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Mechanism matters

The path of drug development is fraught with hurdles. Gaining a clear understanding of how a drug works before it enters clinical trials is the intelligent route to drug discovery and could increase the likelihood for drug success.

Drug development is a risky business. According to the US Food and Drug Administration (FDA), only eight percent of drugs that enter clinical trials are eventually approved. For a drug to gain FDA approval, it must be safe and show some efficacy. Because the FDA does not require any understanding of the mechanism by which a drug acts, it could be tempting to move into clinical trials without this knowledge. However, this may set the stage for failure. An investigational Alzheimer's disease drug called Dimebon is a case in point.

A phase 2 trial of Dimebon reported significant improvements in cognition in individuals with Alzheimer's disease (*The Lancet* **372**, 207–215, 2008), sparking much excitement in the Alzheimer's community. However, on 3 March, Pfizer and Medivation, the companies developing the drug, announced that Dimebon did not affect cognition in a much larger follow-up phase 3 study. The lack of a clear understanding of how the drug worked may have contributed to this unfortunate outcome.

Dimebon has been sold over the counter in Russia since 1983 as an antihistamine. A 2001 paper showed that the drug enhanced cognition in a rat model of Alzheimer's disease and, importantly, in 14 individuals with this disease. The authors attributed a potpourri of mechanistic effects to the drug—blocking calcium currents in intestinal cells, inhibiting acetylcholinesterase and acting as a glutamate receptor blocker (*Ann. NY Acad. Sci.* **939**, 425–435). In 2003, another paper from some of the same authors showed yet another effect of Dimebon—blocking mitochondrial dysfunction triggered by a fragment of amyloid-beta, the neurotoxic molecule that builds up in the brain during Alzheimer's disease (*Ann. NY Acad. Sci.* **993**, 334–344).

Dimebon went into clinical trials largely on the basis of these two studies. But how it exerted all of its effects remained mysterious, and it was unclear which of the several potential mechanisms were responsible for Dimebon's therapeutic effects in the patients in the phase 2 trial. The recent failure of Dimebon in the phase 3 trial highlights the importance of understanding a drug's mechanism before moving forward into clinical trials, as more recent data have indicated that Dimebon actually increases amyloid-beta levels in a mouse model of Alzheimer's disease (*Mol. Neurodegener.* **4**, 51, 2009).

It is true that we use many highly prescribed drugs without a clear idea of how they work—which targets they hit, what processes they alter and which of these actions are required for therapeutic efficacy. For instance, lithium, used to treat bipolar disorder, modulates many molecular targets, but which—or how many—of these are required for its beneficial effects is uncertain. Nevertheless, understanding a drug's mechanism could guide drug development and help to prevent late-stage failures such as Dimebon's.

Knowledge of a drug's mechanism of action enables better dosing through monitoring of the drug's effects on the target pathway in the patient. For example, the proper statin dosage for a given patient is often determined on the basis of the observed reduction in blood cholesterol levels. For Dimebon, without a clear understanding of its molecular targets, it isn't feasible to develop these types of approaches.

Learning how a drug works can help stratify clinical trials to focus them on those patients most likely to respond. For instance, given that ErbB2 is the known target for the breast cancer drug herceptin, tumors can be screened for its presence to identify whether a woman has an increased chance to benefit from the drug. The development of such screens to determine which drugs are more likely to benefit a patient is being pushed by the FDA's Critical Path Initiative as a way to improve the chances for drug approval.

Even when a drug's mechanism is understood, it is often difficult to predict its side effects. For example, the drug Tysabri ameliorates multiple sclerosis through a well-documented mechanism resulting in reduced immune cell entry in the brain. However, scientists had not predicted that this could lead to progressive multifocal leukoencephalopathy, a brain infection that was reported in a few patients. Nevertheless, knowing how a medicine works may allow doctors to monitor for potential side effects in a more pointed fashion and thereby prevent unintentional harm to patients.

Mechanistic studies take time, and delays to the drug development process are not greeted with enthusiasm by doctors or patients. Nevertheless, in the long run, mechanistic knowledge is certainly worthwhile before entering the uncertain world of clinical trials—this knowledge can increase the chances for drug approval, saving money, time and, most importantly, the lives of patients.