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In This Issue

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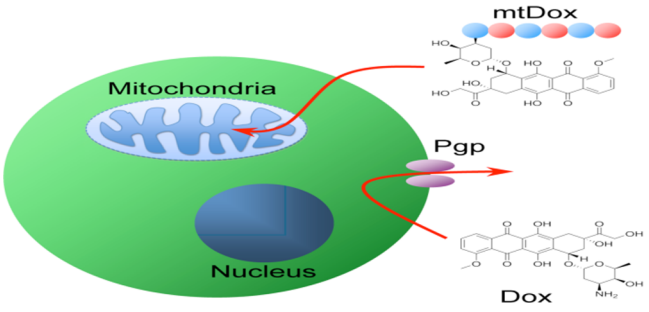
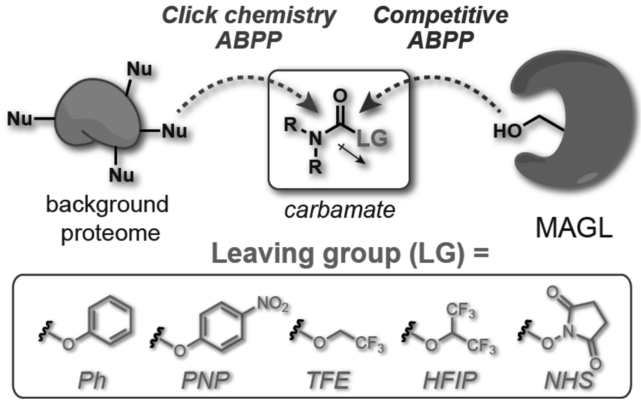
EVADING EFFLUX IN THE MITOCHONDRIA



The development of multidrug resistance mechanisms, such as the expression of efflux pumps in the nuclear and plasma membranes that eject drug molecules, are a major challenge in maintaining drug efficacy. Interestingly however, these efflux pumps are generally not effective in the mitochondrial membrane, pointing to a potential benefit in targeting mitochondrial proteins for therapeutic applications. Chamberlain *et al.* (DOI: 10.1021/cb400095v) now explore this idea by synthesizing a derivative of the common anticancer drug doxorubicin that is selectively localized to the mitochondria.

To create a mitochondria-targeting doxorubicin, referred to as mtDox, the authors conjugate the anticancer agent to a special mitochondria-penetrating peptide designed to escort molecules into the mitochondrial matrix. mtDox was indeed selectively localized to the mitochondria where it inhibited its target enzyme, topoisomerase II, albeit with somewhat diminished toxicity relative to that of its parent compound. Importantly, the conjugate also evaded efflux from the cell. This clever approach enables the creation of unique tools to study mitochondrial enzymes and facilitates exploration of the general therapeutic potential of targeting mitochondrial proteins.

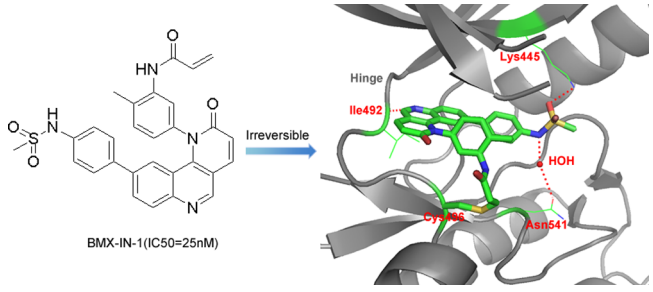
CHARACTERIZING CARBAMATES AS SELECTIVE SERINE PROTEASE INHIBITORS



Despite the successful development of numerous drugs that target serine proteases for the treatment of various conditions including obesity, dementia, and infectious diseases, most of the over 200 serine proteases in the human proteome are not well characterized, nor have selective inhibitors been identified for them. Chang *et al.* (DOI: 10.1021/cb400261h) tackle this challenge by presenting a strategy for characterizing a collection of serine protease inhibitors across the entire mammalian proteome.

Using related chemoproteomic technologies called competitive and click-chemistry activity-based protein profiling, the authors examine the reactivity and selectivity of various activated carbamates (functional groups known to irreversibly inhibit serine proteases) in mouse tissue proteomes. They identify several classes of carbamates that are selective for certain serine proteases, including *O*-hexafluoroisopropyl carbamates that target endocannabinoid hydrolases. On the basis of these structures, they create imaging probes for investigation of endocannabinoid hydrolase activity in live mice. This approach lays the groundwork for further characterization of serine proteases as well as the development of new inhibitors for use as biological discovery tools and as leads for novel therapeutics.

BMX INHIBITORS BY DESIGN



Prostate cancer is the second most common cancer among males, affecting over 900,000 men annually and rising. The nonreceptor tyrosine kinase BMX has been implicated in prostate cancer development, but the inherent challenge in developing selective kinase inhibitors has hindered validation of BMX as a prostate cancer target. Now, Liu *et al.* (DOI: 10.1021/cb4000629) report the design, synthesis, and biological activity of an irreversible BMX inhibitor called BMX-IN-1.

Careful examination of the structures and activities of known but unselective BMX inhibitors, the BMX crystal structure, and molecular modeling analysis led to the creation of a small molecule designed to react covalently with a strategically located cysteine residue in the BMX active site. BMX-IN-1 is potent and selective for BMX over other kinases in both biochemical and cellular assays, though it exhibited only modest inhibition of prostate cancer cell growth. However, the authors identified other kinase inhibitors that, when used in combination with BMX-IN-1, worked synergistically to prevent prostate cancer cell proliferation. Though further studies are needed to determine the therapeutic potential targeting BMX, this irreversible inhibitor is a valuable tool for further investigations of BMX biology.

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