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CAYMAN CURRENTS

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EPIGENETICS

IN THIS ISSUE:

Bromodomain Targeting with PROTACs

by Fred L. Ciske and Thomas G. Brock, Ph.D., Cayman Chemical

A key concept in the field of epigenetics is the generation of persistent changes in gene expression without changing DNA sequence. These persistent changes involve groups of genes regulated in a coordinated manner, resulting in shifts in the 'epigenetic landscape,' first proposed by Conrad Waddington in the 1940s. Today, such changes are considered to drive such processes as cellular differentiation from pluripotent embryonic stem cells to specific lineages or the dedifferentiation of mature cells into cancer cells. Changes in the expression of groups of genes may be ascribed to a variety of factors, such as chromatin remodeling. Current research focuses on revealing the molecular details behind these changes. This review touches on lysine acetylation and its role in changing gene expression and highlights a unique protein degradation strategy notably demonstrated on bromodomains (BRDs).

Lysine Acetylation and Bromodomains

Remarkably, ε-N-acetylation of lysine residues on proteins is one of the most frequently occurring post-translational modifications, with more than 3,600 catalogued lysine acetylation sites on 1,750 proteins.[1] The levels of histone acetylation are maintained by two families of enzymes: the histone acetyltransferases (HATs) and histone deacetylases (HDACs). Acetylation of histones regulates gene transcription, DNA repair, and chromatin condensation.[2] These effects are ultimately determined by the pattern of acetylation marks.

BRDs are the modules on certain proteins that act as the readers of ε-N-lysine acetylation marks placed on histones and other proteins. They are present in diverse nuclear proteins, including BRD and extra-terminal domain (BET) family proteins, HATs (GCN5, PCAF), chromatin-remodeling enzymes (BAZ1B, SMARCA), methyltransferases (MLL, ASH1L), transcription factors (TAF1), and nuclear-scaffolding proteins (PB1). Dysfunction involving BRDs has been implicated in broad categories of diseases, including cancer, obesity, type 2 diabetes, and inflammation.[3,4] Examples of

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more specific diseases associated with mutations or fusions of genes expressing proteins with BRDs include veno-occlusive disease with immunodeficiency syndrome (SP110), X-linked mental retardation (BRWD3), and infant pro-B acute lymphoblastic leukemia (ALL).[5-7]

The BET family protein BRD4 contains tandem BRDs on its N-terminal half (the ET portion resides on the C-terminal portion). The first BRD of the tandem pair displays high affinity for acetylated sites on histone 4 (H4), particularly Lys5, whereas the second BRD binds promiscuously to several acetylated lysines.[8] Full length BRD4 preferentially binds polyacetylated H4 and the specific BRD4 inhibitor JQ1 abrogates this interaction.[9] BRD4 plays key roles in cellular proliferation, including binding nucleosomes during M phase when most nuclear regulatory factors are released into the cytoplasm in response to a global stop of transcription.[10] Knockdown of BRD4 in mouse embryonic stem cells suppresses Nanog expression and abolishes self-renewal of stem cells.[11] Thus, BRD4 binds H4 in a regulated manner, and binding affects proliferation.

BRD4, bound to acetylated H4, serves both as a docking site and a modulator of proteins that regulate gene expression. For example, the ET portion of BRD4 interacts with the positive transcription elongation factor P-TEFb and causes the release of inhibitory proteins, allowing efficient RNA Pol II-mediated transcription.[12] BRD4 promotes P-TEFb-dependent phosphorylation of Ser2 on the carboxy-terminal domain of Pol II, activating its elongation state. The ET portion of BRD4 can also bind several other proteins, including NSD3, a histone methyltransferase, and JMJD6, an arginine demethylase, that function to activate transcription.[13]

Interest in BRDs as a group is underscored by the extensive development of inhibitors as selective chemical probes (www.thesgc.org) and clinical therapeutics.[14,15] Likely the most studied of these, JQ1 displaces BRD4 from nuclear chromatin at nanomolar concentrations, inducing cell cycle arrest and initiating apoptosis in a variety of cancer cells.[16] While JQ1 is not being tested in clinical trials due to its short half-life *in vivo*, it remains a valuable tool compound and has recently been used, along with its analogs, in a design strategy that effectively changes its function from an inhibitor to a BRD degrader.

PROTACs: Tagging Proteins for Destruction

As BRD inhibitors are currently under clinical evaluation, a relatively recent protein degradation strategy has demonstrated new potential and may circumvent some of the compensatory mechanisms associated with enzyme inhibition.[17] Proteolysis Targeting Chimeras (PROTACs) recruit the cells' own housekeeping machinery, the ubiquitin-proteasome system (UPS), to selectively destroy target proteins rather than just inhibit them.[18-20] PROTACs are hetero-bifunctional molecules consisting of two separate but linked structure elements: one binds a target protein of interest while the other engages an E3 ubiquitin ligase for ubiquitin tagging and subsequent proteasomal degradation (**Figure 1**). This tagging of the protein of interest is an event-driven approach that allows for multiple rounds of binding and, therefore, multiple protein targets may be removed per PROTAC molecule.[21] Traditionally 'undruggable' proteins (scaffolds, weak binders, etc.) can also be targeted since any transient binding interaction with the target protein could be exploited and, depending upon a target's propensity for ubiquitination, a promiscuous inhibitor could potentially be rendered a selective degrader.

Thus far, only a few of the more than 600 encoded E3 ligases have been engaged by prepared PROTACs, with von Hippel-Lindau (VHL) and Cereblon (CRBN) E3 ligase components being employed to induce degradation of BRD proteins. These PROTAC molecules

