that the decoy ODNs prevented and treated oxazolone-induced colitis, which is a T_H2-mediated inflammatory process. In each case, decoy ODN administration led to inflammation-clearing effects, suggesting a therapeutic potency applicable to human IBD.

Importantly, treatment of TNBS-induced inflammation by intrarectal administration of NF-κB decoy ODNs did not inhibit NF-κB in other organs. One of the effects of blocking NF-κB is the decrease of interleukin-12, a cytokine that has important anti-apoptotic effects of T_H1 T cells. Local delivery of the decoy ODNs still resulted in T-cell apoptosis, suggesting that such treatment is likely to have a durable therapeutic effect.

Melanie Brazil

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COMPUTATIONAL CHEMISTRY

Ready, steady, screen!

Computational screening methods are established as a complementary approach to high-throughput screening for identifying potential active compounds, but rarely have the two strategies been directly compared. Investigating this issue was one aim of a recent unique competition, in which entrants were challenged to computationally predict the results of a high-throughput screen, and selected results are presented in a special issue of the *Journal of Biomolecular Screening*.

The competition was based on data from high-throughput screens of two 50,000-compound libraries against dihydrofolate reductase (DHFR), an established drug target for the treatment of bacterial infections, cancer and malaria. Entrants were given the structures and measured levels of inhibition for the compounds in a 'training' set of 50,000 diverse compounds that contained 12 competitive DHFR inhibitors to aid in validating computational screening strategies. The structures of the second set of 50,000 compounds were also provided, but not the screening results, and the test was to predict these results.

The approaches used by the competition entrants, the most successful of which are featured in the issue, fell broadly into several categories: those based on quantitative structure–activity relationship analysis; on molecular similarity; on docking; and combinations of these approaches. However, overall, no group predicted more than 15% of the apparent inhibitors in the test set.

Despite this apparent low rate of success, several valuable insights were obtained, including possible reasons for the outcome. Bender *et al.*, who used a fragment-based similarity searching method, found that a key issue was a lack of similarity in the distribution of chemical features of the training and test sets. And Brenk and colleagues, whose strategy was based on docking, predicted that few true inhibitors would be found in the test screen, which indeed turned out to be the case, as none of the hits identified in this screen were validated as potent competitive inhibitors. Furthermore, this group predicted that some of the hits that were identified in the experimental screen could be false positives owing to compound aggregation, highlighting the need for procedures that can cull such molecules from screening libraries.

In addition to such insights, key areas for the improvement of similar competitions were suggested by the judges. Most importantly, prescreening all the compounds and then creating training and test sets based on equal distributions of experimental data and chemical properties, and ensuring the presence of validated competitive inhibitors in both, would allow better comparison of the predictive ability of different strategies. Using additional related and unrelated targets would also be valuable in reducing potential biases owing to the nature of the binding site and in allowing the ability of different approaches to discriminate between selective inhibitors to be evaluated.

Peter Kirkpatrick

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