Clinical takeoff for new epigenetic targets

By Kai-Jye Lou, Senior Writer

There is little doubt that 2014 will be a banner year for next-generation epigenetics companies, with key clinical data expected

for next-generation drugs and first-generation candidates that target new epigenetic regulators. But the big biotech and pharma companies that carved up the space in recent years might have clinical data even sooner, as the **American Society of Hematology** meeting in December should provide a window into at least two candidates in hematologic malignancies.

Clinical data aside, the epigenetics space itself continues to expand and mature, with multiple companies being founded, one going public and larger companies continuing to place bets in the field through partnerships, acquisitions and option deals (*see Table 1, "Selected recent deals and partnerships in the epigenetics space"*).

The landscape in epigenetics can be divided into two major segments. One includes companies developing compounds against epigenetic regulators not already targeted by marketed drugs. The other includes companies developing second-generation compounds against validated epigenetic drug targets (*see Table 2, "Selected clinical stage compounds that target epigenetic regulators"*).

Table 1. Selected recent deals and partnerships in the epigenetics space. The January 2012 deal between the **Genentech Inc.** unit of **Roche** and **Constellation Pharmaceuticals Inc.** set off a new wave of dealmaking activity in the epigenetics space. **Celgene Corp.** made a \$15 million equity investment in **Acetylon Pharmaceuticals Inc.** that gave the biopharma an observational seat on Acetylon's board and followed up with the **Epizyme Inc.** partnership that included a \$90 million up-front payment and equity investment in the now-public company. Celgene then announced in July that it paid \$100 million up front in exchange for an exclusive option to acquire the company. Other notable deals include **GlaxoSmithKline plc** taking out **Cellzome AG** and **Rodin Therapeutics Inc.**'s partnership with **Proteros biostructures GmbH** and **Johnson & Johnson** to develop new therapies for CNS diseases.

Source: BioCentury Archives

Company/institution	Deal focus	Financial terms	Date
Constellation Pharmaceuticals; Genentech	Three-year partnership to use Constellation's platform to discover and develop small molecules against undisclosed epigenetic targets for cancer and other diseases; excludes rights to BET family of bromodomain-containing proteins and enhancer of zeste homolog 2 (EZH2)	Constellation receives \$95 million up front plus research funding and is eligible for undisclosed milestones and royalties; Genentech has option to acquire Constellation	January 2012
Acetylon Pharmaceuticals; Celgene (NASDAQ:CELG)	Celgene takes equity stake in selective histone deacetylase inhibitor developer Acetylon; gets an observational, nonvoting board seat at Acetylon but does not receive rights or options to any technology	Celgene makes \$15 million equity investment in Acetylon	February 2012
Celgene; Epizyme (NASDAQ:EPZM)	Partnership to discover, develop and commercialize cancer therapeutics that inhibit histone methyltransferases; Celgene gets ex-U.S. rights to B7 and has an exclusive, three-year option to license ex-U.S. rights for unpartnered histone methyltransferase inhibitors, with a potential one-year extension	Epizyme receives \$90 million up front, which includes an undisclosed minority equity investment; Epizyme is eligible for more than \$160 million in milestones for each licensed program, plus double-digit royalties on ex-U.S. sales	April 2012
Cellzome AG; GlaxoSmithKline (LSE:GSK; NYSE:GSK)	GSK acquires Cellzome; companies had partnered in 2010 to discover small molecules against epigenetic targets	GSK acquires the 80.02% of Cellzome it does not already own for £61 million (\$98 million) in cash	May 2012
Oncoethix S.A.; Mitsubishi Tanabe Pharma Corp. (Tokyo:4508; Osaka:4508)	Oncoethix gets exclusive, worldwide rights to BET bromodomain inhibitor OTX015 and will develop the compound to treat leukemia and other hematologic malignancies; Mitsubishi retains rights to OTX015 in certain Asian countries	Undisclosed	June 2012
Life Technologies Corp. (NASDAQ:LIFE); ^A Structural Genomics Consortium; The University of Chicago; University of Toronto	Partnership to develop and commercialize recombinant antibodies against epigenetic targets	Undisclosed	July 2012

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Table 1. Selected recent deals and partnerships in the epigenetics space. (continued)