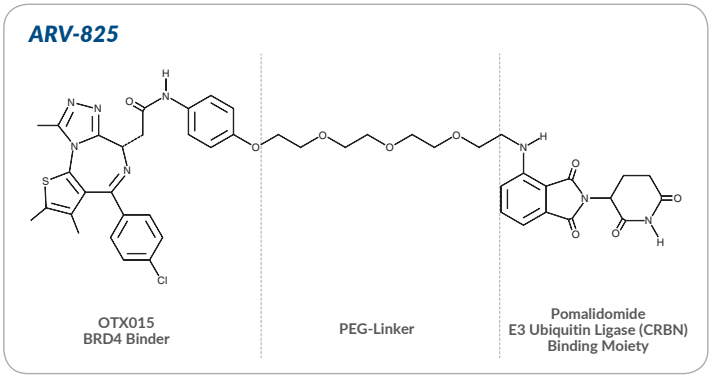
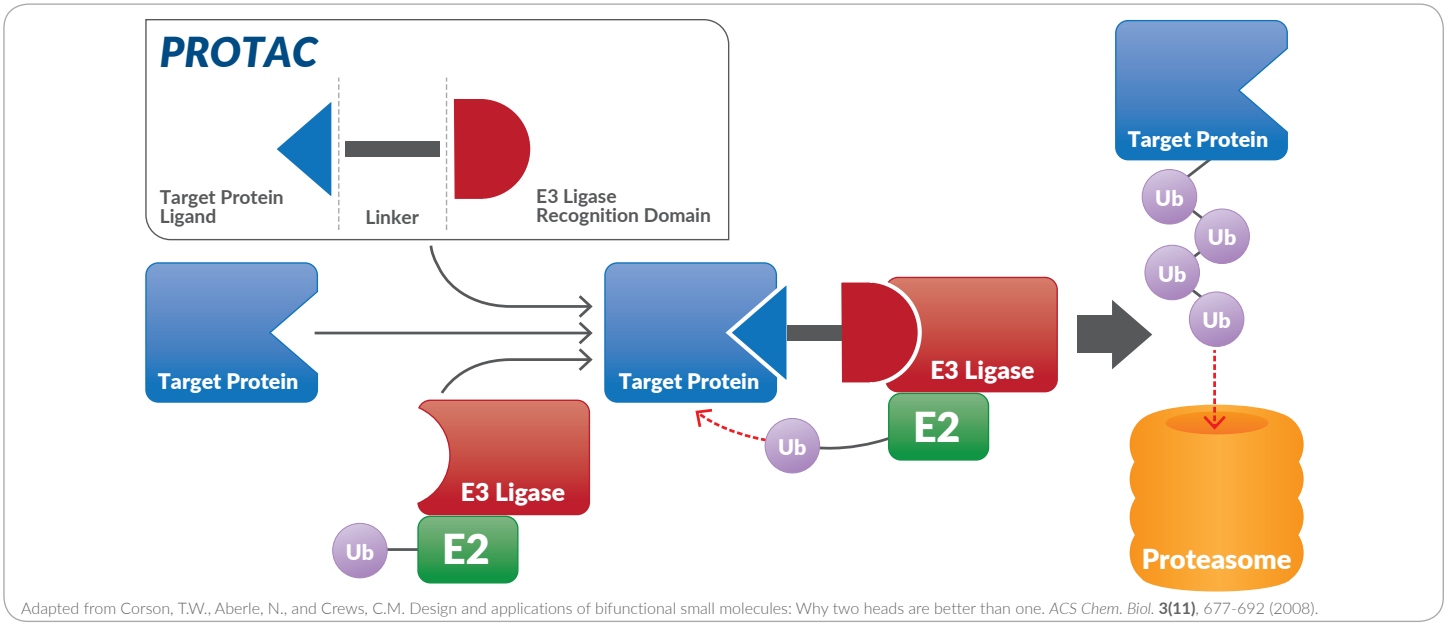


Figure 2. A bifunctional PROTAC molecule ARV-825. The BRD4 protein binder (OTX015) is tethered to a known E3 ligase recognition motif (pomalidomide).



Adapted from Corson, T.W., Aberle, N., and Crews, C.M. Design and applications of bifunctional small molecules: Why two heads are better than one. *ACS Chem. Biol.* **3(11)**, 677-692 (2008).

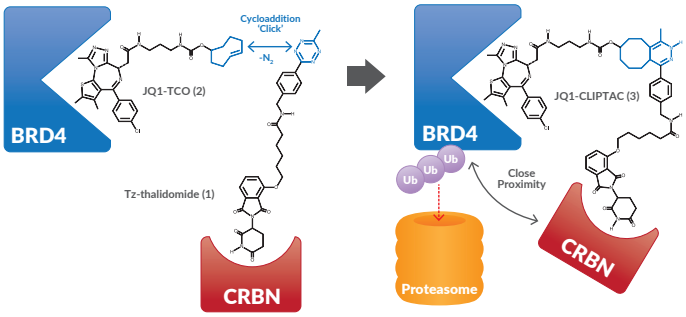
Figure 1. Proteolysis Targeting Chimera (PROTAC) recruitment of an E3 ligase for target protein degradation *via* the ubiquitin-proteasome pathway.

were constructed using an alkyl or polyethylene glycol (PEG) linker to join the known BRD2, BRD3, and BRD4 inhibitors JQ1 or OTX015 to peptide-like VHL binding moieties or to CRBN binders like pomalidomide as shown in **Figure 2** for ARV-825.[22-25]

In target protein degradation studies, ARV-825 dramatically knocked down BRD4 levels within 6 hours, and the effect lasted more than 24 hours. Effectiveness of the PROTAC was evidenced by the fact that OTX015 and CRBN moieties separately display binding affinities of 10 nM and 3 µM for their respective targets while the degradation constant (DC_{50}) of ARV-825 was 1 nM, suggesting a catalytic effect.[23] In a separate leukemia study, ARV-825 was synergistic with co-administered JAK inhibitor ruxolitinib and induced high levels of apoptosis in ruxolitinib-resistant cells. Studies on ARV-771, a JQ1-linked, VHL-binding PROTAC, demonstrated cellular activity and delayed leukemia progression in mouse xenografts.[24,26]

Both BRD4 and ERK1/2 kinase degradation was demonstrated in HeLa cells using the 'click' chemistry approach, wherein PROTAC molecules were generated *in situ* from separate partner-reactive motifs (**Figure 3**).[27] With the aim of improving drug-like properties of solubility and cell permeability, in-cell generation of these 'CLIPTACs' may circumvent potentially difficult linker optimization and expand the inhibitor toolkit available to biologists.

Key to the success of future PROTAC drug efforts will be the discovery and development of relevant E3 ligase recognition motifs (degron mimics) and their utilization to generate optimal binder-linker-E3 ligase motif combinations with good *in vivo* properties. PROTAC analog libraries might be generated, for instance, by appending different linker-E3 ligand combinations to a non-critical position on the ligand of the protein of interest (**Figure 4**).[28,29]



Adapted from Lebraud, H., Wright, D.J., Johnson, C.N., et al. Protein degradation by in-cell self-assembly of proteolysis targeting chimeras. *ACS Cent. Sci.* **2(12),** 927-934 (2016).

Figure 3. CLIPTAC approach uses 'click' chemistry linkage (blue) to enable in-cell self-assembly of a protein degrader (3).

In addition to BRDs and the other proteins mentioned here, PROTAC technology may have broad potential for application over much of the proteome. This will surely be aided by the further elucidation of cell context-dependent ubiquitination processes, E3 ligase activation mechanics, and identification of new E3 ligase binders. PROTACs targeting nuclear hormone receptors, oncoproteins, kinases, and tau proteins have been successfully demonstrated, and new target proteins, including those currently described as 'undruggable', offer exciting possibilities for this emerging therapeutic approach.[17,30]

