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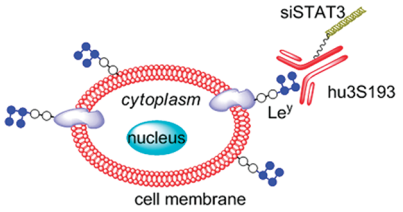
New Approach to Cancer Therapeutics

Small interfering RNAs (siRNAs) are double-stranded RNAs that, upon processing by the RNA induced silencing complex (RISC), bind and promote degradation of complementary mRNA. siRNAs have enormous therapeutic potential, but the lack of efficient cell-specific delivery systems has hampered their realization as a practical drug. Ma *et al.* (DOI: 10.1021/cb200176v) offer a robust approach for siRNA delivery by conjugation with humanized monoclonal antibodies targeting an antigen that is expressed in over 70% of epithelial cancers.



The Lewis-Y (Le^y) antigen is a blood-group-related antigen expressed in several cancers including those of the breast, colon, and lung. Due to their limited expression in normal cells, these antigens offer a potential means to localize anticancer therapeutics. Humanized monoclonal antibody hu3S193 specifically binds Le^y . To target cancer cells, the authors conjugated two different constructs of hu3S193 with STAT3-siRNA, which targets STAT3, a key cancer proliferator. Both constructs displayed significant gene silencing of STAT3. Thus, conjugation of hu3S193 and siRNAs directed against key pro-cancer targets offers a promising new approach for designing cancer therapeutics.

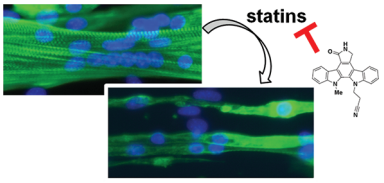
Crosstalk Crosses Over to Cell Signaling

Post-translational protein modifications, such as phosphorylation, acetylation, and methylation, play important roles in regulating diverse cellular processes. Post-translational modifications are generally perceived to be one step along a pathway that culminates in a specific action like gene transcription or protein degradation. However, recent evidence suggests that crosstalk between post-translational modifications may participate in the regulation of these signaling pathways. Though post-translational crosstalk is best characterized in histones, Rust and Thompson (DOI: 10.1021/cb200171d) now review the evidence and implications of crosstalk between serine/threonine phosphorylation and arginine/lysine modifications in nonhistone proteins.

The importance of post-translational crosstalk in cell signaling pathways is illustrated by the connection between the methylation of arginine or lysine and the inhibition of serine or threonine phosphorylation. This molecular banter has been shown to affect various processes, including protein transport, activity, and stability, gene transcription, DNA repair, cell cycle progression, and apoptosis. These findings highlight the importance of continued characterization of post-translational crosstalk, both for deepening our understanding of signaling pathways and facilitating our ability to interrupt post-translational crosstalk for therapeutic benefit.

Reducing Statin-Induced Myopathy

Statins are a class of drugs used for preventing cardiovascular disease by lowering cholesterol levels. The mechanism of action of these drugs is *via* inhibition of 3-hydroxy-3-methylglutatryl-coenzyme A or HMG-CoA, an enzyme important in cholesterol production in the liver. However, a potentially life-threatening side-effect associated with statins is muscle toxicity. In the current issue, Wagner *et al.* (DOI: 10.1021/cb200206w) describe a screening strategy that resulted in the identification of a lead compound that reduces statin-induced myopathy.

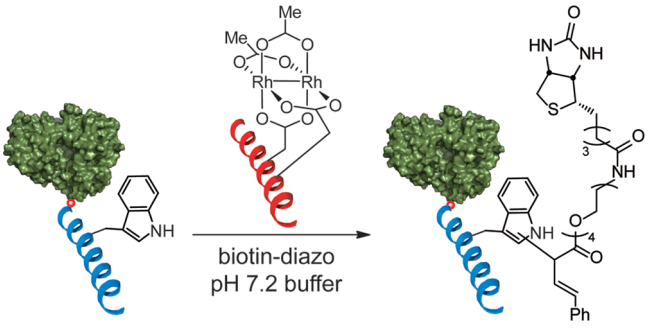


To find new lead compound suppressors of statin-induced muscle damage, the authors screened 2240 small molecules using *in vitro* cell-based assays. Overall, four compounds were found to reduce myopathy, of which Gö6976 was found to be the most efficient. Most importantly, muscle protection was observed when Gö6976 was administered to zebrafish along with statins. Hence, this report provides a valuable solution to preventing cardiovascular disease by the coadministration of this compound with statins.

Novel Site-Specific Protein Functionalization Method

The development of protein functionalization methods is an important goal in chemical biology. A major technical challenge is implementing site-specific reactivity to proteins of interest. Currently, several functional modification methods exist ranging from the introduction of unnatural amino acids to the use of tag sequences that site-specifically modify proteins. However, the application of these tools lacks broad applicability and is severely hampered by condition and buffer compatibility. In this issue, Chen *et al.* (DOI: 10.1021/cb2001523) have developed an

efficient new approach for the universal functionalization of proteins.



The method detailed in this work involves the molecular recognition by a dirhodium metallopeptide that binds the protein in the vicinity of a functional group targeted for modification. Molecular shape recognition by the peptide component of the metallopeptide catalyst ensures specific binding, while the promiscuity of dirhodium catalysis allows site-specific modification of the targeted functional group. Importantly, the authors demonstrate the compatibility of this method with a range of buffers (including physiological pH), and its applicability in crude cell lysates. Moreover, they developed a biotin-diazo reagent for direct tagging with the dirhodium metallopeptide catalyst. This new approach provides an important breakthrough in site-specific functionalization of proteins in complex mixtures.

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