Drug discovery process more accurate, less expensive using novel mass spectrometry application

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Cancer and cell biology experts at the University of Cincinnati (UC) have developed a new mass spectrometry-based tool they say provides more precise, cost-effective data collection for drug discovery efforts.

Preliminary studies have shown that the new mass spectrometry tool—known as MALDI-QqQMS (matrix-assisted laser desorption ionization-triple quadruple mass spectrometer)—provides a superior means of measuring the enzyme reactions critical to drug discovery at speeds comparable to currently available high-throughput screening systems at significantly lower costs.

"If introduced broadly, the new generation mass spectrometry-based method we are proposing could significantly reduce the cost of running drug compound screening assays while also saving drug development teams substantial time by improving the accuracy of data collected," explains Ken Greis, PhD, associate professor and director of proteomics for the UC College of Medicine's cancer and cell biology department.

Greis and his colleague Rakesh Rathore, PhD, report their findings online ahead of print Sept. 17, 2009, in the scientific journal *Rapid Communications in Mass Spectrometry*.

In the drug discovery field, scientists use what is known as a "high-throughput screening system" to rapidly run thousands to millions of

tests to screen for inhibitors of molecular targets that could be useful in pharmaceutical drug development and in furthering of understanding of the overall biological mechanisms behind a particular disease.

Typical assays for enzyme screening are fluorescence and chemiluminescence-based systems. To make those assays universal, vendors have developed standard kits using specialized—and costly—reagents to identify changes in the fluorescent or chemiluminescent signals.

"There are a couple of problems with the current approach: For starters, it's an imperfect method that generates many false-positive "hits" and for due diligence, you have to follow up on all inhibitors identified, which results in a lot of time and money wasted on false leads," says Greis.

"Reagents are very costly often ranging between 50 cents to $1 per sample. That adds up very quickly when you're screening against a million-compound library," adds Rathore, a postdoctoral fellow in Greis' laboratory.

Greis and Rathore have developed a custom high-throughput screening method using a generalized platform. Unlike the commercially available systems that analyze byproducts and coupled reactions, their system directly measures and quantifies the substrate and the end product of the reaction.

They say using mass spectrometry to measure the mass and quantity of the product gives researchers a direct measure of the assay and more reliable compounds to explore, eliminating the chances for molecular interference common with chemiluminescence and fluorescence-based systems.

"Analytically, our mass spectrometry-based application provides

superior data and also eliminates the issue of producing high numbers of false results, saving a tremendous amount of time chasing down bad leads on drug targets. And because we are using these non-tagged reagents, it only costs us 3 to 5 cents per sample to run these assays, which is a huge cost savings," adds Greis. "That can mean the difference between $50,000 and $1 million in reagent costs for a single screening project."

The approach developed by the UC group also holds appeal in that it has multiplexing capabilities—making it possible to, measure inhibitors for two or more enzymes with one pass through the compound repository. Typical assays start with one target enzyme and that is tested against an entire compound repository to look for inhibitors. Once inhibitors are identified, researchers must then follow up on each one to see if it has any validity as a drug target.

"Now instead of doing a million-dollar campaign that takes a month to run and then another million-dollar campaign that takes another month to run, we can do both at the same time while still avoiding the false-positives and false-negatives common with currently available methods," says Greis. "This is one of those disruptive technologies that could completely change the way people do this type of screening work."

Source: University of Cincinnati (news : web)