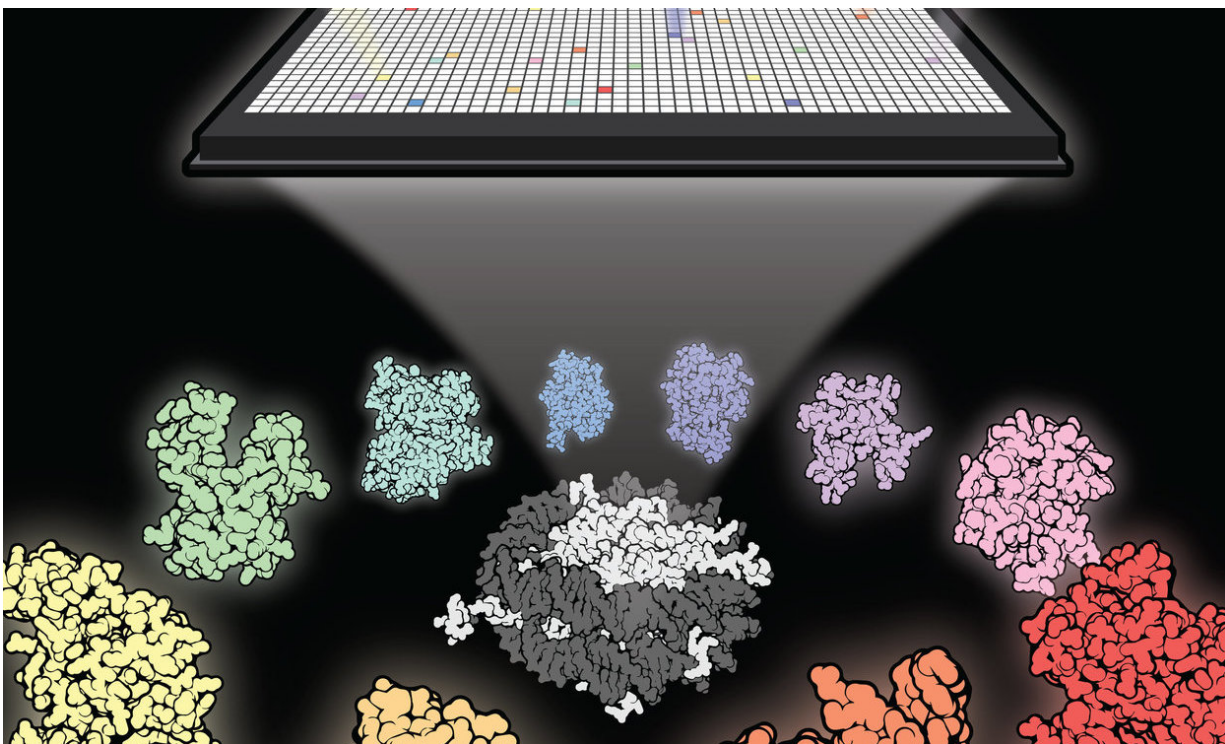


Scanning thousands of molecules against an elusive cancer target

September 6 2018



A new study developed a set of methods to screen thousands of small molecules to find inhibitors of the cancer target NSD2. Credit: Matthew Hall, NCATS

Researchers at the National Center for Advancing Translational Sciences (NCATS), part of the National Institutes of Health, have developed a system to accelerate the discovery of chemical compounds that inhibit an enzyme implicated in a number of cancers. The set of tools and methods,

which the researchers used to test more than 16,000 compounds, is described in a new paper published in the *Journal of Biological Chemistry*.

The enzyme, NSD2, is overactive in cancers such as [acute lymphoblastic leukemia](#) and certain types of multiple myeloma, so inhibiting NSD2 activity seems like a promising strategy for treating those conditions. But, so far, researchers have not been able to find any chemicals that reliably block NSD2 even in a test tube in the laboratory, much less to test as drug candidates in living models.

"There's a total lack of available [chemical](#) probes, druglike molecules, to help study (NSD2) function," said Matthew Hall, the NCATS scientist who oversaw the new work.

Part of the reason it's been difficult to discover [chemical inhibitors](#) of NSD2 is that the enzyme is difficult to work with in the laboratory. NSD2 modifies histones, the proteins around which DNA is wound. For technical reasons, scientists ordinarily would study this kind of activity using a fragment of the enzyme and a fragment of histone protein. But NSD2 works on only whole nucleosomes: units of histone protein in combination with DNA.

"(NSD2 and similar proteins) are very picky, because they prefer to only act on whole nucleosomes," Hall said. "They're snobby when it comes to what they're willing to interact with."

Collaborating with the biotechnology company Reaction Biology, Hall's team, including lead author Nathan Coussens, developed laboratory tests involving whole nucleosomes that could be used to see whether NSD2 was able to modify [histone proteins](#) in the presence of various compounds. The [compounds](#) the team tested came from NCATS's massive library of bioactive chemicals.

But finding a compound that appears to block NSD2 activity is only the beginning. To confirm that the chemicals identified in the initial massive screen were indeed bona fide inhibitors that would reliably and reproducibly perform this function in future researchers' studies, the NCATS team needed to use multiple types of biochemical methods to confirm the activity of each compound.

"We screened 16,000 molecules, and we got 174 hits, but that doesn't mean they all really work," Hall said. "When we whittle away through the (additional screening methods), we get down to 44 molecules. You triage candidates out of your screen after you rigorously ask your molecule to prove itself to you."

With several molecules now having proved themselves in this round of screening, Hall's team hopes to continue the search for reliable NSD2 inhibitors that can be used as research tools and then, further down the road, possibly as medicines.

"We are in the process of planning to screen hundreds of thousands of molecules in order to find [molecules](#) that can be optimized for inhibition of NSD2 and disseminate these to the research community," Hall said.

More information: Nathan P. Coussens et al, High-throughput screening with nucleosome substrate identifies small-molecule inhibitors of the human histone lysine methyltransferase NSD2, *Journal of Biological Chemistry* (2018). [DOI: 10.1074/jbc.RA118.004274](https://doi.org/10.1074/jbc.RA118.004274)

Provided by American Society for Biochemistry and Molecular Biology

Citation: Scanning thousands of molecules against an elusive cancer target (2018, September 6) retrieved 10 April 2024 from

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