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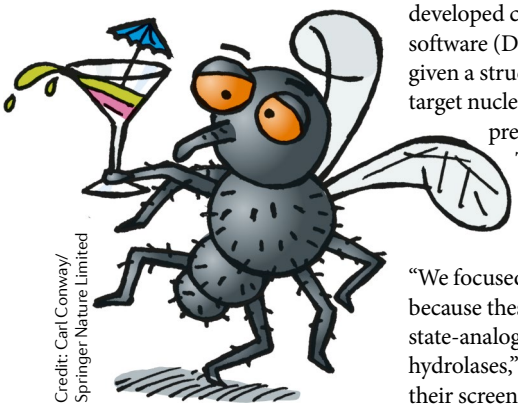
DRUG DISCOVERY

Inhibiting the inhibitor

> “This synergistic approach allows us to extend the useful lifetime of these pesticides and to reduce the amount that needs to be applied”

Food and health security are two of our main global challenges. Among several approaches towards these fundamental needs is the development of pesticides and insecticides that can annihilate disease vectors. However, most pests and disease vectors have developed resistance mechanisms that make them immune even to potent pesticides and insecticides. Writing in *Proceedings of the National Academy of Sciences of the United States of America*, Colin J. Jackson, Nir London and co-workers propose a new paradigm, in which an organophosphate insecticide is coupled with a computationally designed inhibitor of resistance-mediating carboxylesterases.

Many of the most common insecticides are based on organophosphates or carbamates. They inhibit acetylcholinesterase (AChE), an enzyme involved in nerve signal transduction, by phosphorylating or carbamoylating the nucleophilic serine residue at its active site. Some insects have developed resistance to both classes of insecticides either by overexpressing carboxylesterases — enzymes able to sequester the insecticide — or by developing a mutation in a gene encoding carboxylesterase that confers on the enzyme hydrolytic activity towards the pesticide, such that the latter cannot target AChE.



Credit: Carl Conway/ Springer Nature Limited

Both types of resistance have been thoroughly investigated for the sheep blowfly *Lucilia cuprina*. “I have been working on the problem of insecticide resistance with collaborators at the Commonwealth Scientific Research Organization (led by Dr John Oakeshott) for many years. They had identified the αE7 carboxylesterase to be the key enzyme involved, and we had determined the structures of both the wild-type and mutant enzymes that confer resistance. We thought it would be interesting to see if we could make selective inhibitors for it, to knock out the resistance,” explains Jackson. London and co-workers developed covalent virtual screening software (DOCKovalent) that, given a structure of a protein and a target nucleophile, can screen and predict covalent inhibitors. The team screened 2,300 boronic acids against the active site of the carboxylesterase. “We focused on boronic acids because these are known transition-state-analogues for serine hydrolases,” says London. After their screening, the team had a shortlist of only five compounds for experimental validation.

While all five candidates worked, they were further optimized to target both the wild-type enzyme and the common resistance mutation. The in vivo efficacy of common insecticides improves 12–16-fold when combined with the boronic acids selected. Moreover, the combinations were also effective against peach-potato aphid *(Myzus persicae*, another widely spread pest) and exhibited almost no toxicity in human cells and mice.

“Currently, we tend to move on from pesticides or increase the amount that we use once resistance has developed. We are constantly searching for new classes of pesticides but it’s debatable how long this approach can continue for. This synergistic approach allows us to extend the useful lifetime of these pesticides and to reduce the amount that needs to be applied,” says Jackson. “To our knowledge, this is the first example of a synergist that effectively potentiates common insecticides through this mechanism of action. Furthermore, this study is one of the rare examples in which cutting edge, structure-based drug discovery tools are being applied to the agrochemical arena. We hope it inspires better incorporation of methodologies from drug discovery into this important field that impacts global problems such as food safety and disease vector control,” concludes London.

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