Repositioning Idle Drugs via Systematic Serendipity

Systems-based Approaches for Boosting Stalled Drugs

Gail Dutton

When it comes to drug repurposing, companies may be searching for a systematic approach to serendipity. The emphasis, however, still seems to be on the serendipity part of the equation.

In this regard, companies are turning back the clock, eschewing targeted drug discovery for the more systems-oriented approaches that were used decades ago. The feeling on this side of the industry seems to be that the human system is so complex that targeted approaches invariably miss things.

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“As an industry, our work is only as good as the knowledge base we work from, and the knowledge base is incomplete,” notes Andrew G. Reaume, Ph.D., president, CEO, and cofounder of Melior Discovery (www.meliordiscovery.com). Or, as another executive says, “you can’t find what you’re not looking for.” Those unexpected features oftentimes make the difference between a new blockbuster drug and a failed compound.

“These drugs are assets to which a lot of time and money have already been invested, but they are sitting idle now,” elaborates Scott Turner, Ph.D., vp of research for KineMed (www.kinemed.com). “Typically, they have been advanced to a stage in preclinical or clinical work that shows they are bioavailable and have cleared the basic requirements for drugs in terms of chemistry and safety. But, they failed for the indications for which they were developed.” The quest, then, is to find what these compounds do effectively.

Shotgun Approach

A shotgun approach would be an apt description of Melior’s repurposing strategy. Dr. Reaume calls it a “blue sky approach that cuts to the end result.” Whatever you call it, this method doesn’t rely on knowing targets’ linkages, pathways, or even the method of action.

Instead, Melior has developed a multiplexing platform of 40 different animal models through which druggable compounds are taken indiscriminately, without compromising the quality of the models. To do that, Dr. Reaume explains, “you need to know something about all the permutations of assays used with the model, and you need a way to ensure they don’t interfere with one another.”

The basic process was used in the 1970s, but not multiplexed, Dr. Reaume says. The approach, he adds, “is very effective. In 18 months we’ve developed a robust pipeline. Of the first nine discontinued drugs we researched, we found three therapeutic candidates.”

One, originally a lead for diabetes, was pursued through Phase III trials in the late 1970s and developed in the 1980s for gastric ulcers, but showed a lack of efficacy when compared to the new H1 antagonists that were entering the market. “We ran it through the TheraTrace platform,” Dr. Reaume says, “where it showed effectiveness in treating metabolic disorders.”

“People are surprised by the high success rates,” Dr. Reaume continues. Melior achieves them by carefully selecting the type of compounds investigated. “Biology is more complex than people predict,” he says, affecting many receptors outside the scope of the original studies. “We don’t try to predict the full biology. We just go test it.”

“There’s a huge cost benefit,” Dr. Reaume emphasizes. “One-third of the
compounds we tested became therapeutic targets meriting further investigation, at a cost of less than $2 million."

**Stalled Compounds**

KineMed's approach looks at stalled compounds, searching out new indications. Thus, the complexity of late-stage failures offers an opportunity to uncover novel activities by identifying both on-target and off-target effects. "The idea is to get early proof of concept in man," Dr. Turner says.

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