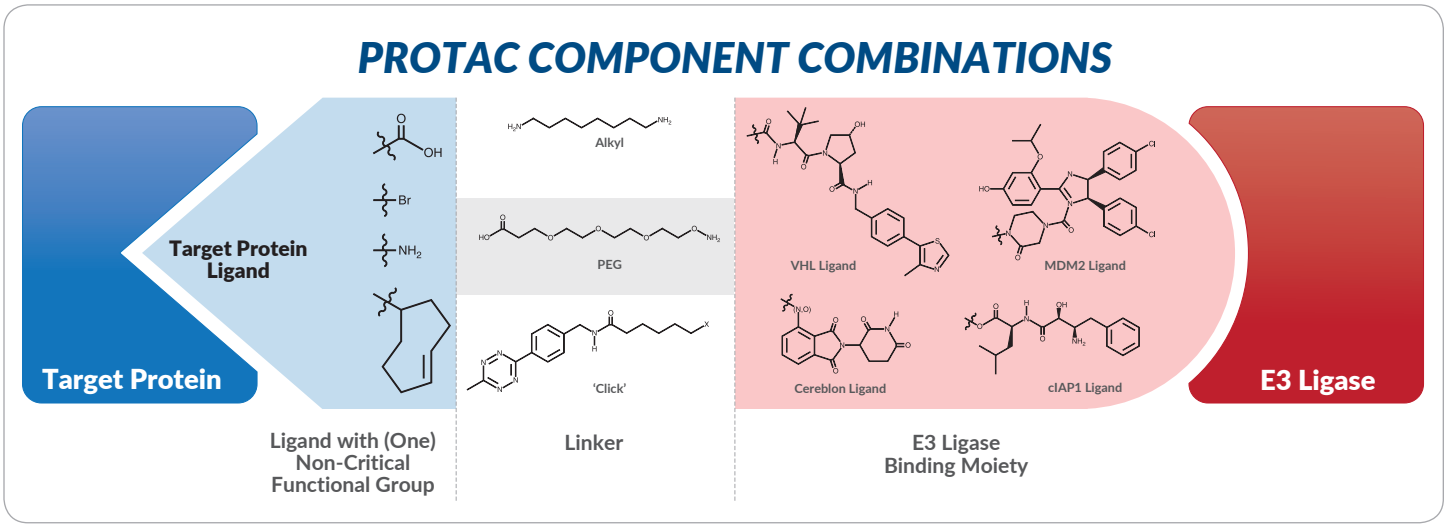


Figure 4. PROTAC library possibilities. Degree of target protein degradation and drug-like properties might be optimized by 'mix and match' of variable linker-E3 ligand combinations for linking to a single functional group on the target protein ligand.

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Writer Inhibitors

Inhibitors of enzymes that place epigenetics marks on proteins, including methyl- and acetyltransferases, as well as arginine deiminases

DNA Methyltransferases (DNMTs)

Item No.	Product Name	Selective Target(s)	Activity
11164	5-Azacytidine	DNMT	N/A
13373	2',3',5'-triacetyl-5-Azacytidine	DNMT	N/A
11166	Decitabine	DNMT	N/A

Item No.	Product Name	Selective Target(s)	Activity
13302	RG-108	DNMT	IC_{50} = 115 nM
11165	SGI-1027	DNMT1, DNMT3A, and DNMT3B	IC_{50}s = 12.5, 8, and 7.5 µM
10975	Zebularine	DNMT	N/A

Histone Acetyltransferases (HATs)

Item No.	Product Name	Selective Target(s)	Activity
13144	Anacardic Acid	p300 and PCAF	IC_{50}s = 8.5 and 5 µM
12095	Butyrolactone 3	Gcn5	IC_{50} = 100 µM
10549	C646	p300	IC_{50} = 1.6 µM
10974	CAY10669	PCAF	IC_{50} = 662 µM
16086	CAY10685	Gcn5	N/A

Item No.	Product Name	Selective Target(s)	Activity
12086	CPTH2 (hydrochloride)	Gcn5	N/A
11012	Delphinidin (chloride)	p300/CBP	IC_{50} = ~30 µM
10566	Garcinol	p300 and PCAF	IC_{50}s = 7 and 5 µM
19835	HAT Inhibitor II	p300	IC_{50} = 5 µM
17778	L002	p300	IC_{50} = 1.98 µM

Lysine Methyltransferases (KMTs)

Item No.	Product Name	Selective Target(s)	Activity
18317	A-196	SUV420H1 and SUV420H2	IC_{50}s = 25 and 144 nM
16081	A-366	G9a	IC_{50} = 3.3 nM
18238	BAY 598	SMYD2	IC_{50} = 27 nM

Item No.	Product Name	Selective Target(s)	Activity
13124	BIX01294 (hydrochloride hydrate)	G9a	IC_{50} = 1.7 µM
11787	BRD4770	G9a	EC_{50} = 5 µM
11788	BRD9539	G9a and PRC2	IC_{50} = 6.3 µM

Writer Inhibitors *Continued*

Lysine Methyltransferases (KMTs) Continued

Item No.	Product Name	Selective Target(s)	Activity
13156	Chaetocin	G9a, SU(VAR)3-9, and DIM5	IC_{50}s = 2.5, 0.8, and 3 µM
18299	CPI-169	EZH2	IC_{50} = 0.24 nM
19125	CPI-360	EZH2	IC_{50} = 0.5 nM
19146	EI1	EZH2	IC_{50} = 15 nM
16173	EPZ004777 (formic acid salt)	DOT1L	IC_{50} = 0.4 nM
13966	EPZ005687	EZH2	K_i = 24 nM
19161	EPZ011989	EZH2	IC_{50} = <3 nM
16175	EPZ5676	DOT1L	K_i = 80 pM
16174	EPZ6438	EZH2	K_i = 2.5 nM
15415	GSK126	EZH2	K_i = 0.57 nM
14094	GSK343	EZH2	IC_{50} = 4 nM
18531	GSK503	EZH2 (wild- and mutant type)	K_i^{app} = 3-27 nM
16441	LLY-507	SMYD2	IC_{50} = 15 nM

Item No.	Product Name	Selective Target(s)	Activity
11620	MI-2 (hydrochloride)	menin-MLL	IC_{50} = 0.45 µM
14678	(R)-PFI-2 (hydrochloride)	SET7/9	IC_{50} = 2 nM
13967	SGC0946	DOT1L	IC_{50} = 0.3 nM
13829	Sinefungin	SET domain-containing MTs	IC_{50}s = 0.1-20 µM
13631	UNC0224	G9a	IC_{50} = 15 nM
10582	UNC0321 (trifluoroacetate salt)	G9a	K_i = 63 pM
16400	UNC0379	SET8	IC_{50} = 7.3 µM
11084	UNC0631	G9a	IC_{50} = 4 nM
10734	UNC0638	G9a and GLP	IC_{50}s = <15 and 19 nM
14604	UNC0642	G9a and GLP	K_i = 3.7 nM
11085	UNC0646	G9a and GLP	IC_{50}s = 6 and 15 nM
14621	UNC1999	EZH2	IC_{50} = 2 nM
11796	Wedelolactone	EZH2-EED interactions	K_d = 2.8 µM

Protein Arginine Deiminases (PADs)

Item No.	Product Name	Selective Target(s)	Activity
17079	BB-Cl-Amidine	PAD4	EC_{50} = 8.8 µM
10599	Cl-Amidine (trifluoroacetate salt)*	PAD4	IC_{50} = 5.9 µM
10610	F-Amidine (trifluoroacetate salt)*	PAD4	IC_{50} = 21.6 µM

Item No.	Product Name	Selective Target(s)	Activity
17491	GSK121 (trifluoroacetate salt)	PAD4	IC_{50} = 3.2 µM
17489	GSK199 (hydrochloride)	PAD4	IC_{50} = 200 nM
17488	GSK484 (hydrochloride)	PAD4	IC_{50} = 50 nM

