confirming the *in vivo* functionality of the reporter. Furthermore, analysis of the transgenic animals revealed that accumulation of the reporter was induced in primary neurons by an aberrant ubiquitin found in Alzheimer's disease.

The role of the ubiquitin/proteasome sytem in diverse disorders, as well as its identification as a therapeutic target, makes these GFP-transgenic animals an important tool for monitoring the status of the ubiquitin/proteasome system in physiological or pathological conditions.

Melanie Brazil

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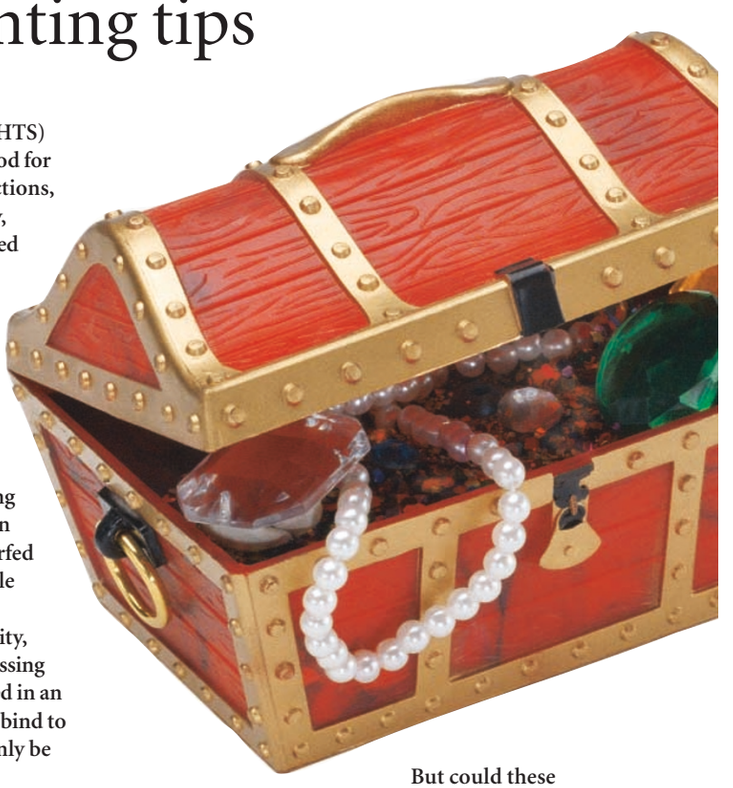
VIRTUAL SCREENING

Treasure-hunting tips



Although high-throughput screening (HTS) is firmly established as a valuable method for identifying hits from compound collections, it is widely recognized that the quantity, quality and diversity of the hits identified has been below original expectations. A recent paper in the *Journal of Medicinal Chemistry* describes a strategy that could increase the chances of screening campaigns striking gold.

The approach put forward by Mestres and Veeneman aims to address the intrinsic incompleteness of screening libraries. Such libraries typically contain ~10^6 compounds, a number that is dwarfed by the potential number of synthesizable drug-like compounds, which has been estimated to be >10^{18}. Given this disparity, it seems unlikely that compounds possessing the optimal structural features, arranged in an optimal way around a core structure to bind to a particular protein target, will commonly be present in a screening collection.

However, as Mestres and Veeneman note, the probability that compounds are present that have almost the right structural features, arranged almost optimally to bind to a target protein (which, therefore, might be easily converted to high-quality hits), might be considerably greater. Such 'latent hits' could well remain undetected in standard HTS campaigns, but might be identifiable with the help of some knowledge of the key structural features for binding — for example, from known ligands of the target protein.

To test the idea that latent hits are present in screening collections and can be identified and easily 'promoted' to hits, the authors set out to find nonsteroidal agonists of the oestrogen receptor-α (ER-α). First, a screening collection containing 133,836 compounds was filtered to remove compounds with a low probability of interacting with ER-α using information on key structural features of ER-α agonists. The resulting set of 11,047 compounds was then virtually screened using a ligand-based flexible superposition approach based on the natural ER-α agonist diethylstilbestrol (DES). Analysis of the top-ranking compounds from this screen identified two potential latent hits — compounds that lacked only one or two of the key binding features of DES — that had insufficient activity (EC_{50} >10 μm) to be identified as hits in a conventional screen.

But could these latent hits be promoted?

Inspection of the predicted binding mode of the compounds indicated simple structural modifications that could be made to fully mirror the key binding features of DES. Indeed, when these modified compounds were synthesized and tested *in vitro*, one had an EC_{50} of 0.004 μm, and the other an EC_{50} of 0.8 μm — that is, both could be considered genuine hits — providing strong support for Mestres and Veeneman's approach. Furthermore, recognizing that all compounds belonging to a chemical series represented by an active compound for a particular target can be considered latent hits for other family-related targets is equivalent to recognizing that the scaffold contained in that active compound has the potential of being a 'privileged scaffold' for the entire target family. The authors' results therefore also provide support for current screening strategies based on targeted libraries designed around scaffolds present in active compounds.

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