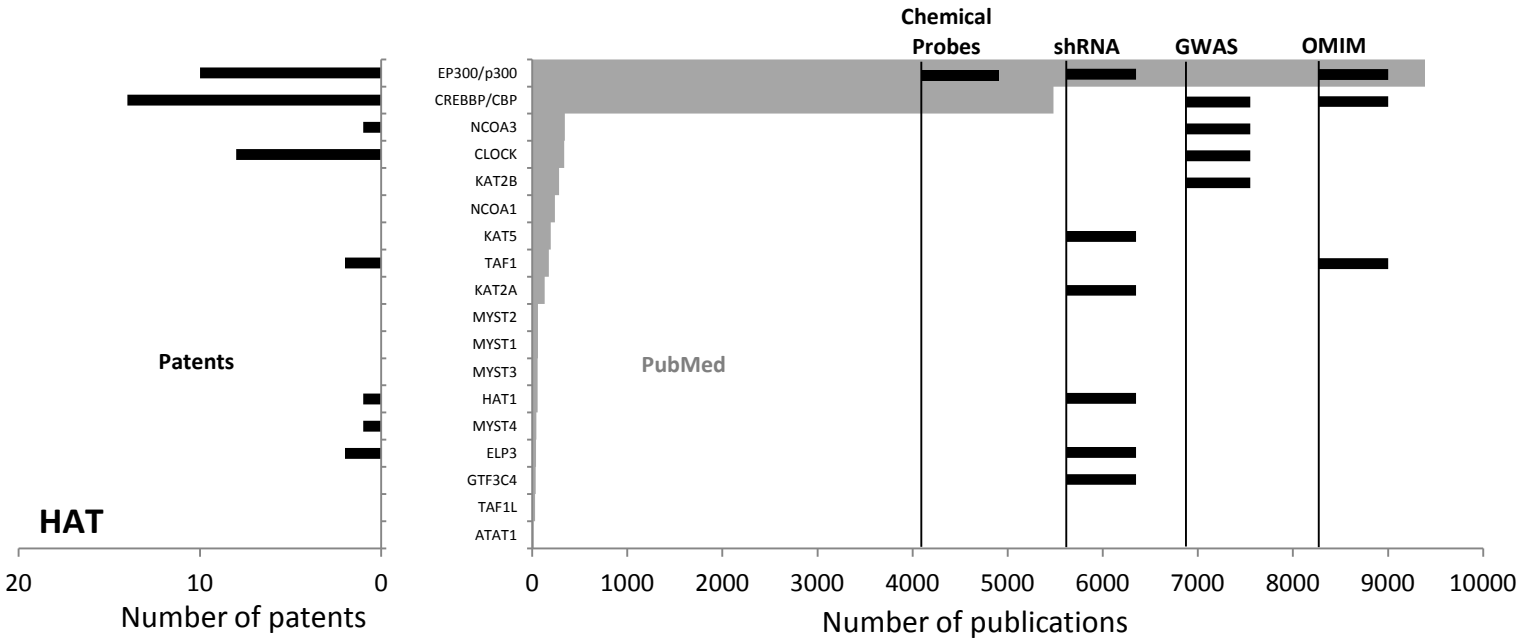
Supp. Figure 1: Exponential growth of epigenetics research. The number of articles indexed in pubmed each year matching the keyword “epigenetics” (red) is growing at a much faster pace than the overall research activity in the life sciences (black).