Protein Arginine Methyltransferases (PRMTs)

Item No.	Product Name	Selective Target(s)	Activity
13965	AMI-1 (sodium salt)	PRMT1	IC_{50} = 8.8 µM
17285	EPZ015666	PRMT5	K_i = 5 nM
19160	EPZ020411	PRMT6	IC_{50} = 10 nM
18354	GSK591	PRMT5	IC_{50} = 11 nM

Item No.	Product Name	Selective Target(s)	Activity
18361	MS023 (hydrochloride)	PRMT1, 3, 4, 6, and 8	IC_{50}s = 20, 119, 83, 8, and 8 nM
18348	MS049 (hydrochloride)	PRMT4 and PRMT6	IC_{50}s = 34 and 43 nM
11033	PRMT4/CARM1 Inhibitor	PRMT4/CARM1	IC_{50} = 7.1 µM
17017	SGC707	PRMT3	IC_{50} = 50 nM

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Eraser Inhibitors

Inhibitors of enzymes that remove epigenetics marks, including deacetylases, demethylases, and sirtuins

Histone Deacetylases (HDACs)

Item No.	Product Name	Selective Target(s)	Activity
10575	Apicidin	HDAC3/NcoR	IC_{50} = 15.8 nM
19834	BRD4884	HDAC1, 2, and 3	IC_{50}s = 29 nM, 62 nM, and 1.09 µM
19836	BRD6688	HDAC1, 2, and 3	IC_{50}s = 21 nM, 100 nM, and 11.48 µM
89740	CAY10398	HDAC1	IC_{50} = 10 µM
10005019	CAY10433	HDAC	IC_{50} = 30 µM
13146	CAY10603	HDAC6	IC_{50} = 2 pM
15403	CAY10683	HDAC2 and 6	IC_{50}s = 0.119 and 434 nM
13172	CBHA	HDAC1 and 3	IC_{50}s = 10 and 70 nM
13686	Chidamide	HDAC	N/A
12084	CI-994	HDAC1, 2, 3, and 8	IC_{50}s = 0.9-20 µM
16426	CUDC-101	HDAC1, 2, 4, and 5	IC_{50}s = 4.5-13.2 nM
10576	HC Toxin	HDAC	IC_{50} = 30 nM
15200	HDAC6 Inhibitor	HDAC6	IC_{50} = 36 nM
13295	HNHA	HDAC	IC_{50} = 100 nM
15066	HPOB	HDAC6	IC_{50} = 56 nM
11045	ITF 2357	HD2, HD-1B, and HD-1A	IC_{50}s = 7.5-16 nM
14088	JNJ-26481585	HDAC1	IC_{50} = 0.11 nM
16427	LAQ824	HDAC	IC_{50} = 30 nM
14969	LMK 235	HDAC4 and 5	IC_{50}s = 12 and 4 nM
13174	M 344	HDAC1	IC_{50} = 46 nM
18288	MI-192	HDAC2 and 3	IC_{50}s = 30 and 16 nM

Item No.	Product Name	Selective Target(s)	Activity
18287	Mocetinostat	HDAC1 and 2	IC_{50}s = 0.15 and 0.29 µM
13284	MS-275	HDAC1	IC_{50} = 300 nM
13856	5-Nitroso-8-quinolinol	HDAC	N/A
13176	Oxamflatin	HDAC	IC_{50} = 15.7 nM
13280	Panobinostat	HDAC1-11	IC_{50}s = 0.6-31 nM
20059	PCI 24781	HDAC1	K_i = 7 nM
10444	PCI 34051	HDAC8	IC_{50} = 0.01 µM
15205	2-hexyl-4-Pentynoic Acid	HDAC	IC_{50} = 13 µM
13212	Pimelic Diphenylamide 106	HDAC1, 2, 3, and 8	IC_{50}s = 150-5,000 nM
13870	Pyroxamide	HDAC1	IC_{50}s = 0.1-0.2 µM
17553	Resminostat (hydrochloride)	HDAC1, 3, and 6	IC_{50}s = 43-72 nM
17130	Romidepsin	HDAC1, 2, 3, and 8	IC_{50}s = 26-53 nM
10009929	SAHA	Class I, II, and IV HDACs	IC_{50}s = 50-200 nM
10495	4-iodo-SAHA	Class I and II HDACs	IC_{50} = ~1 µM
10443	SB939	HDAC1	IC_{50} = 77 nM
10574	Suberohydroxamic Acid	HDAC1 and 3	IC_{50}s = 0.25 and 0.30 µM
17738	TMP269	HDAC4, 5, 7, and 9	IC_{50}s = 19-126 nM
89730	Trichostatin A	Class I, II, and IV HDACs	IC_{50} = 70 nM
13691	Tubacin	HDAC6	IC_{50} = 4 nM
15785	Tubastatin A	HDAC6	IC_{50} = 15 nM
10559	Tubastatin A (trifluoroacetate salt)	HDAC6	IC_{50} = 15 nM

Eraser Inhibitors *Continued*

Sirtuins (SIRTs)

Item No.	Product Name	Selective Target	Activity
13145	AGK2	SIRT2	IC_{50} = 3.5 µM
14004	AK-7	SIRT2	IC_{50} = 15.5 µM
10009798	EX-527	SIRT1	IC_{50} = 98 nM
19771	Inauhzin	SIRT1	IC_{50}s = 0.7-2 µM
14648	JFD00244	SIRT2	IC_{50} = 56.7 µM

Item No.	Product Name	Selective Target(s)	Activity
10641	JGB1741	SIRT1	IC_{50} = 15 µM
13178	Salermide	SIRT1 and 2	IC_{50} = ~20 µM
14407	SIRT1/2 Inhibitor IV	SIRT1 and 2	IC_{50}s = 56 and 59 µM
10523	Sirtinol	SIRT1 and 2	IC_{50}s = 131 and 38 µM
13086	Tenovin-6	SIRT1, 2, and 3	IC_{50}s = 10-67 µM

Lysine Demethylases (KDMs)

Item No.	Product Name	Selective Target(s)	Activity
20811	AS-8351	KDMT	N/A
19705	Bizine	LSD1	$K_{i(inact)}$= 59 nM
12033	Daminozide	KDM2A, PHF8, and KDM7A	IC_{50}s = 0.55-2.1 µM
19403	GSK2879552	LSD1	EC_{50}s = 2-240 nM
12054	GSK-J1 (sodium salt)	JMJD3 and UTX	IC_{50}s = 18 and 56 µM
12073	GSK-J4 (hydrochloride)	JMJD3	IC_{50} = >50 µM
16439	GSK-LSD1 (hydrochloride)	LSD1	IC_{50} = 16 nM
11572	IOX1	JMJD2A and 2E	IC_{50}s = 1.7 and 2.4 µM
15338	JIB-04	pan-JMJ KDMs	IC_{50}s = 0.23-1.1 µM

