PTSD: rewriting fearful memories

By Michael J. Haas, Senior Writer

A **Massachusetts Institute of Technology**-led team has outlined a strategy for addressing the underlying causes of post-traumatic stress disorder.¹ The approach centers on blocking histone deacetylase 2, which is the only class I histone deacetylase target with a growing body of evidence suggesting a role in learning and memory.

Future studies will need to identify a selective histone deacetylase 2 (HDAC2) inhibitor and determine its optimal human dosing to avoid unwanted effects on memory.

Post-traumatic stress disorder (PTSD) is caused by a traumatizing event that the individual re-experiences episodically when environmental or situational cues trigger its recollection. Approved PTSD drugs help manage the anxiety associated with the traumatic memory and include antidepressants or anxiolytics, sometimes in combination with atypical antipsychotics.

Behavioral approaches include exposing the patient to the trauma-associated cues in a safe setting. This allows the patient to reinterpret those cues as neutral and thus develop reduced anxiety responses to them—a process known as extinction.

Neither drugs nor behavior therapy alters the underlying memory of the original trauma that triggers PTSD episodes. Moreover, patients may be averse to recalling the traumatic event and thus may not complete the series of exposure therapy sessions needed for extinction.

Over the past seven years, multiple groups have shown that inhibitors of class I HDACs improved the effectiveness of extinction protocols in fear-conditioned mice when given a day after the completion of fear conditioning.²⁻⁷

These studies did not examine the effect of combining class I HDAC inhibition and extinction protocols in mice several days or weeks after fear conditioning—an approach that would more closely model human PTSD.

Thus, the role of class I HDACs in the extinction of anxiety responses to long-term traumatic memories was poorly understood.

That began to change in 2009 and 2012 when teams led by Li-Huei Tsai showed that HDAC2—but not other class I HDACs—blocked memory formation in mice⁸ and contributed to long-term memory impairment in patients with Alzheimer's disease (AD).⁹

Also in those studies, Hdac2 reduced memory deficits in the normal mice and mouse models of AD.

Tsai told *SciBX* that those studies led her to speculate that inhibiting HDAC2 might have a therapeutic effect on long-term memories in fear-conditioned mouse models of PTSD.

For the recent study, Tsai's new team first compared the effectiveness of extinction protocols in mice one day after fear conditioning (recent memory models) and one month after fear conditioning (remote memory models).

Initially, extinction protocols were effective at eliminating conditioned fear responses in both PTSD models. Over time, however, only the remote memory models exhibited spontaneous recovery of the fear response, thus demonstrating that the extinction protocols could not completely eliminate long-term fear memories.

The fear-memory recall triggered by the extinction protocols was accompanied by elevated Hdac2-chromatin dissociation and a consequent reduction of Hdac2 activity in the hippocampal neurons of the recent memory models—but not in the neurons of the remote memory models. Moreover, the duration of the reduction in Hdac2 activity in the recent memory models coincided with the reconsolidation window, a six-hour period in mice during which a recalled memory can be altered or rewritten.¹⁰

These results suggested that extinction therapy was not completely effective in the remote memory models because the retention of hippocampal Hdac2 activity following fear-memory recall made the memory resistant to alteration. Indeed, the team showed that in the remote memory models undergoing the extinction protocol, Hdac2 blockade with a CNS-penetrating research compound that inhibited class I HDACs during the six-hour reconsolidation window decreased the conditioned fear response and spontaneous recovery of that response and increased the synaptic and structural plasticity

of hippocampal neurons compared with no Hdac2 blockade.

Taken together, the results suggest that inhibition of HDAC2 could improve the ability of extinction therapies to rewrite the long-term traumatic memories that underlie PTSD, the team wrote in its report in *Cell*.

Tsai is director of the Picower Institute for Learning and Memory and a professor of neuroscience at the Massachusetts Institute of Technology (MIT). She is also a senior associate member at the **Broad Institute of MIT and Harvard**.

Her team included researchers from the **Massachusetts General Hospital, Harvard Medical School, the Howard Hughes Medical Institute** and the **Washington University in St. Louis School of Medicine**.

"This study is important because it shows that an old memory of fear can be successfully extinguished and spontaneous recovery of fear memory—which can occur in PTSD patients—can be abolished as well," said Yossef Itzhak, a professor of psychiatry and behavioral sciences and of molecular and cellular pharmacology at the **University of Miami Miller School of Medicine**.

