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In This Issue

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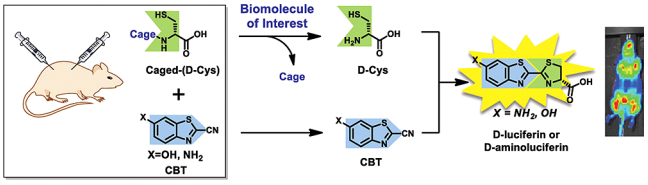
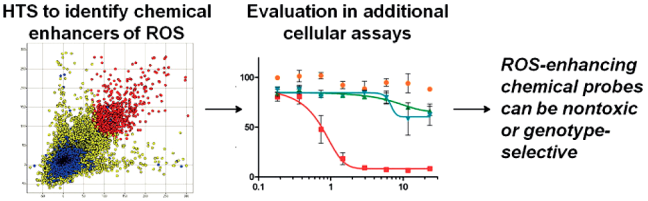
A SPLIT STRATEGY FOR WHOLE ANIMAL IMAGING



An increasingly popular method for imaging biological processes is to tag a biomolecule of interest with a compound that enables its visualization. Numerous biocompatible reactions have been developed recently that facilitate this type of imaging in cells, but few are capable of enabling imaging in live animals. Now, Godinat *et al.* (DOI: 10.1021/cb3007314) report development of the "split luciferin ligation reaction", which can proceed in cells and in mice for various noninvasive imaging applications.

The key to the success of this strategy is the biocompatible reaction between D-cysteine and 2-cyanobenzothiazoles, which forms a substrate for the enzyme luciferase. The authors demonstrate that this reaction can take place *in vitro*, in cells, and in mice, and that when luciferase is present, light is emitted. They further show that this method can be used to image the process of programmed cell death, or apoptosis, in luciferase-expressing mice. By enabling imaging studies in live animals, these new molecular tools will facilitate our ability to probe increasingly complex normal and pathological processes.

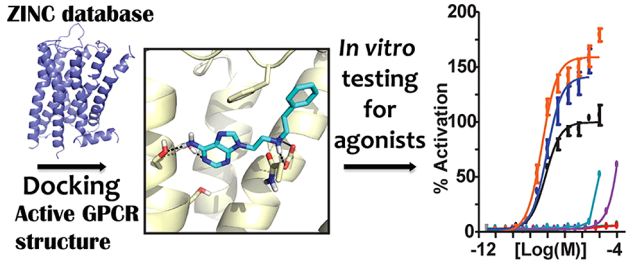
ENHANCING AN ANTICANCER APPROACH



Though they have important signaling, regulatory, and even protective roles in many biological processes, reactive oxygen species such as hydrogen peroxide, nitric oxide, and superoxide are notorious for their ability to damage cells. To this point, enhancing ROS levels is currently being investigated as a strategy for selectively killing cancer cells. In an effort to further explore the potential of small molecule ROS enhancers as anticancer agents, Adams *et al.* (DOI: 10.1021/cb300653v) search for new ROS enhancers using high-throughput screening technology.

Of 41,000 small molecules screened, several hundred were identified as capable of enhancing ROS levels in a cancer cell line. Surprisingly few, however, were effective cancer cell killers. Notably though, the authors discovered that some of the compounds were effective cytotoxic agents when used in combination with inhibitors of glutathione synthesis, and that certain electrophilic compounds were capable of selectively targeting cancer cells. These findings highlight the inherent complexity involved in targeting cancer cells with ROS enhancers, while illuminating potential new strategies for exploiting ROS activity for therapeutic applications.

LESSENING THE AGONY OF AGONIST DISCOVERY



Approximately 40% of all approved drugs target G protein-coupled receptors (GPCRs). At the same time, only a small fraction of the 900 known GPCRs are targeted by these drugs, offering a huge opportunity for future drug discovery efforts. Recent successes in the notoriously challenging structural characterization of various GPCRs has paved the way for virtual screening approaches for GPCR ligand discovery, but the effects of receptor conformation on hit identity has not been well explored. Now, Weiss *et al.* (DOI: 10.1021/cb400103f) report the results of a virtual screen of an active conformation of the β2-adrenergic receptor (β2AR).

Over 3 million compounds were screened. The 22 deemed most promising were tested experimentally in a kidney cell line, and several were potent β2AR agonists. Notably, this is in contrast to the exclusive discovery of inverse agonists from virtual screens based on an inactive conformation of the same receptor. The findings underscore the profound influence of subtle differences in receptor conformation in virtual screening outputs.

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