Company/institution	Deal focus	Financial terms	Date
Astex Pharmaceuticals Inc., ^B Cancer Research UK; The Institute of Cancer Research	Partnership to discover and develop oral therapies against an undisclosed epigenetic target in a blood cancer	Astex and Institute of Cancer Research share undisclosed funding from Cancer Research UK	September 2012
Constellation; Leukemia & Lymphoma Society	LLS to provide funding to support development of Constellation's small molecule BET inhibitors to treat hematologic malignancies through Phase I testing	LLS will provide up to \$7.5 million	September 2012
Evotec AG (Xetra:EVT); Dana-Farber Cancer Institute	Partnership to discover and commercialize cancer treatments that target epigenetic drug mechanisms; partners will validate epigenetic targets and demonstrate the druggability of selected target families	Undisclosed	May 2013
Proteros biostructures; Rodin Therapeutics; Johnson & Johnson (NYSE:JNJ)	Neurology epigenetics startup Rodin partners with Proteros, J&J's Janssen Research & Development LLC unit and the pharma's Boston Innovation Center ; Proteros gives Rodin access to its structural biology platform and will help with early drug discovery work around screening, profiling and early chemical optimization	Rodin has undisclosed financing from Atlas Venture and Johnson & Johnson Development Corp. ; Proteros gets an equity stake in Rodin	June 2013
Acetylon; Celgene	Celgene gets exclusive option to acquire Acetylon	Acetylon receives \$100 million up front; if Celgene exercises the option, Acetylon will receive at least \$500 million up front and Acetylon shareholders would be eligible for up to \$250 million in regulatory milestones and up to \$850 million in sales milestones	July 2013
Astex; Otsuka Pharmaceutical Co. Ltd.	Otsuka acquires Astex	Otsuka acquired Astex for \$8.50 per share, or about \$866 million in cash	September 2013

^ABeing acquired by **Thermo Fisher Scientific Inc.** (NYSE:TMO). ^BAcquired by Otsuka Pharmaceutical.

New compounds for new targets

Researchers started linking new classes of epigenetic regulators to the pathology of many human diseases over a decade ago, particularly in genetically defined subsets of cancers.

These include histone methyltransferases (HMTs), proteins in the BET bromodomain family and lysine demethylases. Specific examples include bromodomain containing 4 (BRD4), lysine-specific histone demethylase 1 (KDM1A; LSD1) and a trio of HMTs: DOT1L, enhancer of zeste homolog 2 (EZH2) and nuclear SET domain-containing protein 2 (WHSC1; MMSET; NSD2).

NSD2 was the first of these epigenetic regulators to be associated with cancer, as separate groups from the Netherlands and **Weill Cornell Medical College** in 1998 linked it to the pathogenesis of multiple myeloma (MM).^{1,2}

Researchers took notice of EZH2 in 2000 after multiple European groups linked it to the pathogenesis of leukemia and lymphoma.^{3,4} BRD4 appeared on the radar a year later after a group at **Brigham and Women's Hospital** linked rearrangements in its gene to aggressive carcinomas.⁵

In 2005, a group at **The University of North Carolina at Chapel Hill** linked DOT1L to leukemogenesis in humans,⁶ and a separate group in Germany suggested that targeting LSD1 could be a new way to regulate androgen receptor function and proliferation in tumor cells.⁷

Despite the disease associations, it was unclear whether the epigenetic regulators were druggable. Recently, researchers in academia and at companies began publishing compounds as well as structural and biological data to suggest these proteins are, indeed, druggable.⁸

Constellation Pharmaceuticals Inc., **Epizyme Inc.** and **GlaxoSmithKline plc** have been at the forefront of R&D activity

against these newer classes of epigenetic regulators.

Epizyme has partnerships with GSK, **Eisai Co. Ltd.** and **Celgene Corp.**, which were announced in January and March of 2011 and April 2012, respectively.⁹ Constellation signed an R&D partnership with the **Genentech Inc.** unit of **Roche** last January.¹⁰

In September 2012, Epizyme started a Phase I trial of its DOT1L inhibitor, EPZ-5676, in leukemia with rearrangements in the *myeloid-lymphoid or mixed-lineage leukemia (MLL; HRX)* gene. The company said that it plans to report top-line data and expand the Phase I trial this quarter. The compound is partnered with Celgene.

