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Strategy

Epigenetics land grab

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After about 20 years of academic research on epigenetics, large drug developers have decided the time is right to move in, making bets on biotechs that can provide platforms and compounds. Last week, **Genentech Inc.** threw its hat into the ring with $95 million in upfront payments and research funding to **Constellation Pharmaceuticals Inc.**, the largest amount disclosed to date for an epigenetics deal, which includes a takeout option.

The **Roche** unit said epigenetics is ripe for investment because advances in biology have definitively linked targets to particular cancers. In addition, the last few years have also seen the publication of the first sets of small molecules that modify epigenetic proteins that are not already targeted by marketed drugs.

"The field is maturing so that we know what the molecular players are — and there are hundreds of them. And academic teams have started to link together the proteins with cancer phenotypes," James Sabry, VP of Genentech partnering, told BioCentury.

"Now there is a chance to develop drugs against these targets," he added. "This happens in every field: there is an explosion in research and then at a certain point companies like us are ready to jump in."

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>
> **James Sabry, Genentech**

Including Genentech, at least five large companies have partnered with small biotechs that have epigenetic drug discovery capabilities.

The most active is **GlaxoSmithKline plc**, which has disclosed four deals worth at least $73.9 million in upfront payments and paid milestones, including ongoing projects with **Cellzome AG**, **Chroma Therapeutics Ltd.** and **Epizyme Inc.**

The pharma also has received undisclosed research and assets from one of the targets from a 2009 epigenetics deal with **Astex Pharmaceuticals Inc.**, which partners terminated last week.

There are at least nine biotechs working on next-generation targets, three of which have no partners. All the programs are preclinical *(see "Epigenetics Landscape," page 2)*.

Genentech chose Constellation because it believes the biotech has the best assays for validating a breadth of epigenetic targets and identifying small molecules that modulate them.

Details of Constellation's technologies have not been disclosed. However, the biotech might be the only company that does target discovery and screens for compounds that simultaneously modulate more than one epigenetic target across different families *(see BioCentury, June 9, 2008)*.

Maturing science

Epigenetic enzymes regulate histones or DNA via chemical modifications such as methylation or acetylation without changing the DNA sequence. These modifications determine whether genes are turned on or off, and dysregulation of the processes often plays a central role in diseases such as cancer and immune disorders.

According to the **Structural Genomics Consortium** (SGC), there are 377 known epigenetic targets. But epigenetics has so far yielded only two target classes with approved drugs: HDACs and DNA methyltransferases, which together account for only 23 known proteins.

Over the past couple of years, papers have begun appearing that link cancer phenotypes to mutations in epigenetic proteins.

For example, in 2010, Epizyme published research in the *Proceedings of the National Academy of Sciences* showing that mutations in methyltransferase enhancer of zeste homolog 2 (EZH2) are required for a malignant B cell lymphoma phenotype *(see SciBX: Science-Business eXchange, Dec. 9, 2010)*.

The last couple of years also have seen the first disclosures of small molecules targeting next-generation epigenetic proteins, enabled by the availability of protein X-ray crystal structures since about 2005.

In late 2010, two papers published independently in *Nature* described the identification of small molecule inhibitors of the BET family of bromodomain-containing proteins. One paper was published by researchers from GSK and **The Rockefeller University**, and the other by researchers at the **Dana-Farber Cancer Institute** and SGC *(see SciBX: Science-Business eXchange, Oct. 21, 2010)*.

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Mark Bunnage, executive director of worldwide medicinal chemistry at **Pfizer Inc.**, told SciBX that the Dana-Farber paper represented "a major development in the field of epigenetics, illustrating for the first time that the interaction between bromodomain epigenetic mark readers and their acetyl-lysine recognition motifs can be blocked by small, drug-like molecules."

Pfizer has said it is looking for partners in epigenetics in oncology and pain indications and has joined a precompetitive epigenetics consortium led by SGC. GSK, **Eli Lilly and Co.** and **Novartis AG** also are part of the consortium.

In 2011, a third paper published in *Cancer Cell* by Epizyme described a small molecule inhibitor of histone methyltransferase DOT1L that increased overall survival in a mouse model of mixed-lineage leukemia *(see SciBX: Science-Business eXchange, Aug. 4, 2011)*.

Epizyme EVP and CBO Jason Rhodes told BioCentury the finding was the first evidence for *in vivo* efficacy for any histone methyltransferase inhibitor.

The Dana-Farber and Epizyme papers relied almost solely on structural data for the protein active site to guide the synthesis of small molecules that bound the protein and inhibited its function.

