Binding time—not just affinity—gains stature in drug design

In the early twentieth century, German scientist Paul Ehrlich coined a phrase that has since served as a framework on which pharmaceutical companies develop drugs: *corpora non agunt nisi fixata*—a substance will not work unless it is bound to its target. As such, drug developers have selected the drugs that bind most tightly to their targets in preclinical studies to use in early-stage clinical trials. Paradoxically, many of the drug candidates brought into the clinic fail to have much of an effect in patients. Scientists started looking at binding time more closely in the late 1990s and early 2000s. In 2006, chemist Robert Copeland put forth the term ‘drug-target residence time’ to explain why drugs lack efficacy in humans. He argued that it’s not only how tightly a drug binds to its target that matters, but rather, how long the drug stays bound to its target. (*Nat. Rev. Drug Discov.* 5, 730–739, 2006).

Ever since Copeland detailed the residence time idea almost a decade ago, scientists have attempted to use the concept of binding time to predict *in vivo* efficacy. Although these previous attempts yielded insights, Copeland says that a new paper offers an improved model for the residence time concept. “What’s new and really important about [this study] is that [the researchers] have developed an elegant, mathematical model for incorporating residence time and kinetic variables into a single equation,” Copeland says. “There have been cruder models before, but this is a really elegant model.” The study, completed by researchers at Stony Brook University in Stony Brook, New York, and AstraZeneca in Waltham, Massachusetts, offers a mathematical model to predict the clinical efficacy of a compound on the basis of its residence time. In accordance with Copeland’s proposal, the new findings provide evidence that the most accurate predictions of drug efficacy must take into account not just how tightly a drug binds to its target but also how long it binds to it (*Nat. Chem. Biol.*, 11, 416–423, 2015).

“Most compounds fail in clinical trials,” says Peter Tonge, a chemist at Stony Brook University and an author of the new study. “We became very interested in understanding why we’re so unsuccessful as a community in designing drugs, and this led us to think about some of the basic concepts of how drugs work. We were brought back to our interest in studying how binding time affects target inhibition and realized most people ignore time-dependence when

Marking time: How long a drug stays bound to its target matters for efficacy.

thinking about selecting and identifying the best compound to move forward with in drug discovery.”

“In industry, everyone is used to working in a certain mode,” says Michael Mesleh, a chemist at the Broad Institute in Cambridge, Massachusetts, who has worked in drug development for over a decade and was not involved in the current paper. “People could read papers and think, ‘residence time probably matters,’ but people don’t often stop and take a step back and ask, ‘why am I just calculating the binding affinity? Is this the best way to find a drug candidate?’”

Time for a change

Tonge and his colleagues first screened six candidate antibacterial compounds for activity against *Pseudomonas aeruginosa*, a bacterium responsible for infections in people who are hospitalized or who have weakened immune systems. The colonies of bacteria were incubated with one of six candidate drugs for 24 hours before any excess, unbound drug was washed away. Only drugs that remained bound to LpxC, a known antibiotic target involved in the synthesis of bacterial cell walls, were able to kill the bacteria. Drugs with a longer residence time were more efficient in clearing *P. aeruginosa* infections in mice.

Prior to this study, researchers would

often first find that a drug was efficacious in patients, but they couldn’t explain why until long after the drug was approved. For example, Maraviroc, first approved in 2007 by the US Food and Drug Administration, based in Silver Spring, Maryland, is a drug that blocks HIV entry into cells by binding to CCR5, a viral surface protein. Maraviroc must stay bound to CCR5 in order to sequester the virus from infecting human cells. It took researchers seven years after its approval to learn that residence time is critical to Maraviroc’s clinical success (*Br. J. Pharmacol.* 171, 3364–3375, 2014).

The new model offered by Tonge and his collaborators may allow pharmaceutical companies to test for binding affinity and residence time so that they can design better drugs. Although the researchers focused their study on an antibacterial compound, their approach and model is applicable to other disease areas, such as cancer or inflammatory disease, and to other drug classes.

Although the mathematical model proposed cannot predict off-target effects, it may better inform drug developers about which compounds to bring into clinical trials by considering binding time. “One of the biggest problems in the preclinical stages of drug discovery is that you often have to pick one compound from eight or ten possible ones,” Mesleh says. “Inevitably, you don’t find there’s something wrong with the drug you pick until you’re putting it in animal models. By then, you’ve spent about a year working on one drug.”

It could also help prevent the development of drugs with nasty side effects, explains Stewart Fisher, a chemist at AstraZeneca and a coauthor of the study. “If prolonged residence time causes toxicity, long residence time can be a problem,” he says. “Whether you want a longer or shorter residence time, this model can help predict that.”

“Why was residence time ignored? Probably because it is a pain to measure, and therefore a pain to optimize. If you can’t measure it, you can’t select for it,” says Ann Kwong, founder and CEO of InnovaTID, a consulting group for pharmaceutical companies based in Cambridge, Massachusetts. She echoes the sentiment of the study authors that binding time is only part of the picture, though: “Although affinity is very important, focusing on it to the exclusion of residence time is missing one of the legs of the stool.”

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