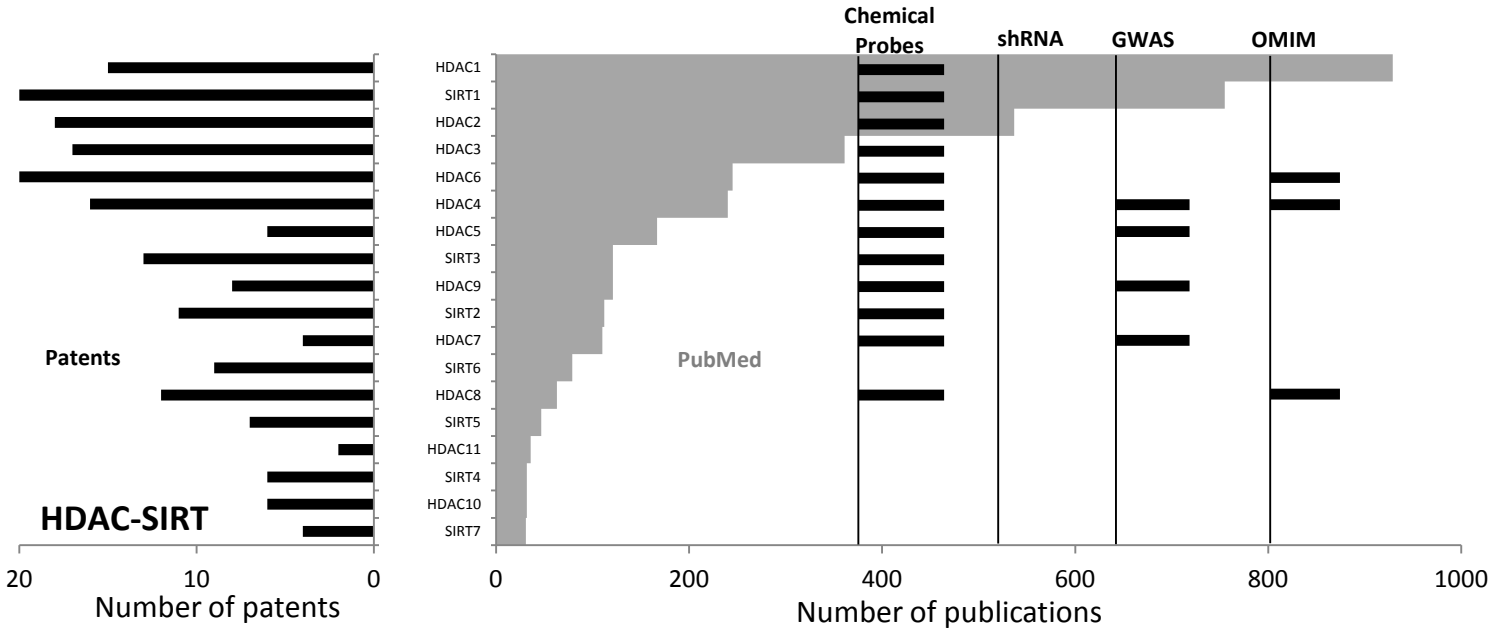
Chemical Probe Poly-specificity:
1-BRD2, BRD3, BRD4
2-BRPF1,BRD1/BRPF2,BRPF3
3-BRD7,BRD9
4-BAZ2A,BAZ2B
5-CREBBP/EP300
6-SMARCA4,PB1

