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In This Issue

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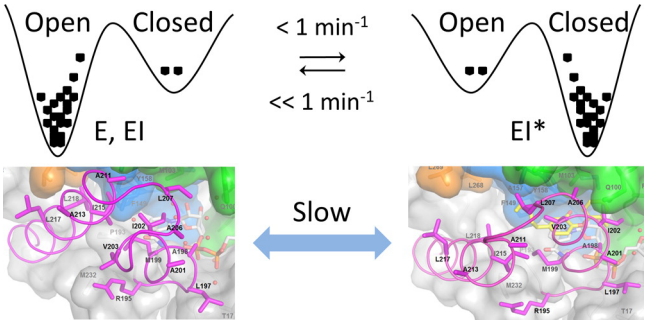
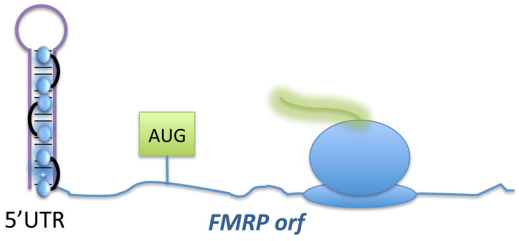
SLOWING INHIBITION DOWN, ON PURPOSE



Slow-onset enzyme inhibitors are inhibitors that tend to hang out on their target enzyme for a while before dissociating, at least relative to the rate of the catalytic reaction. This property endows them with certain favorable pharmacodynamic properties from a drug discovery standpoint. However, the molecular basis of slow-onset inhibition is not well understood, making the rational design of such compounds a challenging endeavor. Tackling this challenge, Li *et al.* (DOI: 10.1021/cb400896g) explore the slow-onset inhibition of InhA, an enoyl-acyl carrier protein reductase from the bacterial pathogen *Mycobaterium tuberculosis*.

The authors use X-ray crystallography and molecular dynamics simulations to examine how inhibitor binding affects the structure and energetics of the substrate-binding loop in InhA. They find that, unlike substrate binding, inhibitor binding promotes the refolding of a helix in the substrate-binding loop from an open to a closed conformation, which results in the slow-onset kinetics of the interaction. These findings offer insight into the molecular basis for slow-onset inhibitors and lay the groundwork for the rational design of improved inhibitors.

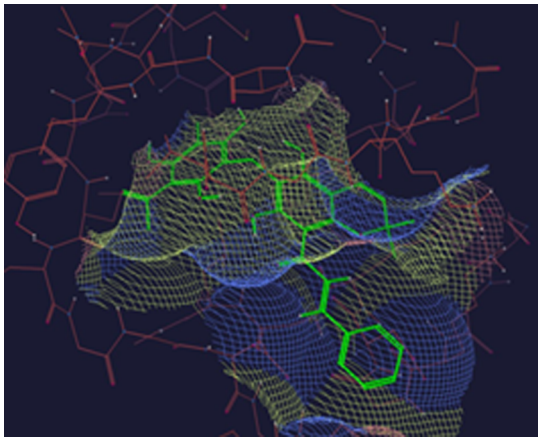
A FRAGILE TARGET



Dysregulated RNAs are associated with various diseases, such as the neuromuscular disorder fragile X-associated tremor ataxia syndrome (FXTAS). FXTAS is caused by the presence of expanded r(CGG) repeats ($r(CGG)^{exp}$) in an untranslated region of mRNA, which prevents proper posttranscriptional processing. Targeting $r(CGG)^{exp}$ is a potential therapeutic strategy for FXTAS, and though there are obvious advantages to using oligonucleotides to target RNA, their pharmacological properties typically preclude their development as drugs. Tran *et al.* (DOI: 10.1021/cb400875u) now explore the potential of strategically designed, modularly assembled small molecules as therapeutic agents for this devastating condition.

Previously identified r(CGG)-binding small molecules were incorporated into a peptoid backbone to yield $r(CGG)^{exp}$-binding oligomeric compounds that varied in the distance between RNA-binding modules. When tested in cellular models of FXTAS, the compounds reduced $r(CGG)^{exp}$ toxicity. In addition, in contrast to oligoneculeotide-based inhibitors, they did not inhibit downstream protein translation, highlighting their potential superiority to oligonucleotides for targeting FXTAS.

TARGETING RAS THROUGH PKCδ



Melanoma currently claims nearly 10,000 lives annually in the United States alone, and its incidence is on the rise. The two most commonly mutated genes in melanoma are BRAF and NRAS, which are part of the mitogen-activated protein kinase signaling pathway. Though drugs targeting BRAF are available, RAS has been less amenable to targeting by small molecules. However, cancer cells with RAS mutations are sensitive to inhibitors of the serine/threonine kinase protein kinase C δ (PKCδ). Now, Takashima *et al.* (DOI: 10.1021/cb400837t) report the design, synthesis, and activity of novel PKCδ inhibitors.

The authors' innovative inhibitor design combines key binding elements from two naturally occurring PKCδ inhibitors to yield novel potent and selective PKCδ inhibitors. The inhibitors prevented growth of several melanoma cell lines, and also restored sensitivity to melanoma cells lines that had acquired resistance to BRAF inhibitors. These results support the strategy of targeting PKCδ for RAS-mutated and RAF-resistant melanomas.

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