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In This Issue

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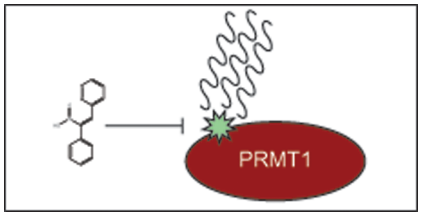
ASSAYING FOR ARGININE METHYLATION INHIBITORS

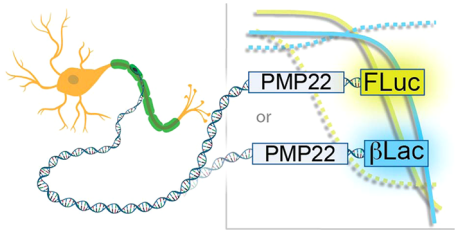
After translation, proteins are decorated with various modifications, such as carbohydrates, phosphates, or methyl groups, which modulate their function. Protein arginine methyl transferases (PRMTs) are the enzymes responsible for adding methyl groups to arginine residues, an alteration that has been implicated in cell signaling and transcriptional regulation. In addition to their potential therapeutic utility, inhibitors of PRMTs could be valuable tools for exploring PRMT function, but identification of compounds selective for specific PRMTs such as PRMT1 has proved a formidable challenge. Now, Dillon *et al.* (DOI: 10.1021/cb300024c) report the identification of several novel, selective PRMT1 inhibitors.



The authors cleverly develop a high-throughput screen for small molecule inhibitors of PRMT1 by combining the power of fluorescence polarization assays with a technique called competitive activity-based protein profiling. Key to the success of this approach was the exploitation of a uniquely reactive cysteine in the active site of PRMT1. Further use of this strategy for identifying selective PRMT1 inhibitors will enhance our understanding of arginine methylation and could lead to new therapeutics for a variety of diseases.

A NEW WAY TO HIT A NERVE

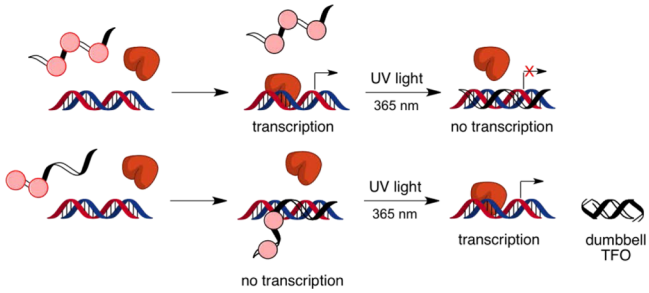
Peripheral myelin protein 22 (PMP22) is an important component of myelin, the substance that insulates axons and facilitates the efficient transmission of impulses along nerve cells. Duplication of the *PMP22* gene and its consequent overexpression has been implicated in Charcot-Marie-Tooth disease type 1A (CMT1A), a neurodegenerative disorder in which the myelin sheath of motor and sensory nerves does not function properly. Discovery of small molecule therapeutics for CMT1A has been hampered by challenges in developing assays that target pathways relevant to the disease. Now, Jang *et al.* (DOI: 10.1021/cb300048d) report the development of a high-throughput screen for small molecules capable of reducing expression of the *PMP22* gene.



Unlike many assays that are designed to find compounds that directly inhibit the protein of interest, this screen identifies compounds that reduce transcription of the *PMP22* gene. This clever strategy can be applied to the discovery of small molecule therapeutics for other diseases affected by gene duplications, such as Parkinson's and Alzheimer's diseases.

TRIPLING UP TO CONTROL GENE TRANSCRIPTION

Triplex-forming oligonucleotides (TFOs) are single-stranded oligonucleotides that can bind to the major groove of certain regions of double-stranded DNA, resulting in the formation of a triple-stranded structure. Triplex formation can block transcription factor binding to DNA, making TFOs exciting molecular tools for manipulating gene transcription. To expand the utility of TFOs as gene transcription regulators, Govan *et al.* (DOI: 10.1021/cb300161r) developed a method for temporally controlling TFO activity with light.



Using the cell cycle regulator cyclin D1 as a model system, two caged TFOs were designed and synthesized. In the first, the caging groups functioned to block interaction with DNA. Exposure to light triggered release of the caging groups, leading to DNA binding and prevention of gene transcription. In the second, the caging groups did not prevent interaction with DNA, but their release promoted formation of a dumbbell structure within the TFO that renders it inactive, leading to activation of gene transcription. This study illuminates an innovative approach for the temporal control of gene transcription with broad biological and potential therapeutic applications.

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