http://www.thesgc.org/chemical-probes/epigenetics

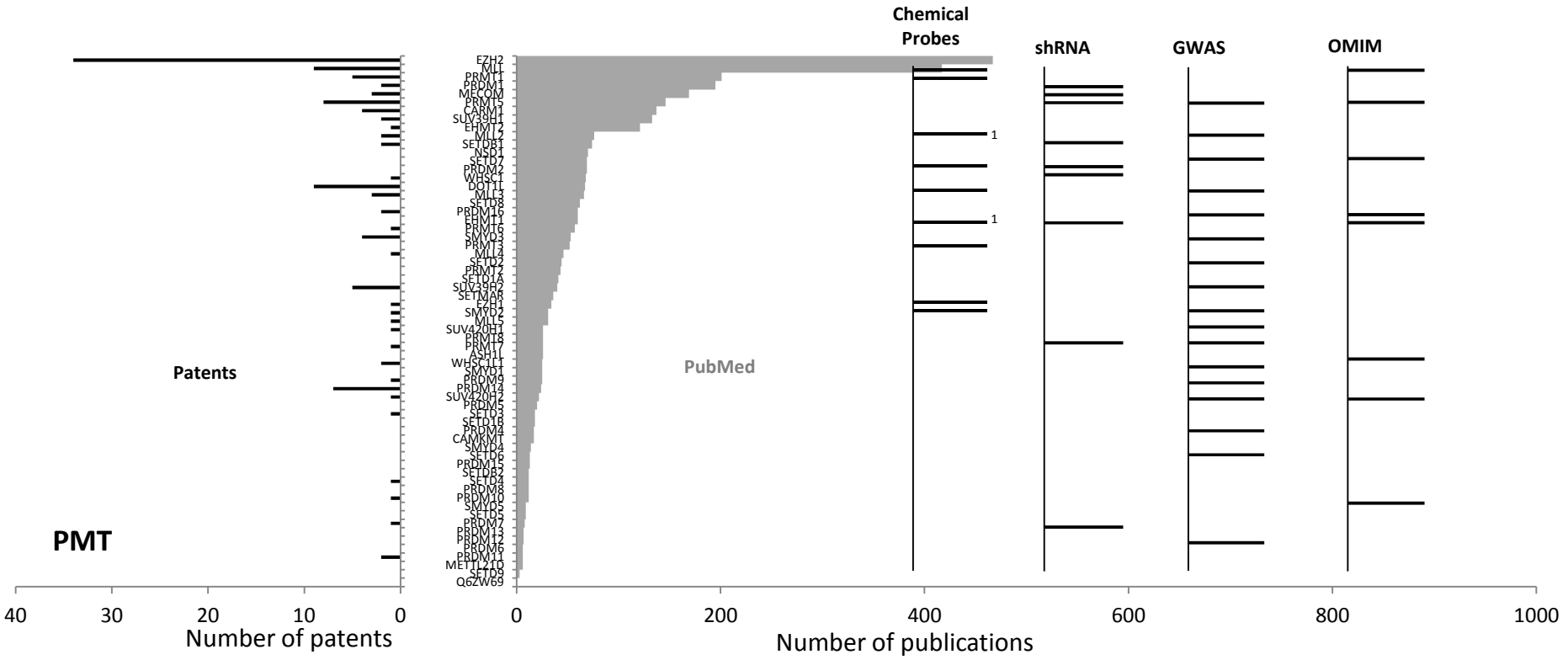
Supp FIGURE 2 a



Supp FIGURE 2 b