Only the GSK group relied on a screening library to initially identify its compound. The screen used in the pharma paper was not particularly unusual for *in vitro* discovery programs, consisting of a cell line carrying a reporter gene that is up-regulated in the presence of a BET-targeting compound.

Complex complexes

According to companies working in the field, the main challenge for drug discovery is that most epigenetic targets form

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Epigenetics landscape

Large companies have been stepping up deal activity in the epigenetics space over the last three years. **GlaxoSmithKline plc** (LSE:GSK; NYSE:GSK) has disclosed the most deals covering the broadest range of epigenetic targets, including histone methyltransferases, BET family proteins and HDACs. But last week's deal between **Constellation Pharmaceuticals Inc.** and **Genentech Inc.**, a unit of **Roche** (SIX:ROG; OTCQX:RHHBY), has the largest disclosed upfront payment and includes a "broad" number of undisclosed targets. In the precompetitive space, the non-profit **Structural Genomics Consortium** is leading an epigenetics research effort that includes **Eli Lilly and Co.** (NYSE:LLY), GSK, **Pfizer Inc.** (NYSE:PFE) and **Novartis AG** (NYSE:NVS; SIX:NOVN). At least three companies with programs against novel epigenetic targets have not yet announced partnerships. *Source: BCIQ: BioCentury Online Intelligence*

Selected partnerships	Deal focus	Financial terms	Date
Constellation Pharmaceuticals Inc./ Genentech Inc.	Three-year deal to use Constellation's technology to discover and develop small molecules against undisclosed epigenetic targets for cancer and other diseases; excludes BET family of bromodomain-containing proteins and enhancer of zeste homolog 2 (EZH2), to which Constellation retains rights	$95M in upfront payment and research funding, plus undisclosed milestones and royalties; Genentech received an option to acquire Constellation	Jan-12
Epizyme Inc./Eisai Co. Ltd. (Tokyo:4523; Osaka:4523)	Epizyme will use its technology and small molecule library to discover, develop and commercialize EZH2 inhibitors to treat lymphoma and other cancers	Up to $6M in upfront and initial milestones, up to $200M in additional milestones, plus up to double-digit royalties; Eisai will fund through proof of concept, after which Epizyme will have option to profit-sharing and co-commercialization	Mar-11
Epizyme Inc./GlaxoSmithKline plc (LSE:GSK; NYSE:GSK)	The companies will discover, develop and commercialize small molecules targeting histone methyltransferases, excluding EZH2 and DOT1L, for cancer and other diseases; Epizyme is responsible for research through candidate selection	Up to $20M up front, undisclosed research funding, up to $630M in milestones, plus double-digit royalties	Jan-11
EpiTherapeutics ApS/ Abbott Laboratories (NYSE:ABT)	Three-year deal to use EpiTherapeutics' technology to discover and develop small molecules against undisclosed epigenetic cancer targets	Undisclosed upfront, research, milestone and royalty payments	Dec-10
EpiTherapeutics ApS/Nuevolution A/S/ ExpreS2ion Biotechnology ApS/ University of Copenhagen	JV to discover and develop small molecules to treat epigenetic disorders using Nuevolution's screening technology, EpiTherapeutics' and the University's biological activity assays, and ExpreS2ion's CRO services	DKK24M ($4.5M) from Danish High Technology Fund; profits will be shared by EpiTherapeutics and Nuevolution	Oct-10

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large complexes that are difficult to work with.

As an example, Cellzome CSO David Simmons noted multiple companies are looking at EZH2 as a target. EZH2 combines with at least three other proteins to form polycomb repressive complex 2 (PRC2), a histone methyltransferase.

"People have made recombinant EZH2, but you also have to reconstitute the entire PRC2 in order to reconstitute anything like EZH2 activity. And you would have to do that with all histone methyltransferases," Simmons told BioCentury.

Cellzome's Episphere technology allows epigenetic targets to be screened in their native environment as part of their protein complexes without the need for recombinant protein or any artificial labeling.

Episphere beads capture proteins in their native form directly from cells. A compound that is added to the cells competes with the beads for binding the targets. This competition is then quantified with mass spectrometry and a full target profile can be determined from a single tissue sample.

Simmons said Cellzome's technology can be applied to any class of targets.

"We started in kinases about six or seven years ago. We moved into epigenetics about three years ago because they are large complexes, and studying them as complete structures is a problem in the field, and we get around that," he said.

While the technology could be used to discover proteins and to screen compounds against multiple targets at the same time, Simmons said the company primarily uses it to discover compounds against a particular binding site.

