In the mood for HDAC inhibitors

By Tim Fulmer, Senior Writer

Mount Sinai School of Medicine researchers and colleagues elsewhere have shown that HDAC inhibitors, already established as cancer therapeutics, could also be useful antidepressants.[1] The molecules will likely require modifications to improve both brain permeability and selectivity for specific HDAC isoforms before the new indication can be pursued in the clinic.

The histone deacetylase (HDAC) enzymes, of which there are 11 isoforms, catalyze the removal of acetyl groups from histone proteins. This triggers a conformational change that leads to the remodeling of chromatin, the tightly packed complex of DNA and histones in the nucleus.

Chromatin normally undergoes remodeling to alter the accessibility of genes to transcription factors. In certain cancers, this remodeling process is impaired and proteins are expressed at incorrect levels, thus affecting proper cell growth and signaling. There is one HDAC inhibitor on the market—**Merck & Co. Inc.**'s Zolinza vorinostat to treat cutaneous T cell lymphoma (CTCL).

The Mount Sinai group and other researchers previously have shown that aberrant chromatin remodeling also underlies psychiatric disorders such as depression and addiction.[2,3] Those findings suggest that inhibiting HDAC could treat some psychiatric disorders.

To test that hypothesis, a team led by Mount Sinai's Eric Nestler measured histone acetylation levels in the nucleus accumbens in mice with stress-induced depression. The nucleus accumbens is a brain region involved in the development of depressive-like behaviors.[4] Nestler is a professor of psychiatry, neuroscience, pharmacology and systems therapeutics, and director of Mount Sinai's Brain Institute.

Indeed, histone acetylation levels were significantly higher 15 days after chronic stress compared with those in unstressed control mice ($p<0.05$). Separately, the researchers found that postmortem tissue from depressed humans showed significantly greater histone acetylation than tissue from healthy controls ($p<0.01$).

The group then treated depressed mice with two different HDAC inhibitors—Zolinza or **Syndax Pharmaceuticals Inc.**'s SNDX-275 (MS-275), which is in Phase I and Phase II testing to treat multiple cancers.

Direct infusion of either inhibitor into the nucleus accumbens led to significant reductions in depressive-like social avoidance behavior compared with infusion of vehicle ($p<0.01$ for both inhibitors).

The findings were published in *The Journal of Neuroscience*.

Getting selective

Testing HDAC inhibitors in neuropsychiatric disorders will require more than simply repurposing compounds already tested in the clinic for cancer.

A first challenge will be identifying which HDAC isoforms are worth targeting in neuropsychiatric disease and then designing inhibitors selective for those isoforms in order to reduce side effects.

In the paper, the researchers found that HDAC2 mRNA levels, but not those of HDAC1 or HDAC3, were significantly decreased 24 hours after induction of stress ($p<0.0001$), suggesting that HDAC2 could play an important role in depression, at least in this particular mouse model.

Moreover, in postmortem brain samples from depressed patients, HDAC2 levels were significantly lower than those in samples from controls ($p=0.02$).

The HDAC inhibitors used to treat cancer target many, if not all, of the HDAC isoforms. For example, Zolinza is a pan-specific inhibitor, targeting every isoform, whereas SNDX-275 inhibits four isoforms.

According to Zolinza's label, the most common side effects associated with treatment are fatigue, diarrhea, nausea and thrombocytopenia.

Such toxicity profiles would probably limit the usefulness of HDAC inhibitors in neurological disorders, said Elizabeth Thomas, associate professor of molecular biology at **The Scripps Research Institute**.

> **"New HDAC inhibitors that are selective for specific HDAC isoforms implicated in neuropsychiatric disease will have to be developed."**
> *—Elizabeth Thomas, The Scripps Research Institute*

"That means new HDAC inhibitors that are selective for specific HDAC isoforms implicated in neuropsychiatric disease will have to be developed," she said.

Thomas, along with Joel Gottesfeld, professor of molecular biology at Scripps, have designed HDAC inhibitors that selectively target the HDAC3 isoform to treat neurodegenerative disorders such as Huntington's disease (HD) and Friedrich's ataxia. Oral delivery of one such inhibitor reduced striatal atrophy and improved the motor performance of a transgenic HD mouse model.[5]

In addition to the selectivity issue, a second challenge will be getting the HDAC inhibitors across the blood brain barrier (BBB).

"Most of the HDAC inhibitors out there show poor penetration of the blood brain barrier. That means chemical modifications will be necessary to create a compound that acts as an orally available antidepressant," said Peter Jensen, CEO of **TopoTarget A/S**.

TopoTarget's belinostat, a pan-HDAC inhibitor, is in Phase III testing to treat peripheral T cell lymphoma and Phase II testing to treat CTCL, acute myelogenous leukemia (AML) and various types of solid tumors.

Nestler, corresponding author on the paper, told *SciBX* that "the next step is to develop more selective HDAC inhibitors that penetrate the

brain and study the antidepressant potential of those compounds."

There could be a big payoff to overcoming both hurdles. Jeffrey Besterman, EVP of R&D and CSO of **MethylGene Inc.**, said the mechanism underlying HDAC inhibitors could offer advantages over marketed antidepressants.

"Because HDAC inhibitors affect the expression of proteins potentially involved in multiple signaling pathways that contribute to depression, they could offer an advantage over marketed antidepressants like the SSRIs [selective serotonin reuptake inhibitors], which generally have a single molecular target," he said.

EVP-0334, a brain-penetrating HDAC inhibitor created by MethylGene in collaboration with **EnVivo Pharmaceuticals Inc.**, is in Phase I testing to treat cognitive deficits associated with Alzheimer's disease (AD).

"Based on Nestler's preclinical work and our own, it's clear that HDAC inhibitors could have real therapeutic value in depression and other neuropsychiatric disorders," said Schahram Akbarian, associate professor of psychiatry and director of the Brudnick Neuropsychiatric Research Institute at the **University of Massachusetts Medical School**.

He thinks the molecules would likely be used as part of a combination therapy for depression. Akbarian and colleagues have reported that a combination of an HDAC inhibitor plus Prozac fluoxetine had antidepressant effects in mice when administered acutely or chronically. The HDAC inhibitor alone was effective only in the chronic setting, and the efficacy of Prozac monotherapy was limited to the acute setting.[6]

Prozac fluoxetine, an SSRI, is marketed by **Eli Lilly and Co.** to treat depression.

"Other HDAC inhibitor combination therapies are also conceivable in the longer term. For example, administering an HDAC inhibitor together with electroconvulsive therapy or, in the case of severe depression, with deep brain stimulation could be a way of boosting the efficacy of those treatments," said Akbarian.

The paper's findings are not patented or available for licensing, according to Nestler.

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COMPANIES AND INSTITUTIONS MENTIONED

Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.
EnVivo Pharmaceuticals Inc., Watertown, Mass.
Merck & Co. Inc. (NYSE:MRK), Whitehouse Station, N.J.
MethylGene Inc. (TSX:MYG), Montreal, Quebec, Canada
Mount Sinai School of Medicine, New York, N.Y.
The Scripps Research Institute, La Jolla, Calif.
Syndax Pharmaceuticals Inc., Waltham, Mass.
TopoTarget A/S (CSE:TOPO), Copenhagen, Denmark
University of Massachusetts Medical School, Worcester, Mass.