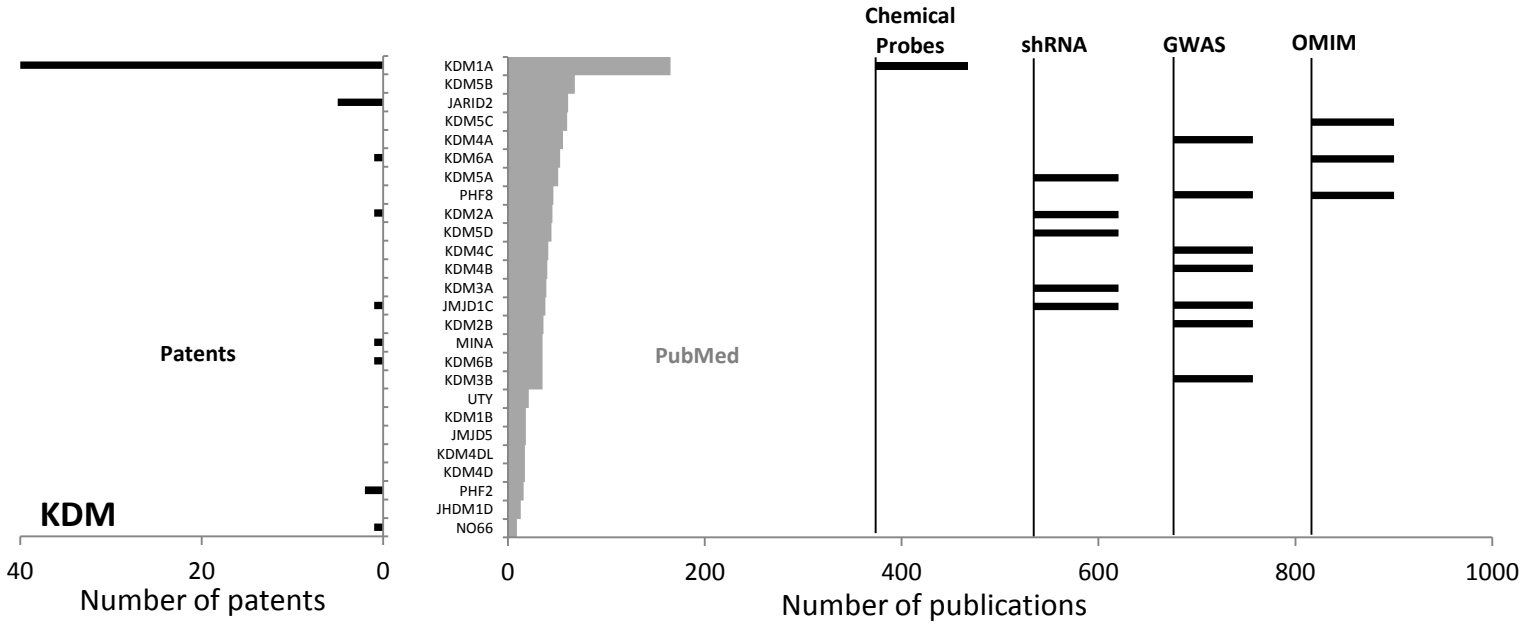


Supp FIGURE 2 c

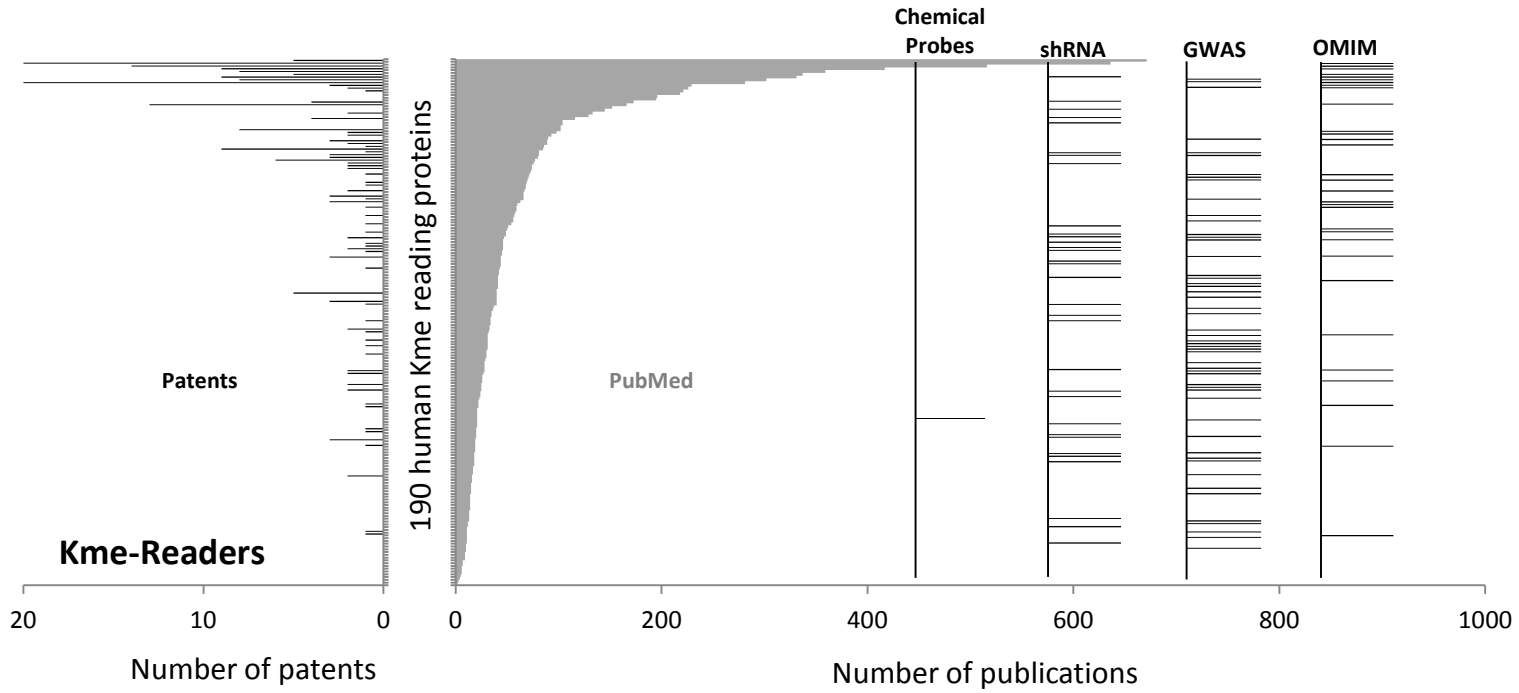


Chemical Probe Polyspecificity:
1-EHMT1, EHMT2

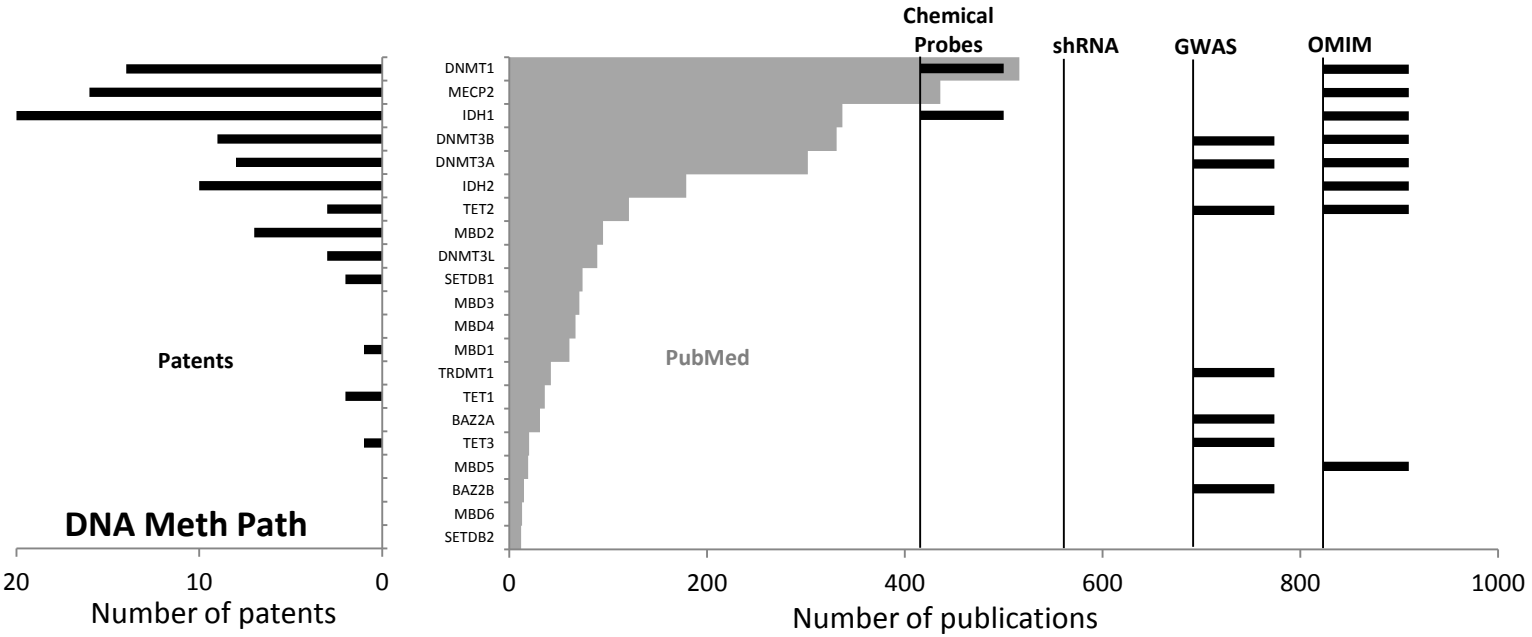
Supp FIGURE 2 d



Supp FIGURE 2 e



Supp FIGURE 2 f



Supp FIGURE 2 g