Item No.	Product Name	Selective Target(s)	Activity
17472	ML-324	JMJD2E	IC_{50} = 920 nM
13944	N-Oxalylglycine	JMJD2A, 2C, and 2E	IC_{50}s = 24-500 µM
17471	OG-L002	LSD1	IC_{50} = 0.02 µM
19136	ORY-1001	LSD1	IC_{50} = <20 nM
16272	PBIT	JARID1A, 1B, 1C, and 1D	IC_{50}s = 3-28 µM
10010494	2-PCPA (hydrochloride)	LSD1	IC_{50} = 20.7 µM
18124	RN-1 (hydrochloride)	LSD1	IC_{50} = 70 nM
15487	SP2509	LSD1	IC_{50} = 13 nM

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Reader Inhibitors

Inhibitors of proteins containing dedicated domains, including bromodomains, chromodomains, and MBT domains, for binding specific epigenetic marks on other proteins, DNA, or RNA

Bromodomains (BRDs)

Item No.	Product Name	Selective Target(s)	Activity
20864	AZD 5153	BRD4	IC_{50} = 5 nM
19777	BAY-299	BRD1	IC_{50} = 6 nM
17448	BAZ2-ICR	BAZ2A and B	K_ds = 109 and 170 nM
20311	BI-7273	BRD9	K_d = 15.4 nM
17897	BI-9564	BRD9 and 7	K_ds = 14.1 and 239 nM
14119	Bromosporine	pan-Bromodomain	N/A
19956	CeMMEC1	TAF1	K_d = 1.8 µM
20224	CeMMEC13	TAF1	IC_{50} = 2.1 µM
15479	CPI-203	BRD4	EC_{50} = 91 nM
14120	GSK2801	BAZ2A and B	K_ds = 0.26 and 0.14 µM
18123	GSK5959	BRPF1	IC_{50} = 80 nM
11181	I-BET151	BRD2, 3, and 4	EC_{50}s = 0.25-0.79 µM
10676	I-BET762	BET family proteins	K_d = 32.5-42.5 nM

Item No.	Product Name	Selective Target(s)	Activity
17749	I-BRD9	BRD9	pK_d = 8.7
14468	I-CBP112 (hydrochloride)	CBP and EP300	K_ds = 0.142 and 0.625 µM
11187	(+)-JQ1	BRD4 bromodomains 1 and 2	K_ds = ~50 and 90 nM
17662	NI-57	BRPF1B, 2, and 3	K_ds = 31-408 nM
18316	NVS-CECR2-1	CECR2	IC_{50} = 0.047 µM
17124	OF-1	BRPF1B, 2, and 3	K_ds= 0.1-2.4 nM
15947	OTX015	BRD2, 3, and 4	EC_{50}s = 10-19 nM
18811	PF-CBP1	CBP and p300	IC_{50}s = 125 and 363 nM
11155	PFI-1	BRD2 and 4	IC_{50}s = 98 nM and 0.22 µM
15267	PFI-3	SMARCA4 and PB1	K_ds = 89 and 48 nM
17663	PFI-4	BRPF1	K_d = 13 nM
14469	SGC-CBP30	CREBBP and EP300	IC_{50}s = 21-69 and 38 nM
17123	UMB-32	BRD4	K_d = 550 nM

Chromodomain (CB)/MBTs

Item No.	Product Name	Selective Target(s)	Activity
17533	MS37452	CBX7	K_i = 43 µM
10875	UNC669	L3MBTL1	IC_{50} = 6 µM
13968	UNC1215	L3MBTL3	K_d = 120 nM

Looking for a different epigenetic inhibitor?
Contact us for more information about custom organic synthesis at
contractresearch@caymanchem.com

Additional writer, reader, and eraser inhibitors can be found at www.caymanchem.com

Epigenetic Screening & Profiling Services

Cayman offers a dedicated epigenetic screening laboratory designed to be flexible and innovative in order to help you meet your research goals. High-throughput capabilities allow us to screen a chemical library against specific epigenetic biochemical targets. Alternatively, our broad collection of epigenetic enzymes, substrates, and off-the-shelf assays enables biochemical profiling of the activity of a few compounds against several targets.

Researcher Spotlight

What is your current role at the SGC? How did your career bring you to this position?

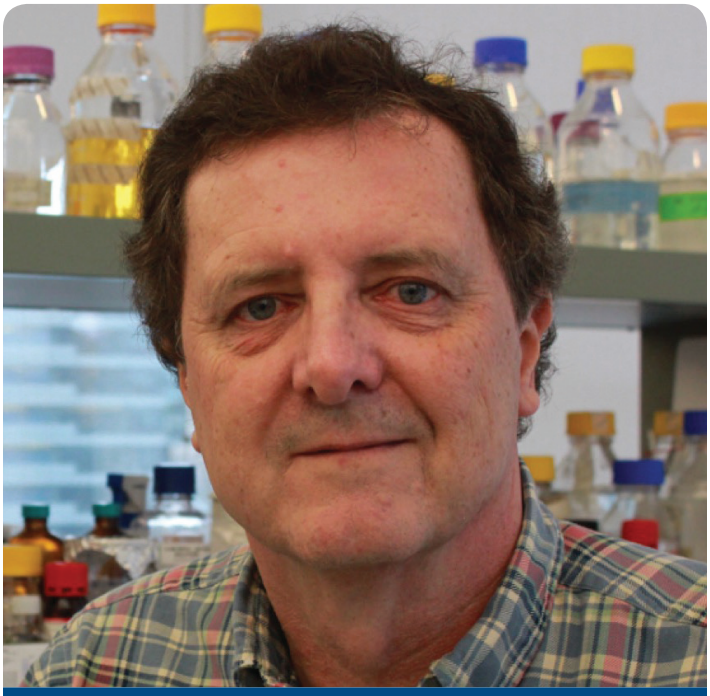
My current role is Principal Investigator, Epigenetics at the Structural Genomics Consortium (SGC) at the University of Toronto. The SGC is a not-for-profit organization engaged in open-access research program from which our protein crystal structures, chemical probes, and protocols are freely available to the scientific community without restriction. The SGC files no patents on their discoveries. The SGC comprises scientists from several academic institutions including Oxford University, the University of North Carolina at Chapel Hill, University of Toronto, Karolinska Institute, University of Campinas, and Goethe University Frankfurt. The SGC was founded as a structural biology organization and was responsible for solving more than 1,100 human protein structures in their early years (2004-2011) as part of a public-private partnership (PPP) with several pharmaceutical companies. In 2008, one of the partners suggested extending this PPP to develop chemical probes for epigenetic targets, which was an emerging area of high interest with a dearth of quality molecules available for target validation studies.

I was trained as an organic chemist and developed my skills as a medicinal chemist during 23 years in the pharmaceutical industry, primarily in early-phase discovery projects, and I was hired in 2009 to facilitate chemical probe discovery. My role involves organizing the progression of compounds from early hits to chemical probes, achieved *via* interactions with molecular biophysicists and structural and cellular biologists. In addition, I collaborate with eight pharmaceutical partners and four academic partners.

Can you describe the focus of your current research programs?

My research programs encompass two main themes. First, our goal is to deliver novel protein crystal structures that can form the basis of new drug discovery efforts. Historically, this was the foundation upon which the SGC was established, and the SGC has delivered more than 50% of epigenetic structures in the public PDB protein database.