This past June, Epizyme began a Phase I/II trial of its selective EZH2 inhibitor, EPZ-6438, to treat patients with non-Hodgkin's lymphoma (NHL) who have a mutation in the gene. The company said that it plans to report top-line data and start Phase II testing next year. The compound is partnered with Eisai.

"These two compounds represent the first HMT inhibitors to transition into the clinic, and they will provide the first tests of the concept of treating genetically defined cancers with potent and selective HMT inhibitors in patient populations that are defined by genetic lesions affecting specific HMTs," said Robert Copeland, EVP and CSO at Epizyme.

No compounds have been disclosed under the Epizyme-GSK partnership, which covers small molecules that target undisclosed HMTs, excluding DOT1L and EZH2.

Public investors were quick to reward Epizyme for its clinical and partnering progress. In May, the company raised \$88.7 million in an IPO that valued it at \$426.2 million. Shares in the company rose from the \$15 IPO price to \$22.99 after the first day of trading. Epizyme closed at \$35.85 on Oct. 11, with a valuation just north of \$1 billion.

Table 2. Selected clinical stage compounds that target epigenetic regulators. The availability of new research tools and data on epigenetic regulators has driven the development of a new wave of compounds. Many of these compounds recently entered Phase I trials, and companies now point to Phase II data as the next milestone that will be key to determining which molecules and their respective targets will pan out for the field. Table excludes class-selective and pan-histone deacetylase (HDAC) inhibitors.

Source: *BCIQ: BioCentury Online Intelligence; BioCentury Archives*

Company	Compound	Description	Indication	Status	Milestone(s)
Acetylon Pharmaceuticals Inc.	ACY-1215	Oral selective HDAC6 inhibitor	Multiple myeloma (MM)	Phase Ib	Start Phase II (early 2014); additional Phase Ib data (December 2013)
Astex Pharmaceuticals Inc. ^a	SGI-110	Small molecule DNA methyltransferase inhibitor	Liver cancer; acute myelogenous leukemia (AML); myelodysplastic syndrome (MDS); ovarian cancer	Phase II; Phase I/II; Phase I/II; Phase I/II	Phase II data (December 2013)
Constellation Pharmaceuticals Inc.	CPI-0610	BET bromodomain inhibitor	Lymphoma	Phase I	Undisclosed
Epizyme Inc. (NASDAQ:EPZM); Eisai Co. Ltd. (Tokyo:4523; Osaka:4523)	EPZ-6438	Selective inhibitor of enhancer of zeste homolog 2 (EZH2)	Non-Hodgkin's lymphoma (NHL)	Phase I/II	Phase I data (2014); start Phase II (2014)
Epizyme; Celgene Corp. (NASDAQ:CELG)	EPZ-5676	Histone methyltransferase DOT1L (DOT1L) inhibitor	Leukemia	Phase I	Phase I data (4Q13)
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK)	GSK525762	Bromodomain inhibitor	Epithelial cancer	Phase I	Phase I data (YE14 or early 2015)
Oncoethix S.A.; Mitsubishi Tanabe Pharma Corp. (Tokyo:4508; Osaka:4508)	OTX015	Synthetic small molecule inhibitor of BET bromodomain containing 2 (BRD2), BRD3 and BRD4	Hematologic malignancies	Phase I	Unavailable
Resverlogix Corp. (TSX:RVX)	RVX-208 ^b	Inhibitor of the BET family of bromodomain-containing proteins, including BRD4	Atherosclerosis	Phase IIb	Unavailable

^aAcquired by **Otsuka Pharmaceutical Co. Ltd.** ^bCompany had reported top-line Phase II data from the 324-patient trial showing that RVX-208 missed the primary endpoint of 0.6% reduction in atheroma volume from baseline at 26 weeks, but subsequent analysis identified a 92-patient subgroup with 1.4% reduction in atheroma volume from baseline at 26 weeks.

GSK started a Phase I trial of its bromodomain inhibitor, GSK525762, in March 2012. Data are expected in late 2014 or early 2015. The pharma is evaluating the inhibitor in patients who have nuclear protein in testis (C15orf55; NUT) midline carcinoma and other cancers.

Data from more recent studies also suggest that the bromodomain inhibitor could have therapeutic utility in nononcology indications.

