Rethinking mechanisms of drug discovery

By Tim Fulmer, Senior Writer

A Roche team has concluded that overreliance on simplistic, target-centered screens early in drug development may inadvertently select for compounds destined to fail in late-stage trials.¹ The resulting high attrition rates and low R&D productivity could be reversed, the researchers believe, by refocusing discovery strategies on phenotypic screens that account for complex mechanisms of action and cell signaling pathways.

“Late-stage drug failures involving, for example, poor bioavailability or off-target toxicity may ultimately derive from a preclinical optimization process that considered the target in an overly simplified setting—as typified, for example, by the classic *in vitro* binding assay, which doesn’t enable optimization of the therapeutic index,” corresponding author David Swinney told SciBX.

He suggests that, if they have not already done so, drug developers need to retool their preclinical programs to identify therapeutic candidates that have more subtle modes of action at their targets than simply high-affinity binding.

Swinney is cofounder, president and CEO of the not-for-profit **Institute for Rare and Neglected Diseases Drug Discovery** (iRND3). He previously was director of virology and biochemical pharmacology at Roche’s unit in Palo Alto, Calif., before it closed in 2010 and consolidated with Roche R&D in Nutley, N.J.

R&D managers contacted by SciBX said they have come to similar conclusions and are altering their early stage discovery programs to better reflect the complexity of a given target’s biological context. Some biotechs, however, are tackling the issue by adopting

Box 1. Booting up the computers.

Whereas David Swinney’s paper in *Nature Reviews Drug Discovery* suggests ways to develop and use complex assays that efficiently identify a target and decrease late-stage attrition,¹ some biotechs think a better approach to increasing R&D productivity would rely on computational methods to identify entire networks of interacting proteins that drive disease.

“A key reason for late-stage failure may well be the focus of many developers on single therapeutic targets as the key drivers of disease. That approach ignores a fundamental fact of biology: most diseases are driven by a highly complex network of interacting pathways that can, in effect, compensate for the effects at any one target. Therefore it is unlikely that focusing on a single target within that network will give the strongest or safest therapeutic effect,” said Malcolm Young, CEO of **e-Therapeutics Ltd.**

To deal with that problem, Young and colleagues at e-Therapeutics are taking a network pharmacology approach, “which uses computational methods in combination with *in vitro* and *in vivo* assays to generate a so-called molecular footprint of the ideal therapeutic for a given disease,” said Young.⁵

In cancer, for example, “we first of all use a computational step to identify proteins that could be targeted to induce apoptosis in tumor cells. That is, from the outset we are focused not on a single target but on multiple targets or nodes that occur in a network of proapoptotic pathways. An analysis of that network then yields a molecular footprint or signature, revealing which node or nodes would be the most effective to hit to get a therapeutic effect. We then use that signature to help us identify and/or design compounds that hit all or most of those nodes simultaneously,” said Young.

The company’s lead compound, ETS2101, resulted from that process. The small molecule is in preclinical testing to treat metastatic cancer. ETS2101’s mechanism is undisclosed.

“Of course, we used phenotypic and target-based screens as part of our identification of ETS2101, but we did so only in tandem with a rigorous computational approach that gave us insight into the network complexity underlying cancer,” said Young.

While e-Therapeutics uses computational techniques to tackle the biological complexity of targets, **BioLeap Inc.** uses the computer to

deal with the complexity associated with target-ligand binding.

“In our opinion, a key reason for failure in late-stage trials is that the binding mechanism of ligands to the target has been poorly worked out at the preclinical stage,” said CEO David Pompliano. “There’s often too much of a rush to identify a compound that simply binds with high affinity to the target, without accounting for subtle binding interactions that determine the residence time of a compound at its target and, ultimately, affect key clinical parameters” such as pharmacokinetics and pharmacodynamics.

To help work out those subtle binding interactions, BioLeap uses computational methods to generate small molecular weight fragments *in silico* that are ranked according to their ability to bind and modulate the X-ray crystal structure of a target. The best candidates are then synthesized by design chemists and further tested in phenotypic and target-based assays.

BioLeap is pursuing a variety of preclinical targets to treat multiple diseases, including cancer, infectious diseases and metabolic diseases.

—TF

in silico–driven approaches to R&D (see **Box 1**, “**Booting up the computers**”).

“We recognize that one driver of late-stage pipeline attrition may be the use of oversimplified binding assays that poorly reflect the target’s therapeutic mechanism of action *in vivo*. One way we can perhaps deal with that problem more efficiently is by using a series of assays that accurately represents the disease phenotype,” said Miguel Barbosa, VP and head of immunology research at the Centocor R&D unit of **Johnson & Johnson**.