Secondly, for each epigenetic protein target, our goal is to deliver at least one chemical probe. These are small molecule enzyme inhibitors or interaction antagonists with IC_{50} or K_d values less than 100 nM which are selective within the target family and show substantial activity in cells at 1 µM. Ideally, a close structurally related inactive compound that can be used as a control in cellular experiments is also identified. In some cases, multiple probes are discovered for the same protein, but to ensure that each new probe adds value, these should either contain a different chemical template or act *via* an alternative mechanism of action. Many epigenetic proteins contain multiple domains of different function and each of these domains can be considered a unique epigenetic target. Two of the SGC sites contribute to the epigenetics chemical probe program: the Toronto site is focused on histone methyltransferases (HMTs) and methyl lysine binders, while the Oxford site is focused on bromodomains and lysine demethylases (KDMs). For more details of SGC chemical probes, visit www.thesgc.org/chemical-probes/epigenetics.



Peter J. Brown, Ph.D.
Principal Investigator, Epigenetic Chemical Probes
Structural Genomics Consortium
University of Toronto

How important has the SGC's public-private partnership been in generating ideas for new drug targets?

The value of SGC's open-access approach resides in our ability to work on projects of unknown clinical value (high risk in pharma-talk) using a protein family-targeted approach. Historically, drug discovery efforts have started with a hypothesis that inhibiting protein X will help cure disease Y and the ultimate test of that hypothesis is a positive clinical outcome. This is obviously a highly expensive and timely endeavor, and efforts over the last 30 years have focused on using target-driven optimization of lead molecules and finding early endpoints to predict clinical success. By taking a disease-agnostic approach, we first find potent, selective compounds for targets of unknown value and ask the question: "What effect does this compound-target interaction have on various diseases?" This approach benefits both academia and pharma by forging close working relationships. While contributing to an open-access consortium, members are able to learn from each other and share the risk of working on targets of unknown value.

continue to page 10

RESEARCHER SPOTLIGHT

Want to have your research featured in the Cayman Currents?
Send a brief background to **marketing@caymanchem.com**

What are the real-world applications of your research in healthcare outcomes?

The best example of this collaborative approach is JQ1, which is a BET bromodomain antagonist. One of our partners identified a compound from a phenotypic screen and was performing pull-down studies to identify the target. Meanwhile, the SGC screened this molecule in all their epigenetic assays available at the time and discovered this molecule bound to the BET family of bromodomains. By optimizing potency and selectivity for this target in collaboration with Dana-Farber Cancer Institute, JQ1 was identified as a chemical probe for BET bromodomains which shows promising results in models of cancer, inflammation, and male contraception. Since the discovery of JQ1 and publication in high-impact, peer-reviewed journals, many companies have started drug discovery efforts in this area, and several molecules have entered clinical trials. There are also many examples of chemical probes for histone methyltransferases (EZH2, DOT1L, and PRMT5 for example) that are showing promise for oncology. Many inhibitors of these targets have progressed into clinical trials.

What excites you most about the field of epigenetics?

While the concept of epigenetics is well-established, the chemical biology of epigenetic targets is fairly young and new ligand discoveries enable scientists to evaluate the possible therapeutic value of various targets. The use of small molecule ligands for specific protein domains provides a better understanding of therapeutic value, compared to using gene knockout/knockdown experiments where the expression of full-length protein is disrupted. Using these chemical probes, biologists can start to unravel the mechanisms by which gene expression is regulated. This leads to a better understanding of diseases and insights into possible mechanisms of clinical intervention.

What advice do you have for researchers entering the field of epigenetics?

The study of epigenetics is becoming more complicated as new mechanisms for gene regulation are discovered. In the early days, methylation and acetylation were the only post-translational modifications (PTMs) studied. Nowadays, there are over ten PTMs recognized for histone modification. This means that researchers need to develop new methodologies to assess cellular changes in PTMs for both histone and non-histone proteins and also find ways to monitor cellular target engagement for protein-protein interactions. The epigenetics field is expanding rapidly and researchers need to respond to new discoveries that may change the value placed on a particular target. The cellular context of epigenetics is the nucleosome, in which two copies of four different histones are packaged with DNA, and emphasis should be placed on understanding this context, to enable good translation of activities from *in vitro* screening to cellular assays.

Address for Correspondence

Room 710 MaRS South Tower
101 College Street
Toronto, ON M5G 1L7
CANADA
Phone: (416) 978-7408
Email: peterj.brown@utoronto.ca

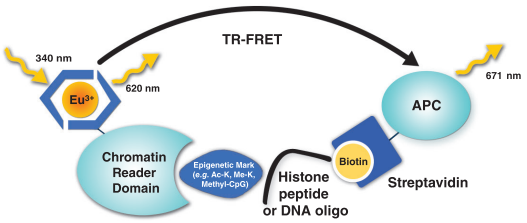
Assay Kits

Biochemically profile the activity of a few compounds against several targets

Chromatin Reader Domain TR-FRET Assay Kits

Characterize inhibitors of chromatin reader domain peptide interactions

- Homogeneous mix-and-read TR-FRET assay in 384-well format
- Substrate-independent, non-kinetic assay
- Miniaturized to final assay volume of 20 µl
- Plate-based, time-resolved fluorometric measurement (ex 340 nm, em 620 and 670 nm)



Cayman's TR-FRET assays screen compounds that block the interaction between a chromatin reader domain and its substrate. The assays utilize a europium-labeled recombinant chromatin reader domain as the donor and an acetylated histone peptide coupled with streptavidin-APC as a FRET acceptor.

Item No.	Product Name	Description
600710	BAZ2B bromodomain TR-FRET Assay Kit	Screen for inhibitors of the BAZ2B bromodomain, which plays a role in establishing regular nucleosome spacing during chromatin assembly
600500	BRD2 bromodomain 1 TR-FRET Assay Kit	Screen for inhibitors of BRD2 isolated individual or tandem bromodomains, which serve to couple histone acetylation marks to the transcriptional regulation of target promoters
600810	BRD2 bromodomains 1 and 2 TR-FRET Assay Kit	
600510	BRD2 bromodomain 2 TR-FRET Assay Kit	
600630	BRD3 bromodomain 1 TR-FRET Assay Kit	Screen for inhibitors of BRD3 isolated individual or tandem bromodomains, which serve to couple histone acetylation marks to the transcriptional regulation of target promoters
600820	BRD3 bromodomains 1 and 2 TR-FRET Assay Kit	
600640	BRD3 bromodomain 2 TR-FRET Assay Kit	
600520	BRD4 bromodomain 1 TR-FRET Assay Kit	Screen for inhibitors of BRD4 isolated individual or tandem bromodomains, which serve to couple histone acetylation marks to the transcriptional regulation of target promoters
600830	BRD4 bromodomains 1 and 2 TR-FRET Assay Kit	
600530	BRD4 bromodomain 2 TR-FRET Assay Kit	
600650	BRDT bromodomain 1 TR-FRET Assay Kit	Screen for inhibitors of BRDT bromodomain 1, which binds to histone acetylation marks to facilitate transcriptional regulation
600720	BRG1 bromodomain TR-FRET Assay Kit	Screen for inhibitors of the BRG1 bromodomain, which facilitates binding to histone acetylation marks to regulate tumor suppressor activity
600730	BRM bromodomain TR-FRET Assay Kit	Screen for inhibitors of the BRM bromodomain, which enables binding to acetylated histone tails to facilitate tumor suppressor activity
600850	CBP bromodomain TR-FRET Assay Kit	Screen for inhibitors of the CBP bromodomain, which plays a critical role in regulating gene transcription
700960	JMJD2A Tudor Domains TR-FRET Assay Kit	Screen for inhibitors of JMJD2A tudor domains, which bind methylated H3K4, allowing formation of a complex that represses transcription
601030	L3MBTL1 MBT Domains TR-FRET Assay Kit	Screen for inhibitors of the three L3MBTL1 MBT domains, which selectively recognize and bind to monomethyl H3K4 and dimethyl H4K20
600870	TAF1 bromodomain 1 TR-FRET Assay Kit	Screen for inhibitors of TAF1 isolated individual or tandem bromodomains, which direct TAF1 binding to the core promoter sequences at the transcription start site
600930	TAF1 bromodomains 1 and 2 TR-FRET Assay Kit	