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The HDAC2 inhibitor “induced epigenetic changes that shaped the brain to be more responsive to changes in behavior,” he said.

“That’s what’s exciting to us about the therapeutic strategy in the *Cell* paper,” added Martin Jefson, CSO of **Rodin Therapeutics Inc.** and an entrepreneur in residence at **Atlas Venture**. “It takes advantage of the cognitive flexibility that occurs when memory is recalled and provides an opportunity to alter the expression of genes associated with formation of synapses and memory—thus breaking the association between fear and the recalled memory.”

K. Matthew Lattal, an associate professor of behavioral neuroscience at **Oregon Health & Science University**, agreed. The ability of an HDAC2 inhibitor to potentially promote memory formation at the molecular level “could strengthen the patient’s perception that the memories previously associated with trauma have become safe” as a result of exposure therapy, he said. The combination of HDAC2 inhibition and exposure therapy may “result in the long-term suppression of the traumatic memory and increase the likelihood that the treatment will have a long-term impact.”

He said that an important feature of the study was the long interval of time between fear conditioning and the combined HDAC2 inhibition–extinction therapy. “This may provide a more effective way to model human PTSD because treatment in patients often does not occur until well after the traumatic experience,” Lattal told *SciBX*.

Selectively fearless

Jefson said that the findings are ready for clinical testing. “There’s not much more to be explored here preclinically. PTSD is a complex human behavior, and it’s not adequately modeled in animals,” he noted.

Ankit Mahadevia, acting CBO of Rodin and a venture partner at Atlas, agreed, noting that the real challenge will be identifying a selective HDAC2 inhibitor.

Indeed, most of the safety issues associated with HDAC inhibitors arise from their nonselectivity for individual HDACs, Jefson said. As examples, he cited preclinical studies showing that double knockout of *Hdac2* and *Hdac1* in mice resulted in anemia, thrombocytopenia, peripheral nervous system and CNS abnormalities, cardiomyopathies and other pathologies not observed in single-knockout mice.^{11,12}

There are two nonselective HDAC inhibitors on the market—Istodax romidepsin and Zolinza vorinostat. Istodax’s side effects include nausea, fatigue, thrombocytopenia, anemia and electrocardiographic changes, whereas the side effects of Zolinza include nausea, diarrhea, fatigue, thrombocytopenia and anorexia.

Celgene Corp. markets Istodax to treat cutaneous T cell lymphoma (CTCL) and lymphoma. **Merck & Co. Inc.** and **Taiho Pharmaceutical Co. Ltd.** market Zolinza to treat CTCL.

“It will be important to identify specific inhibitors of HDAC2 that target only the brain circuits and genes” involved in memory, said Itzhak.

“Good selectivity in an HDAC2 inhibitor would thus provide a wide therapeutic index for PTSD and open the door to using the inhibitor in other conditions where it could enhance cognition,” such as AD, phobia and cognitive impairment in schizophrenia, Mahadevia said.

“Selectivity of the inhibitor would also be important because there is still a lot to be worked out about how it would be dosed in humans,” added Mahadevia. “We don’t know yet whether a patient would need to be exposed to the inhibitor periodically, acutely or chronically” to

achieve the desired effect on rewriting fear memories in patients with PTSD.

Lattal cautioned that dosing and duration of HDAC2 inhibition will have to coincide closely with the exposure therapy session to avoid inducing new, potentially detrimental associations in the patient.

“For example, let’s say you have a recovering alcoholic who is on an HDAC2 inhibitor to treat PTSD and he experiences an episodic relapse in his alcoholism,” he said. If that patient walks into a bar for a drink while the inhibitor is in his system, the result could be “a strengthened association between the bar environment and the positive intoxication state—meaning that an unintentional side effect of the inhibitor could be an increased probability of another relapse” in his alcoholism.

Rodin is developing selective HDAC inhibitors but has not disclosed details about its pipeline, including specific targets or indications.

Tsai is a member of Rodin’s scientific advisory board, but Mahadevia declined to disclose whether the company would in-license the findings her team reported in *Cell*. But he added, “We have composition of matter around selective HDAC inhibitors that we could use to explore these findings.”

Tsai said that her team’s planned work includes looking for other targets that play roles in cognitive function and could be targeted with small molecules.

She said that the findings reported in *Cell* are covered by both issued patents and patent applications owned and filed by MIT, and the IP is available for licensing.

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