Focusing on the MMOA

For more than a decade at Roche and now at iRND3, Swinney has focused on the contribution that molecular mechanism of action (MMOA) makes to a drug’s therapeutic index.²

MMOA encompasses more than simply the tight binding affinity medicinal chemists look for in an *in vitro* equilibrium assay. Other components of MMOA include non-equilibrium mechanisms, such as irreversible binding and conformational changes, which often play an important role in target-drug interactions *in vivo*.

“We were struck by how, on the one hand, the full MMOA determines the way a drug modulates its target and generates the effect that maximizes the therapeutic index, and yet, on the other hand, the details of the MMOA often don’t become a research focus until relatively late in drug development, when problems crop up, for example, with bioavailability or toxicity,” noted Swinney.

He thus hypothesized that if the MMOA were elucidated much earlier—at the preclinical stage using complex phenotypic assays in combination with target-based approaches—it might be possible to lower late-stage attrition rates and increase R&D productivity.

In vivo phenotypic assays are typically cell, tissue or animal based and are designed to reflect the activity of the therapeutic target in its biological setting. In contrast, *in vitro* target-based assays generally focus on a purified target that is isolated from its biological context and therefore easier to chemically characterize.

To find support for his hypothesis, Swinney enlisted Roche colleague and coauthor Jason Anthony to help him analyze the discovery strategies and MMOAs of all small molecules and biologics approved by the **FDA** between 1999 and 2008. They reasoned that a trend in those data might provide some evidence that early use of complex phenotypic assays improves the chances of success later in clinical trials.

Over that 10-year period, a total of 259 agents were approved by the FDA, of which 72 were first-in-class drugs with new MMOAs. Of those 72 drugs, 50 (69%) were small molecules and 22 (31%) were biologics.

Swinney and colleagues focused on the small molecules and reported that phenotypic screening contributed to more approvals than target-based screening (28 vs. 17). Phenotypic approaches were more common in CNS disorders and infectious diseases, and target-based

approaches were more common in cancer and metabolic diseases.

“We’re not saying that phenotypic assays should be used to the exclusion of target-centered approaches, but we are suggesting that phenotypic assays should perhaps play a bigger role in drug discovery than they have recently in the target-focused genomics era,” Swinney told *SciBX*.

He added: “The basic idea is to bridge the reductive approach of the medicinal chemist with the systems approach of the pharmacologist and biologist. In practice, that might mean using a series of phenotypic assays—in cell and tissue culture, for example—to elucidate the MMOA and then *in vitro* target-centered assays to further optimize therapeutic candidates.”

The work was published in *Nature Reviews Drug Discovery*.

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—David Swinney,
*Institute for Rare and Neglected
Diseases Drug Discovery*

Adding in biomarkers

Paul Workman, deputy chief executive and professor of pharmacology and therapeutics at **The Institute of Cancer Research**, agreed with Swinney that both biochemical and cell-based phenotypic assays are needed to elucidate a compound’s mechanism of action. “However, I think it’s equally important to identify molecular biomarkers of activity as soon as possible, especially for first-in-class compounds that have novel mechanisms,” he said.

Workman views the preclinical drug development process as a “pharmacological audit trail,” which uses a series of biomarker-driven assays and animal models to assess the efficacy and safety of candidates as they move from discovery into the clinic.^{3,4}

“At the preclinical stage the idea is to have a panel of molecular biomarkers associated with the assays, and those markers will ultimately help guide selection of patients and trial endpoints if the compound shows promise for the clinic,” said Workman. “By keeping a close molecular audit on a therapeutic candidate, we should improve our chances of detecting problems earlier in drug development and reduce the likelihood of late-stage attrition.”

At least one pharma is applying similar ideas in its preclinical programs. “At J&J Immunology, our strategy is to design an assay cascade that combines phenotypic and *in vitro* screens with the goal of measuring readouts and biomarkers that accurately reflect the disease phenotype we see in patients,” Barbosa said.

“By referencing the patient at the outset, we avoid two problems that increase the potential of late-stage attrition: individual assays that poorly reflect human pathology and assay series that are badly correlated and run the risk of optimizing the wrong molecular properties. Both of those problems can lead to bad trial design and late-stage failure,” Barbosa added.

According to William Hait, a combination of phenotypic and target-based screens can help direct clinical development to those patients harboring the molecular abnormalities originally identified in a particular malignancy.

Hait is global therapeutic head of oncology at the Ortho Biotech Oncology R&D unit of J&J.

Applying the findings

With the founding of iRND3 this year, Swinney and medicinal chemist and iRND3 CSO and cofounder Marc Labelle hope to be able to put their ideas about MMOA to the test.

The first goal of the not-for-profit will be to focus on infectious diseases including malaria and Chagas disease. “In this case, the best candidates will likely be molecules that have slow on and off rates at their targets—in other words, compounds that bind their target strongly and stay there, perhaps even binding irreversibly. That particular MMOA is ideal for infectious disease since it allows you to achieve inhibitory potency at the parasite target without requiring high blood levels of the compound that could be toxic to the host,” said Swinney.

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