UNLOCKING THE DOOR TO EPIGENETIC MEDICINE

HIGHLY SPECIFIC HMT-PROFILING PANELS have opened access to a class of drug discovery candidates most believed out of reach.

In January, the US Food and Drug Administration (FDA) signaled a milestone in epigenetic medicine with its approval of tazemetostat. The drug targets a class of epigenetic regulators known as histone methyltransferases, or HMTs. While this class has long held therapeutic potential, it was considered undruggable, by many, based on the past challenges in identifying potent, selective inhibitors.

Tazemetostat is evidence to the contrary. With advances in HMT identification and characterization, researchers are now using large HMT panels and new assays to develop HMT inhibitors as drug candidates. Matthew Hall, the acting chief of the National Center for Advancing Translational Science (NCATS) in the National Institutes of Health, says large panels and assays are "providing the confidence we need to explore opportunities along this promising pathway".

Haiching Ma, chief science officer at Reaction Biology, a Pennsylvania-based life sciences supplier that provides integrated drug discovery services, including assay services and protein production, says, "HMT selectivity profiling panels are crucial for showing that a given candidate hits only its intended target."

More precise precision medicine

The first approved epigenetic drugs are still relatively young and fairly blunt instruments. The histone deacetylase (HDAC) inhibitor vorinostat, for example, was approved to treat cutaneous T cell lymphoma in 2006, but like other epigenetic drugs, it hits more than one target.

In contrast, tazemetostat inhibits a single target called enhancer of zeste homologue 2 (EZH2). The normal role of EZH2 in the cell is to methylate lysine 27 on histone 3, and promote chromatic compaction and gene silencing. When EZH2 is aberrantly over-expressed, it can hasten the growth of cancer cells[1].

Given the diversity of methylation sites[2], identifying compounds that modulate a single target can be challenging. Ma's company, Reaction Biology, has developed a number of analytical tools to screen for hits, and assess potency, specificity, and binding kinetics. HMT profiling, for instance, involves screening compounds for selectivity against a suite of targets. HMT drug candidates can also be subjected to off-target profiling to ensure they don't inhibit other target classes, such as kinases, G-coupled protein receptors or proteases. During apoptosis profiling, HMT inhibitors are screened against cell lines for cancer subtype-specific therapeutic effects.

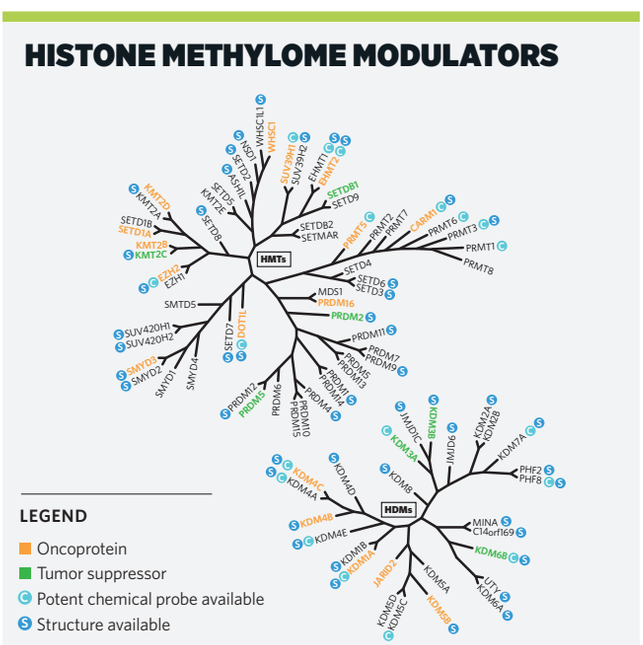
Reaction Biology has also developed biochemical and biophysical platforms that help elucidate a drug candidate's mechanism of action. The The HotSpot™ platform, a miniaturized radioisotope filter binding assay, can be used to evaluate inhibition activity and enzyme kinetics. Surface plasmon resonance (SPR) can be used to assess the kinetics of drug/target binding.

"Two compounds may bind to the same target with similar binding potency, but the rates of target engagement and occupancy may be different. SPR can be used to differentiate those on-and off-rates" Ma says. "Compounds with slow off rates perform better in-vivo. SPR can also tell you whether a compound is competitive with a cofactor or substrate, or if it is cofactor dependent, like for PRMT5—another important HMT cancer target."

Blue(r) sky for HMTs

Though still far from having a substantial clinical impact, epigenetic medicine is showing promise. Hall, from NCATS, points out that tazemetostat is now also useful as a validated probe for studying EZH2 biology in other disease settings.

Meanwhile, other HMTs are entering clinical trials, including multiple PRMT5 inhibitors for solid tumors and non-Hodgkin's lymphoma and DOT1L inhibitors for acute myeloid leukemia. The clinical trials and the recent success of tazemetostat show "the time is right for developing drugs against this tough class of targets," Ma says. "All you need is to find a selective inhibitor to start with." ■



▲ Histone methyltransferases (HMTs) and histone demethylases (HDMs) are enzymes that aid in the transfer of methyl groups (—CH3) to or from specific sites on histones. Phylogenetic trees show the relationships between genes predicted to encode HMTs and HDMs.

REFERENCES:

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