Assay Kits *Continued*

Writers

Monitor the activity of histone acetyltransferases and methyltransferases and screen for potential inhibitors

Item No.	Product Name	Description
600570	GLP SAM-Screener™ Assay Kit	Homogeneous fluorescence polarization assay to screen for SAM-binding site inhibitors
10006515	HAT Inhibitor Screening Assay Kit	Screen for inhibitors of PCAF
700140	Methyltransferase Colorimetric Assay Kit	Continuous assay to monitor SAM-dependent methyltransferases
700150	Methyltransferase Fluorometric Assay Kit	Continuous assay to monitor SAM-dependent methyltransferases
600580	MLL1 SAM-Screener™ Assay Kit	Homogeneous fluorescence polarization assay to screen for SAM-binding site inhibitors
701390	PAD2 Inhibitor Screening Assay Kit (AMC)	Low background, high sensitivity screen for inhibitors of PAD2
701400	PAD2 Inhibitor Screening Assay Kit (Ammonia)	Screen for inhibitors of PAD2
701320	PAD4 Inhibitor Screening Assay Kit (AMC)	Low background, high sensitivity screen for inhibitors of PAD4
700560	PAD4 Inhibitor Screening Assay Kit (Ammonia)	Screen for inhibitors of PAD4
700270	SET7/9 Methyltransferase Inhibitor Screening Assay Kit	Screen for inhibitors of SET7/9
600490	SET7/9 SAM-Screener™ Assay Kit	Homogeneous fluorescence polarization assay to screen for SAM-binding site inhibitors
700350	SET8 Methyltransferase Inhibitor Screening Assay Kit	Screen for inhibitors of SET8

Erasers

Screen modulators of histone deacetylases and demethylases

Item No.	Product Name	Description
600150	HDAC Cell-Based Activity Assay Kit	Screen for modulators of HDAC activity in whole cells
10011563	HDAC Fluorometric Activity Assay Kit	Measure class I and class II HDAC activity in nuclear extracts
10011564	HDAC1 Inhibitor Screening Assay Kit	Screen for inhibitors of HDAC1
700230	HDAC8 Inhibitor Screening Assay Kit	Screen for inhibitors of HDAC8
700120	LSD1 Inhibitor Screening Assay Kit	Screen for inhibitors of LSD1
10010401	SIRT1 Direct Fluorescent Screening Assay Kit	Screen for modulators of SIRT1 activity
10010991	SIRT1 FRET-Based Screening Assay Kit	Screen for modulators of SIRT1 activity
700280	SIRT2 Direct Fluorescent Screening Assay Kit	Screen for modulators of SIRT2 activity
10011566	SIRT3 Direct Fluorescent Screening Assay Kit	Screen for modulators of SIRT3 activity

Additional assay kits for epigenetics research can be found at www.caymanchem.com

Antibodies

Detect and characterize common histone modifications, DNA/RNA alterations, and other epigenetic post-translational modifications

Histones and Histone Modifications

Item No.	Product Name	Application(s)
10010567	Acetyl Lysine Monoclonal Antibody (Clone 7F8)	ELISA, ICC, WB
20726	Anti-Histone H3 K36M Rabbit Monoclonal Antibody (Clone RM193)	ELISA, ICC, IHC, IF, WB
20724	Anti-Histone H3 pan Rabbit Monoclonal Antibody (Clone RM188)	ELISA, ICC, Multiplex, WB
20720	Anti-Phospho-Histone H3 (Ser10) Rabbit Monoclonal Antibody (Clone RM163)	ELISA, ICC, Multiplex, WB
20719	Anti-trimethyl Histone H3 (Lys27) Rabbit Monoclonal Antibody (Clone RM175)	ELISA, IHC, Multiplex, WB
20718	Anti-trimethyl Histone H3 (Lys4) Rabbit Monoclonal Antibody (Clone RM137)	ELISA, Multiplex, WB
20721	Anti-γH2AX (phospho-Ser139) Rabbit Monoclonal Antibody (Clone RM224)	ELISA, ICC, Multiplex, WB
17939	Histone H3 (Citrullinated R2 + R8 + R17) Monoclonal Antibody	ELISA, WB
17855	Histone H3 (Citrullinated R2 + R8 + R17) Polyclonal Antibody	ELISA, WB
13784	Histone H3.3 Polyclonal Antibody	IHC, WB
13543	Histone H4 Polyclonal Antibody	WB

DNA/RNA

Item No.	Product Name	Applications
20722	Anti-5-methyl Cytosine Rabbit Monoclonal Antibody (Clone RM231)	Dot blot, ELISA, ICC, IHC, MeDIP
20723	Anti-5-hydroxy Methylcytosine Rabbit Monoclonal Antibody (Clone RM236)	Dot blot, ELISA, ICC, IHC, hMeDIP
18289	5-Hydroxymethylcytosine Polyclonal Antibody	Dot blot, ELISA
18336	N^6-Methyladenosine Monoclonal Antibody (Clone 17-3-4-1)	Dot blot, ELISA, IP
18337	N^6-Methyladenosine Polyclonal Antibody	ELISA, Southwestern dot blot

Readers, Writers, Erasers, and Other PTM Modifiers

Item No.	Product Name	Application(s)
13479	DNA Methyltransferase 1 Monoclonal Antibody (Clone 60B1220.1)	ChIP, IHC, IP, WB
13482	DNA Methyltransferase 3a Monoclonal Antibody (Clone 64B814.1)	ICC, IF, WB
13485	DNA Methyltransferase 3b Monoclonal Antibody (Clone 52A1018)	ChIP, ICC, IF, IHC, IP, WB
14701	JARID1B/PLU1 (C-Term) Polyclonal Antibody	FC, ICC
10382	JMJD2A Polyclonal Antibody	WB
10383	JMJD2D Polyclonal Antibody	FC, ICC, IP, WB
13787	JMJD6 Peptide Affinity-Purified Polyclonal Antibody	WB

