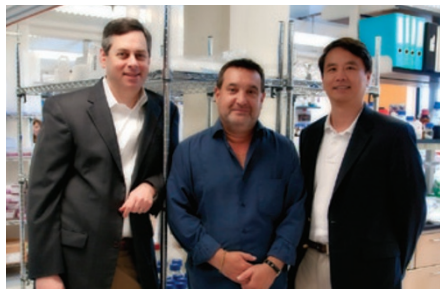
NEWS maker

Constellation Pharmaceuticals

Replete with investor funds, the Cambridge, Massachusetts–based epigenetics firm is taking aim at methylases and demethylases linked to disease.



Seacia Pavao

Left to right: Constellation's CEO Mark Goldsmith, and founders Danny Reinberg, Professor of Biochemistry at NYU School of Medicine, and Yang Shi, Professor of Pathology at Harvard Medical School

Constellation's $22 million series B financing this summer again drew pundits' attention toward a field of research that has been tilled with particular vigor over the past year or so. The basic science underpinning epigenetics—manipulating gene expression without altering the sequence itself—is widely regarded as conceptually sound. Four epigenetic drugs—two that take aim at (among other things) histone deacetylases (HDACs) and two that target DNA methyltransferases (DNMTs), which control chemical tags on histones or cytosines in the gene sequence, respectively—have thus far received US Food and Drug Administration (FDA) approval. For Constellation, the question is whether its therapeutic focus, histone methylases and demethylases, which modify the proteins that package and order DNA, will prove as successful.

Constellation started out, fueled by $32 million in series A funding, in April 2008. It spent the first year and a half hiring key personnel, building infrastructure and optimizing assays. Part of that initial funding came from Third Rock Ventures, and a partner at the fund, Mark Levin—the former CEO of Cambridge, Massachusetts–based Millennium Pharmaceuticals—served as interim CEO of Constellation. One industry insider says Levin's reputation at Millennium enabled him to sell the figurative sizzle to investors before there was any clinical 'steak'. Constellation work remains only at the preclinical stage.

Now with 50 employees—up from about 30 this time last year—the company aims to develop drugs targeting a broad range of histone methylation enzymes. So far, Constellation scientists have published evidence that the histone lysine methyltransferase G9a/KMT1C regulates chromatin structure by promoting the methylation of the histone H1.4K26 *in vivo* in mammals (*J. Biol. Chem.* **284**, 8395–8405, 2009). Constellation claims to have nailed down programs that identify enzymes with specific linkages to disease. The company will not reach the clinic by next year, but could by 2012.

Mark Goldsmith, Constellation's president and CEO, says the firm's research is bolstered by enhanced understanding of the role of histone methylation in modulating chromatin through action by enzymes and proteins that act as 'writers', 'readers' and 'erasers' to activate or deactivate genes. 'Writers' add chemical groups, 'readers' bear binding regions that recognize changes and 'erasers' remove the marks. Now that a survey of human methylomes—the map of human methylation patterns—has been published (*Nature* **462**, 315–322, 2009), Goldsmith says the linkage between DNA methylation and biological consequences can be brought into sharper focus.

Skepticism concerning the safety and efficacy of pharmacological interventions in the DNA and chromatin remodeling machinery has receded with the approval of several drugs in hematological cancers: HDAC inhibitors Istodax (romidepsin) and Zolinza (vorinostat), and DNMT inhibitors Vidaza (azacitidine) and Dacogen (decitabine). Indeed, big pharma is investing heavily in the area, with such deals as the $200 million agreement in March between Cambridge, UK–based CellCentric and Takeda Pharmaceutical, of Tokyo. The same month, London-based GlaxoSmithKline inked a $644 million epigenetics pact with Cellzome, of Cambridge, UK. Both deals grew out of existing relationships with nonepigenetic concerns, and say little about whether Constellation can prove itself to suitors as well, but a bubbling epigenetics pot has led would-be partners to discuss potential arrangements, according to Goldsmith.

Meanwhile, as the company holds fast to three programs of special focus, Constellation is casting a wide net to consider target classes beyond those validated so far. Goldsmith wants to leave no would-be opportunities on the table, he says, but the firm's determination to mine varied classes of enzymes for their possibilities could become a rate-limiting factor. Indeed, the nascent biology surrounding many of these targets could make a slowdown inevitable, in the view of Jean-Pierre Issa, co-director of cancer epigenetics at M.D. Anderson Cancer Center, in Houston. Despite acknowledging the considerable scientific expertise at Constellation, he suspects the broad approach will mean only plodding progress. Issa likens the needle-in-the-haystack approach to that taken by companies that first began investigating tyrosine kinases, and predicts the road for epigenetics could be similarly fraught with failure. As an example of one target that almost every company is pursuing, Issa points to histone-lysine *N*-methyltransferase EZH2, an enzyme that in humans is encoded by the *EZH2* gene. This histone-modifying enzyme belongs to the polycomb group family, and three papers published in the past year in *Nature Genetics* (**42**, 181–185; 665–667; 722–726, 2010) have suggested that EZH2 could act as a tumor suppressor. Constellation would not confirm any work on EZH2, but says the target is interesting.

Stuart Hwang, director of business development at SuperGen of Dublin, California, says Constellation's plan to use approaches other than the more popular HDAC and DNMT inhibitors is logical because drugs targeting HDACs do not seem to work against solid tumors, and oral versions bring toxicity, whereas DNMT blockers display only a short half-life, which makes them unsuitable for solid tumors as well. But histone methyltransferases outside of the two main classes come in many flavors, and it's an open question whether their pharmacological inhibition will prove successful. Hwang doesn't think so, mainly because of the problem that has beset EZH2 work: turning on a gene or genes can mean shutting down an equal number of them. Biological benefits are starting to emerge, Hwang says, but outside the two known categories of epigenetic drugs, clinical proof of efficacy could yet lie far off.

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