Cellzome and GSK partnered in 2010 to discover oral small molecules against the BET family of proteins and other undisclosed epigenetic targets to treat immuno-inflammatory diseases. Cellzome received €33 million ($44.9 million) up front, including an equity investment from GSK, and is eligible for €475 million ($647 million) in milestones, plus tiered royalties. Cellzome has since received two undisclosed milestones.

Internally, the only epigenetic program Cellzome has disclosed is a selective HDAC inhibitor in lead optimization.

Astex takes a different approach. Its Pyramid technology uses crystallography to inform fragment-based drug design against validated targets. This technology also is agnostic to target class and works with complexes of epigenetic targets.

Tom Heightman, director of medicinal chemistry, noted Pyramid also is agnostic to the binding site.

"Sometimes you don't want to target the catalytic site. It might be how the protein interacts with other proteins in a complex that is important," he said. "Typical screens look only at orthosteric binding sites, but our structural biology approach can find allosteric sites as well."

Astex retained rights to all but one of the projects that had been partnered with GSK. Details about the program have not been disclosed.

Astex's lead epigenetic-targeted compound in development is SGI-110, a second-generation version of Dacogen decitabine that is in Phase I/II trials for myelodysplastic syndrome (MDS) and

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Epigenetics Landscape,
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Selected partnerships	Deal focus	Financial terms	Date
Cellzome AG/GlaxoSmithKline plc (LSE:GSK; NYSE:GSK)	The companies will use Cellzome's Episphere technology to discover oral small molecules against the BET family of proteins and three undisclosed epigenetic targets to treat immuno-inflammatory disease	€33M ($44.9M) up front including an equity investment, up to €475M ($647M) in milestones, plus royalties	Mar-10
CellCentric Ltd./ Takeda Pharmaceutical Co. Ltd. (Tokyo:4502)	Takeda received exclusive rights to develop a program with an undisclosed target that is not an HDAC or a DNA methyltransferase	Up to $200M in upfront, milestone and royalty payments	Feb-10
Chroma Therapeutics Ltd./ GlaxoSmithKline plc (LSE:GSK; NYSE:GSK)	GSK received options to license exclusive, worldwide rights to four discovery projects, including a macrophage-targeted HDAC inhibitor program for inflammatory disorders	"Significant" upfront payment, over $1B in milestone and option payments, plus tiered royalties; GSK also participated in Chroma's £15M ($24.7M) series D round	Jun-09

Selected unpartnered companies	Platform
Astex Pharmaceuticals Inc. (NASDAQ:ASTX)	Binding-site agnostic Pyramid platform for small molecule screening. (Note: Astex has a discovery deal for an undisclosed epigenetic target with an undisclosed partner, and in-house projects against additional undisclosed epigenetic targets. The company and GSK terminated a 2009 epigenetics deal earlier this month, and Astex transferred all rights to one project to GSK.)
Progen Pharmaceuticals Ltd. (ASX:PGL; Pink:PGLA)	Polyamine platform products that inhibit lysine-specific histone demethylase 1 (KDM1A; LSD1) and HDACs
RaNA Therapeutics Inc.	Oligonucleotides that bind to long non-coding RNA (lncRNA) and prevent the recruit ment of the polycomb repressive complex 2 (PRC2) to target genes *(see "RaNA: Specific in Epigenetics," A9).*
Tensha Therapeutics Inc.	Small molecule bromodomain inhibitors

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acute myelogenous leukemia (AML).

Dacogen, a DNA methyltransferase inhibitor, is marketed for MDS in the U.S., with an FDA advisory committee meeting for AML scheduled on Feb. 9. An MAA is under review in the EU for AML. **Eisai Co. Ltd.** has rights to Dacogen in North America, and **Johnson & Johnson** has rights elsewhere.

Astex is partnered on an undisclosed epigenetic target within one of its two current partnerships, according to SVP of Marketing Timothy Enns. The company has another deal with GSK to discover compounds against undisclosed targets across multiple therapeutic areas, and a deal with J&J's Janssen Pharmaceutica NV subsidiary to discover inhibitors of two undisclosed cancer targets.

Epizyme has focused only on histone methyltransferases and has tackled the complexes in yet another way. CEO Robert Gould said the company has "invested a lot into the enzymology of these targets, for example to figure out when we can study just EZH2 or when we need to study the whole PRC2 complex."

Gould noted that histone methyltransferases move methyl groups on histones in a very specific way. For example, some will add only the first of three methyl groups, another will add the second, and another the third. "We are able to make sure we are looking at the physiologically relevant complex in cell assays," he said.

