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In This Issue

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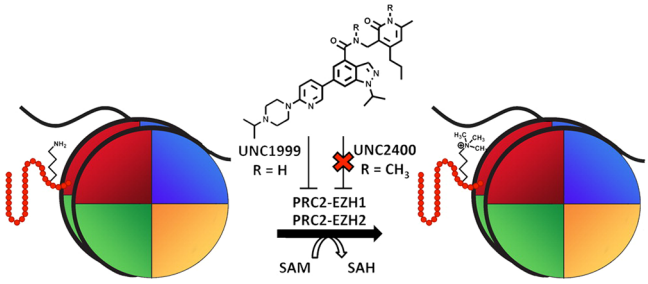
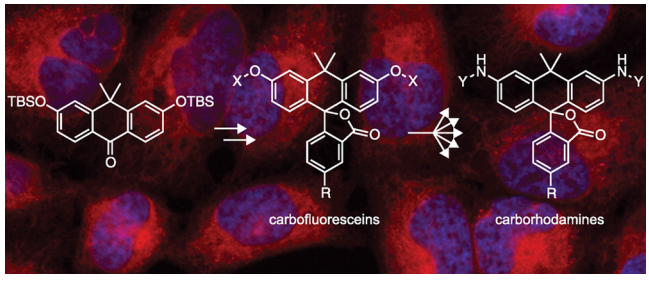
TOOLS FOR EZ ACCESS TO METHYLTRANSFERASES



Protein lysine methyltransferases (PKMTs) belong to the large conglomerate of enzymes responsible for the installation, regulation, and removal of protein postranslational modifications. PKMTs catalyze the methylation of lysine residues on histones, a modification that is increasingly recognized as a key regulator of gene expression, cell differentiation, and organ development. To explore PKMT function, Konze et al. (DOI: 10.1021/cb400133j) designed, synthesized, and characterized UNC1999, an orally available small molecule inhibitor of the PKMT polycomb repressive complex 2 (PRC2).

Molecular modeling studies led to the design of UNC1999, which inhibits the catalytic subunit of PRC2, EZH1, or EZH2. The authors also created a series of UNC1999-derived molecular tools, including biotinylated and fluorescent analogs for various biochemical and cellular studies and an analog with significantly decreased potency for use as a negative control. The oral availability of UNC1999, as well as the accessibility of these molecularly tagged analogs, will greatly facilitate investigation of the biology of PRC2 both *in vitro* and *in vivo*.

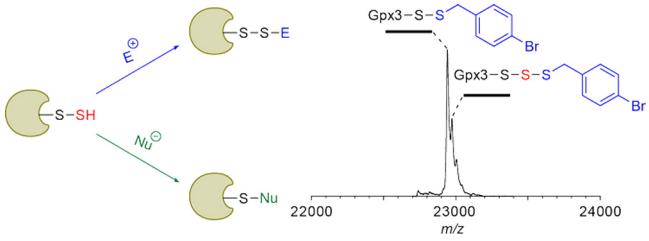
FLUOROGENIC COMPOUNDS GO GREEN



Fluorogenic compounds, molecules that become fluorescent upon a chemical transformation, are important tools in the development of detection and imaging methods for biological exploration. Though various fluorogenic molecules that are excited by ultraviolet, blue, orange, and red light have been developed, none exist that are excited by green light, leaving a black hole of sorts in this molecular toolbox. Grimm et al. (DOI: 10.1021/cb4000822) now report the synthesis of a collection of green-absorbing fluorescent and fluorogenic derivatives of the common fluorophores fluorescein and rhodamine.

The authors cleverly shift the absorption wavelengths of fluorescein and rhodamine from the blue region of the spectrum to the green by replacing the xanthene oxygen with a carbon atom, a seemingly simple but synthetically challenging modification that they accomplish using a divergent synthetic approach. Using this strategy, they create and characterize the chemical and optical properties of numerous novel dyes, setting the stage for their use in various imaging methodologies.

PROBING POSTTRANSLATIONAL PROTEIN PERSULFIDES



Posttranslational modifications on proteins are vital components of cell signaling processes. Cysteine *S*-sulfhydration, which results in the formation of a persulfide group, is emerging as a key regulator of signaling by hydrogen sulfide (H_2S), a gaseous transmitter in the cardiovascular and nervous systems. Exploring the partnership between H_2S signaling and cysteine *S*-sulfhydration, however, has been hindered by difficulties in detecting the persulfide group, whose reactivity profile is similar to that of thiols. Now, Pan and Carroll (DOI: 10.1021/cb4001052) report the development of novel reagents that facilitate investigation of protein *S*-sulfhydryl moieties.

To probe protein *S*-sulfhydration chemistry, the authors built on recent studies suggesting that the alkylating agent *S*-methyl methanethiosulfonate (MMTS) can distinguish between thiols and persulfides using a modified biotin switch technique. They synthesized an MMTS analog and a series of persulfide model compounds, and with these reagents, they were able to characterize the reactivity of protein persulfides with various nucleophiles and electrophiles. This study provides new chemical insight into this intriguing class of postranslational modifcations.

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