Antibodies *Continued*

Readers, Writers, Erasers and Other PTM Modifiers Continued

Item No.	Product Name	Application(s)
13554	LSD1 Polyclonal Antibody (aa 100-150)	WB
19669	PAD4 Monoclonal Antibody (Clone 6D8)	ELISA, WB
19671	PAD4 Monoclonal Antibody (Clone 11F9)	ELISA, WB
13731	SET7/9 Polyclonal Antibody	WB
13477	SIRT7 Polyclonal Antibody	WB
12021	SUMO Monoclonal Antibody	ELISA, WB

Additional antibodies for epigenetics research can be found at www.caymanchem.com

Proteins

Recombinant proteins, expressed and purified from *E. coli*, *Sf*9, or *Sf*21 insect cells for epigenetic readers, writers, and erasers

Readers

Item No.	Product Name	Description
11918	BPTF bromodomain (human recombinant)	N-terminal GST-tagged protein expressed in *E. coli*
11071	BRD2 bromodomain 1 (human recombinant; GST-tagged)	N-terminal GST-tagged protein expressed in *E. coli*
14658	BRD3 bromodomain 2 (human recombinant)	N-terminal GST-tagged protein expressed in *E. coli*
11720	BRD4 bromodomain 1 (human recombinant; His-tagged)	N-terminal His-tagged protein expressed in *E. coli*
11066	BRD4 bromodomain 2 (human recombinant; GST-tagged)	N-terminal GST-tagged protein expressed in *E. coli*
11649	BRDT bromodomain 2 (human recombinant)	N-terminal GST-tagged protein expressed in *E. coli*
11288	CREB-binding protein bromodomain (human recombinant)	N-terminal GST-tagged protein expressed in *E. coli*
11286	MBD2 (human recombinant; methyl binding domain aa 150-220)	N-terminal GST-tagged protein expressed in *E. coli*
11287	MeCP2 (human recombinant; methyl binding domain aa 77-166)	N-terminal GST-tagged protein expressed in *E. coli*
14136	SMN tudor domain (human recombinant)	N-terminal GST-tagged protein expressed in *E. coli*

Writers

Item No.	Product Name	Description
10354	DOT1L (human recombinant)	Active, N-terminal GST-tagged protein expressed in *E. coli*
10353	G9a (human recombinant)	Active, N-terminal GST-tagged protein expressed in *E. coli*
10782	Gcn5 (human recombinant)	Active, N-terminal His-tagged protein expressed in *Sf*21 cells
10658	MLL1 (human recombinant)	SET1 domain- and WIN motif-containing C-terminal fragment (aa 3762-3969) expressed in *E. coli*
10758	NSD2 (human recombinant)	Active, N-terminal GST-tagged protein (aa 941-1240; N- and C-terminal truncations) expressed in *E. coli*

Writers Continued

Item No.	Product Name	Description
10500	PAD4 (human recombinant)	Active, N-terminal His-tagged protein expressed in *E. coli*
10009115	PCAF Histone Acetyltransferase	Active, GST-tagged protein purified from *E. coli*
13866	PRMT6 (human recombinant; baculovirus expressed)	Active, N-terminal His-tagged protein expressed in Sf21 cells
10762	SMYD3 (human recombinant)	Active, N-terminal His- and SUMOpro-tagged protein expressed in *E. coli*
10783	TIP60 (human recombinant)	N-terminal His-tagged protein expressed in Sf21 cells

Erasers

Item No.	Product Name	Description
10009231	HDAC1 (human recombinant)	Active, full length, C-terminal His- and FLAG-tagged protein expressed in Sf9 cells
10009465	HDAC6 (human recombinant)	Active, full length, N-terminal GST-tagged protein expressed in Sf9 cells
10336	JMJD2A (human recombinant)	Active, N-terminal His-tagged protein (aa 1-350) expressed in *E. coli*
11237	JMJD2E-Strep tagged (human recombinant)	Active, N-terminal Strep II-tagged protein (aa 2-337) protein expressed in *E. coli*
10011190	SIRT1 (human recombinant)	Active, N-terminal GST-tagged protein (aa 193-747) purified from *E. coli*
10011191	SIRT2 (human recombinant)	Active, N-terminal His-tagged enzyme (aa 2-389) purified from *E. coli*
10011194	SIRT3 (human recombinant)	Active, N-terminal His-tagged enzyme (aa 101-399) purified from *E. coli*
10318	SIRT5 (human recombinant)	N-terminal GST-tagged enzyme (aa 33-310) purified from *E. coli*
10315	SIRT6 (human recombinant)	Active, N-terminal His-tagged enzyme (aa 1-355) purified from *E. coli*
10774	UTX (human recombinant)	Active, N-terminal proprietary tagged protein (aa 930-1,410) expressed in *E. coli*

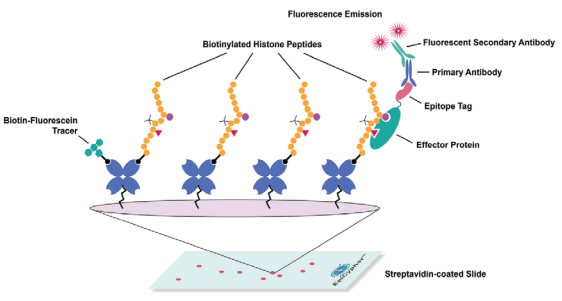
Additional proteins for epigenetics research can be found at www.caymanchem.com

Rapidly screen epigenetic protein interactions with modified histones

EpiTitan™ Histone Peptide Array 17626

This EpiTitan™ Histone Peptide Array platform is designed for rapid semi-quantitative and high-throughput analysis of the binding specificity of antibodies and histone binding effector proteins. It can also be used to determine the substrate specificity of histone-modifying enzymes.

- Array covers over 95 unique modifications on the four core histones
- Perform multiple experiments per array
- Determine the specificity of histone binding proteins, the selectivity of histone antibodies, and identify substrates for histone-modifying enzymes



EpiTitan™ Histone Peptide Array slide design. For detection of the interaction of an effector protein with peptides on the array as shown above, you need a primary antibody to the protein (or to an affinity tag) and a fluorescently labeled secondary antibody to the primary antibody. This is much like the detection procedure employed in immunfluorescence microscopy. For analysis of histone antibody specificity, you need the primary antibody to a histone modification to be studied and a fluorescently labeled secondary antibody recognizing the primary antibody.

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SAPPHIRE BIOSCIENCE

Australia, New Zealand & South East Asia:
Sapphire Bioscience Pty Ltd.
Ph: +61 2 9698 2022
Ph: 1800 062 088 (AU)
sales@sapphirebioscience.com
www.sapphirebioscience.com

Cayman CHEMICAL

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1180 E. Ellsworth Road
Ann Arbor, MI 48108
www.caymanchem.com

CONTACT US

PHONE: (800) 364-9897 (USA and Canada only)
(734) 971-3335

FAX: (734) 971-3640

WEB: www.caymanchem.com

EMAIL: Sales: sales@caymanchem.com
Customer Service: custserv@caymanchem.com
Technical Support: techserv@caymanchem.com