Epizyme can do target discovery, but it decided to focus solely on histone methyltransferases because mutated forms kept coming up as being associated with cancers in cancer genome sequencing studies, Gould said. The company is focusing on 20 of the most validated of the 96 known histone methyltransferases *(see BioCentury, Aug. 30, 2010)*.

Gould said Epizyme's focus on one target class has resulted in more leads than the company would have had if it had diversified its approach. The company has disclosed only two of its programs.

Epizyme partnered with GSK in 2011 to discover small molecules targeting a small, undisclosed set of histone methyltransferases for cancer and other diseases.

The deal did not include the biotech's two lead programs, which are against EZH2 and DOT1L. Both programs are in preclinical development.

Later in 2011, Epizyme partnered its EZH2 inhibitors with Eisai.

Other epigenetic companies also are focusing on single families of targets. For example, **Acetylon Pharmaceuticals Inc.** was formed to discover and develop selective HDAC inhibitors that avoid side effects of marketed pan-HDAC inhibitors, according to President and CEO Walter Ogier.

Acetylon's lead compound, ACY-1215, is an HDAC6 inhibitor in Phase I/IIa testing for relapsed or refractory multiple myeloma (MM).

> ***"We're not interested in managing multiple partnerships and getting on a treadmill of having to do more deals to get more capital in order to do more deals."***
>
> **Mark Goldsmith, Constellation**

Bread for breadth

By contrast, Genentech chose Constellation because of the biotech's ability to do research on a breadth of targets quickly.

"They are well-poised to rapidly understand which targets are most attractive, find compounds that modulate them and move them into clinical development," Sabry said.

CEO Mark Goldsmith said when the company was founded in 2008, it chose to develop a target discovery engine that is not limited by target class.

For example, he noted there can be "cross-talk" between targets from different families, and inhibiting combinations of epigenetic targets might be needed for some indications. Constellation's approach enables the company to find these combinations, he said.

Goldsmith said the company initially developed a suite of assays using bioinformatics, chemical probes and customized RNAi libraries to uncover the activity of epigenetic targets in disease, as well as biochemical assays for compound discovery.

Constellation then developed cell-based assays to assess the compounds' mechanisms and phenotypic effects.

The three-year deal with Genentech includes discovery and development of epigenetic treatments for cancer and other diseases but excludes Constellation's two lead programs, which inhibit the BET family of proteins and EZH2. The company expects to have one of its BET or EZH2 inhibitors ready for Phase I testing by year end.

In addition to receiving $95 million in an upfront payment and research funding, Constellation is eligible for development milestones.

At the end of the three years, the partners will split up the resulting portfolio of compounds in an undisclosed but predefined way. Each company will be eligible for commercial milestones and royalties on products taken forward by the other.

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Genentech also has a call option to acquire Constellation at an undisclosed, predefined point. The acquisition would include an upfront price determined by undisclosed factors, which would provide "venture-type returns" for Constellation investors, according to Goldsmith.

Constellation investors also would be eligible to receive contingent value rights payments.

"At the end of the collaboration, we see two outstanding outcomes. One is that Genentech opts in and we receive liquidity for our shareholders, which is a win for everybody," said Goldsmith. "The other is if they opt out, we should at that point have far more mature assets in the BET and EZH2 areas, as well as assets from the collaboration, and then we will have other opportunities to find other transactions going forward."

He added the partners are working exclusively together on the areas within the scope of the agreement.

"We've aligned ourselves with one global partner so we can focus all our energies on doing the work and managing this one collaboration and our two internal programs," Goldsmith said. "We're not interested in managing multiple partnerships and getting on a treadmill of having to do more deals to get more capital in order to do more deals."

COMPANIES AND INSTITUTIONS MENTIONED

Acetylon Pharmaceuticals Inc., Winchester, Mass.
Astex Pharmaceuticals Inc. (NASDAQ:ASTX), Dublin, Calif.
Cellzome AG, Heidelberg, Germany
Chroma Therapeutics Ltd., Abingdon, U.K.
Constellation Pharmaceuticals Inc., Cambridge, Mass
Dana-Farber Cancer Institute, Boston, Mass.
Eisai Co. Ltd. (Tokyo:4523; Osaka:4523), Tokyo, Japan
Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.
Epizyme Inc., Cambridge, Mass.
Genentech Inc., South San Francisco, Calif.
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
Pfizer Inc. (NYSE:PFE), New York, N.Y.
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
Structural Genomics Consortium (SGC), Toronto, Ontario
The Rockefeller University, New York, N.Y.

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