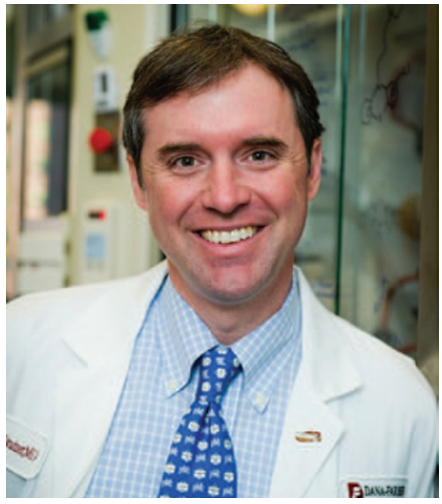
NEWS maker

Tensha Therapeutics

Tensha is staking a claim on drugging bromodomains as an innovative epigenetic approach to novel anti-cancer agents.



Samuel Ogden

Founder James 'Jay' Bradner

Increasing attention on bromodomains (BDs) as key protein motifs in protein-histone association and chromatin remodeling has suggested the possibility of new anticancer agents, prompting venture capital firm HealthCare Ventures, of Cambridge, Massachusetts, to pump a $15-million series A round into Tensha Therapeutics last September. Tensha, also of Cambridge, Massachusetts, joins a growing cadre of companies pursuing epigenetic modulation through targeting histone deacetylases (HDACs), histone acetyltransferases (HATs) and histone methyltransferases. But bromodomains—a conserved class of protein motif that helps 'read' epigenetic marks on genes destined to be active—have not yet been fully exploited as drug targets. Tensha intends to explore these protein domains as targets for first-in-class, small-molecule inhibitors in cancer.

Tensha's scientific focus stems from the academic research of James (Jay) Bradner at the Dana-Farber Cancer Institute in Boston. Bradner's laboratory is broadly interested in discovering small-molecule inhibitors of gene regulatory pathways in cancer, and has a special expertise in chromatin-associated factors.

The idea is to target aberrant gene expression in cancer, not by tackling the genes directly but by modifying chromatin activation. For example, a growth-control protein like c-Myc needs to stably turn on many genes: it does so in part by recruiting HATs and directing them to acetylate lysine residues on the N-terminal tails of relevant histones. But these acetylation marks still need to be interpreted by the cell, which is where bromodomains come in.

The bromodomain motif is short (about 110 amino acids) and highly conserved; the human genome encodes 56 different bromodomains spread across 42 proteins. The bromodomain binds to acetylated lysines on histones, allowing the protein that bears it to recruit the relevant apparatus and thereby assemble a transcription factory. In the absence of the bromodomain, the lysine marks remain unread, so competitively interfering with bromodomain binding represents a potential mechanism for therapeutic intervention in disorders associated with inappropriate gene expression, like cancer.

In 2010, Bradner's group along with collaborators reported that a novel small-molecule bromodomain inhibitor, JQ1, was able to block inappropriate growth in cell lines derived from midline carcinoma, a rare translocation disorder stemming from the fusion of bromodomain protein BRD4 to another protein (*Nature* **468**, 1067–1073, 2010). The beneficial effect also occurred in a mouse xenograph model. JQ1 (named after Bradner's synthetic chemist, Jun Qi) is specific for the bromodomain carried by the BET protein family, of which BRD4 is a member. The BET family plays important roles in cell cycle progression and cell fate decisions, hinting that JQ1 might be effective in other cancers. Indeed, the team's follow-up publications showed that JQ1 could also target BRD4 in acute myeloid leukemia as well as multiple myeloma models, and that its anti-proliferative action was due to the suppression of oncogenic c-Myc.

Bradner is no stranger to the biotech industry. He is already scientific co-founder of two other Boston-area startups exploiting HDAC inhibitors—Acetylon Pharmaceuticals and Shape Pharmaceuticals. He says that this experience prompted him to seek an expert collaborator for bringing bromodomain inhibition to the clinic as well. He approached Douglas Onsi, managing director of HealthCare Ventures, with whom he already had a working relationship through HealthCare's partial funding of Shape. According to Onsi, the new collaboration was a natural fit, and Tensha was born.

Bradner thinks that bromodomain inhibitors have advantages as targets over some other epigenetic modulators that are already on the market. Naturally, he has a stake in HDAC inhibition as well, but he says that bromodomains are better targets than HATs because the latter are very redundant—if you knock down one, another one will step up to the plate. Also, HATs have been shown to be inactivated in cancers, which means that their inhibition could be counterproductive in oncology. And finally, he points out that bromodomain inhibition shows a higher specificity than what you achieve when suppressing HAT activity.

Martin Carroll, a leukemia expert at the University of Pennsylvania, says he can understand why Bradner's work has generated so much excitement: bromodomain inhibition is novel, and the published work showed a dramatic effect in multiple types of cancers. There is, however, still some question about the therapeutic window. JQI should bind to all four members of the BET domain family, not just BRD4, which could broaden its therapeutic reach but equally could lead to unintended consequences. Although the publications showed no significant on- or off-target effects in mice, Carroll notes that JQ1 has a very short half-life, and so wonders whether a more stable compound might elicit some toxicity. Bradner admits that he was surprised how broad the therapeutic window for JQ1 actually is, and says that its commercial successor will be subjected to a more thorough assessment and a full toxicity screen.

Robert Copeland, CSO of Epizyme, whose company works on inhibiting the rival histone methyltransferases, is enthusiastic about the burgeoning field of inhibiting chromatin-modifying proteins. He notes that the bromodomain is eminently druggable owing to its localized binding energy and relative hydrophobicity, and that the very diversity of the bromodomain family suggests a useful biological selectivity, which is what you want to see for therapeutic specificity. Like Carroll, however, he agrees that it's still an unknown whether bromodomain inhibition will achieve a tolerable therapeutic window in humans that require chronic dosing. Still, he points out that this is the case for any novel therapeutic modality, and it shouldn't stop the courageous from addressing those unknowns in further preclinical and clinical studies.

Tensha says that it is moving forward with a clinical candidate chosen from about 500 molecules in and around the JQ1 chemical space. Although it's too soon to reveal their clinical development strategy, Bradner notes that bromodomain inhibition could be broadly applicable outside oncology.

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