In 2010, a group led by researchers at GSK and **The Rockefeller University** showed that GSK525762 had potent, broad-spectrum anti-inflammatory properties.¹¹ A separate group led by researchers at the **La Jolla Institute for Allergy & Immunology** showed in 2012 that the compound also could inhibit autoimmunity.¹² Researchers from GSK's immuno-inflammatory disease-focused EpiNova Epigenetics discovery performance unit (DPU) collaborated on both studies.

The pharma has at least one more DPU dedicated to the epigenetics space—the Cancer Epigenetics DPU.

GSK also is one of several pharmas partnered with the **Structural Genomics Consortium**, a not-for-profit organization that leads a precompetitive consortium focused on the development of open-access chemical probes to modulate epigenetic proteins.

In September, Constellation started a Phase I trial of the BET protein bromodomain inhibitor CPI-0610 in patients with previously treated and progressive lymphomas. The biotech also has inhibitors of EZH2 in preclinical development for cancer.

Constellation declined to disclose when it expects to report data or start Phase II trials of CPI-0610.

For this segment of the epigenetics space, Simon Jones thinks the key milestones are going to be Phase II efficacy data. Jones is VP of biology and preclinical development at **Acetylon Pharmaceuticals Inc.**, which is developing isoform-selective histone deacetylase (HDAC) inhibitors.

"I think everyone in this space is eagerly awaiting the efficacy data that will come from the future Phase II trials evaluating these compounds," Jones told *SciBX*. He noted that such data will be critical for determining which epigenetic regulators to target in new R&D programs and will help drive further deal activity.

"If positive results are observed, these may trigger additional interest within the investment community, perhaps leading to additional public offerings by various companies in the epigenetic space and potentially some movement in M&A activities," Copeland added.

Attention to the old

Companies working in the other segment of the epigenetics space are focused on developing compounds that have better safety and efficacy than first-generation drugs that inhibit HDACs or DNA methyltransferases. The hope is that these second-generation compounds will be more amenable for use in combination therapy and have applicability to a broader range of diseases, including those outside the oncology space.

Companies in this space include Astex Therapeutics Inc. and Acetylon.

On Oct. 11, **Otsuka Pharmaceutical Co. Ltd.** completed its acquisition of Astex for about \$866 million in cash. Astex markets Dacogen decitabine, a first-generation hypomethylating agent that inhibits DNA methyltransferase, to treat myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML).

Astex's next-generation version of Dacogen, a dinucleotide prodrug called SGI-110, is in a Phase II trial to treat hepatocellular carcinoma (HCC), a Phase I/II trial to treat MDS and AML and a Phase I/II trial to treat ovarian cancer. The hope is that SGI-110 will have greater stability, less toxicity and require less frequent dosing than Dacogen.

The company reported top-line Phase II data for the AML and MDS trial this August that showed an overall remission rate of 25% in the 67 evaluable patients with AML who had a minimum follow-up of three months. Astex said that it will present detailed results from the trial at the American Society of Hematology meeting in December.

Whereas Otsuka has taken the acquisition route, Celgene's approach has been strategic investments and option deals.

Celgene made a \$15 million equity investment in Acetylon in February 2012 and received an observational seat on the company's board. This year, Celgene made a \$100 million up-front payment to Acetylon for an exclusive option to acquire the company.

The payment eclipses the \$95 million up-front payment that Genentech made to Constellation, making it the largest disclosed initial dollar outlay in the epigenetics space.

Celgene's partnership with Epizyme includes a \$90 million up-front payment, which also gave it an undisclosed minority equity stake.

Acetylon's ACY-1215, an oral, selective HDAC6 inhibitor, is in Phase Ib testing to treat patients with relapsed or refractory MM. The company is evaluating ACY-1215 in combination with either the immunomodulatory agent Revlimid lenalidomide or the proteasome inhibitor Velcade bortezomib.

The company reported interim Phase Ib data for ACY-1215 in June and plans to report additional data at the American Society of Hematology meeting. Jones said that Acetylon is aiming to start Phase II trials early next year.

In 2005, researchers at **Harvard Medical School** and the **Broad Institute of MIT and Harvard** published data from studies in clinical samples suggesting that inhibition of HDAC6 could have synergistic antitumor effects with Velcade in MM.¹³

Celgene markets Revlimid to treat MM, MDS and mantle cell lymphoma (MCL). **Takeda Pharmaceutical Co. Ltd.'s Millennium Pharmaceuticals Inc.** unit markets Velcade in the U.S. to treat MM and MCL. **Johnson & Johnson** has ex-U.S. rights.

Jones cited two factors that have driven the field's shift toward the development of selective HDAC inhibitors: the known toxicity of pan-HDAC inhibitors, which renders them challenging for use in combination with other cancer drugs, and a deeper understanding of the biology of individual HDACs as therapeutics targets.

The two approved pan-HDAC inhibitors are Celgene's Istodax romidepsin and **Merck & Co. Inc.'s** Zolinza vorinostat. Both are

marketed to treat cutaneous T cell lymphoma (CTCL). Istodax also is marketed to treat peripheral T cell lymphoma (PTCL).

Another notable event in this segment of the epigenetics space is **Syndax Pharmaceuticals Inc.'s** closing of a \$26.6 million series B round in August. The biotech's lead compound is entinostat, an inhibitor selective for class I HDACs that is in multiple Phase II trials to treat various hematologic malignancies and solid tumors.

Compounds that inhibit HDAC1, HDAC2 and HDAC3—all class I HDACs—generally have strong antiproliferative and apoptosis-inducing activity.¹⁴ Dysregulation of HDAC1 and HDAC2 also has been implicated in multiple neurodegenerative conditions.¹⁵

"A further breakthrough for the new generation of selective HDAC inhibitors will be in moving them into nononcology domains in the clinic," Jones told *SciBX*.

In 2010, researchers at the Broad Institute and Harvard Medical School published data from a chemical genetics screen suggesting that combined inhibition of HDAC1 and HDAC2 could help stimulate the production of fetal hemoglobin,¹⁶ which could be useful for treating sickle cell disease and β -thalassemia.

Acetylon has selective inhibitors that target both HDAC1 and HDAC2 in preclinical development for neurodegenerative diseases, sickle cell disease and β -thalassemia.

Last December, the company showed that one of its own selective inhibitors of HDAC1 and HDAC2 could stimulate the production of

fetal hemoglobin in human bone marrow cells.

Jones expects these programs to start Phase I trials by early 2015.

Recent entrants

The heightened degree of industry interest in the epigenetics space also has resulted in the formation of several new companies in recent years. These include **Rodin Therapeutics Inc.**, **Syros Pharmaceuticals Inc.**, **Tensha Therapeutics Inc.** and **Zenith Epigenetics Corp.**

Tensha was founded in July 2011 and closed a \$15 million series A round that September. The company is developing small molecule bromodomain inhibitors to treat cancer and inflammatory diseases.¹⁷

Syros was founded in 2012 and closed a \$30 million series A round this past April. The company is focused on mapping a class of regulatory DNA regions called super-enhancers to identify druggable oncogenic drivers and guide the development of small molecules that selectively inhibit cancer cell growth.¹⁸

Rodin and Zenith were both founded this year. Rodin raised an undisclosed amount in a seed round that is tied to a committed, tranching series A round. The company is developing epigenetic small molecule modulators to treat CNS disorders, including Alzheimer's disease (AD).

Zenith spun out from **Resverlogix Corp.** and is developing compounds that target the BET family of bromodomain-containing proteins for multiple diseases, including autoimmune diseases and cancer.

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—Robert Copeland, Epizyme Inc.**

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COMPANIES AND INSTITUTIONS MENTIONED

Acetylon Pharmaceuticals Inc., Boston, Mass.
American Society of Hematology, Washington, D.C.
Brigham and Women's Hospital, Boston, Mass.

Broad Institute of MIT and Harvard, Cambridge, Mass.
Celgene Corp. (NASDAQ:CELG), Summit, N.J.
Constellation Pharmaceuticals Inc., Cambridge, Mass.
Eisai Co. Ltd. (Tokyo:4523; Osaka:4523), Tokyo, Japan
Epizyme Inc. (NASDAQ:EPZM), Cambridge, Mass.
Genentech Inc., South San Francisco, Calif.
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
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Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
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Millennium Pharmaceuticals Inc. (NASDAQ:MLNM), Cambridge, Mass.
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