to monitor those changes in glycosylation as they take place in real time." Above all, she concludes, "as a fundamental tool for studying glycosylation in living systems, we think this [method] will be very useful to the community."

Michael Eisenstein

RESEARCH PAPERS

Prescher, J.A. *et al.* Chemical remodelling of cell surfaces in living animals. *Nature* **430**, 873–877 (2004).

Saxon, E. & Bertozzi, C.R. Cell surface engineering by a modified Staudinger reaction. *Science* **287**, 2007–2010 (2000).

PROTEOMICS

Getting a handle on protein farnesylation

A new technique based on the Staudinger ligation has enabled researchers to conduct a broad analysis of cellular targets of protein farnesylation, with potential implications for future proteomic analysis of other post-translational modifications.

Proteins can undergo an estimated 200 different post-translational modifications. From the perspective of human disease, one of the most important of these is the enzymatic addition of farnesyl, a precursor in the cholesterol synthesis pathway, as farnesylation of the signaling protein Ras is involved in oncogenic transformation for many cancers. Many other proteins are farnesylated, typically at a conserved 'CAAX box' motif, but not all such motifs are farnesylated, complicating target identification.

Inspired by Carolyn Bertozzi's Staudinger ligation (see box, "Chain Reaction"), University of Texas Southwestern Medical Center (Dallas, TX) researcher Yingming Zhao and his colleagues developed a Staudinger-based tagging strategy. A recent article from the *Proceedings of the National Academy of Sciences*, Zhao's team demonstrates the first test of their technique — which they call 'tagging-via-substrate,' or TAS — for the identification of farnesylated proteins.

They began by treating cells with farnesyl that had been modified to include an azide group. The cells were lysed, and the azidofarnesylated proteins subjected to Staudinger ligation with a phosphine-biotin probe, then affinity-purified and identified by mass spectrometry.

After confirming that TAS can efficiently label known farnesylation targets such as Ras and Hdj-2 *in vivo* without impeding their function, Zhao's team followed up by examining global protein farnesylation in COS-1 cells. They identified 17 'CAAX box' proteins, including several lamins, DnaJ proteins and Ras superfamily members, with only minor interference from a few endogenously biotinylated proteins.

Although this is far from a complete index of farnesylated cellular targets, Zhao's group is encouraged and is currently working to optimize reaction efficiency. Eventually, says Zhao, "we want to scale up in order to catalog all of the farnesylated proteins and to identify the true targets for farnesyltransferase inhibitors under clinical evaluation." He suggests that TAS could one day become a generalized tool for proteomics, and notes, "I think that this strategy will have a lot of applications with other modifications outside of farnesylation."

Michael Eisenstein

RESEARCH PAPERS

Kho, Y. *et al.* A tagging-via-substrate technology for detection and proteomics of farnesylated proteins. *Proc. Natl. Acad. Sci. USA* **101**, 12479–12484 (2004).

NEWS IN BRIEF

GENOMICS

A non-EST-based method for exon-skipping prediction

Efforts to identify alternatively spliced human genes have been hindered by the limitations of EST-based strategies. Sorek *et al.* have identified a number of genomic sequences and structural elements that are conserved between mice and humans and appear to be indicators for alternatively spliced exons, and apply these parameters toward the design of a computational method for prediction of splice variants.

Sorek, R., *et al. Genome Res.* **14**, 1617–1623 (2004).

CHEMICAL TOOLS

An investigation on the analytical potential of polymerized liposomes bound to lanthanide ions for protein analysis

Lanthanide ions, such as Eu^{3+}, offer a potentially promising solution for protein sensing applications, although their usefulness is limited by their weak luminescence. Santos *et al.* found that by incorporating 5-aminosalicylic acid–sensitized Eu^{3+} ions into polymerized liposomes, they could achieve sensitive quantification of protein concentrations in aqueous samples.

Santos, M. *et al. J. Am. Chem. Soc.* **126**, 10738–10745 (2004).

PROTEOMICS

Temporal analysis of phosphotyrosine-dependent signaling networks by quantitative proteomics

Blagoev *et al.* grew individual cell cultures in medium containing one of three different isotope-labeled arginine variants, and then stimulated each with EGF for varying lengths of time. Tyrosine-phosphorylated proteins were affinity purified from the pooled lysates and subjected to mass spectrometry. From the resulting MS profiles, a kinetic time-course of phosphorylation was established.

Blagoev, B. *et al. Nat. Biotechnol.* **22**, 1139–1145 (2004).

CHEMICAL BIOLOGY

DNA-templated organic synthesis and selection of a library of macrocycles

A collection of DNAs consisting of shuffled oligonucleotide tags, each with a corresponding complementary primer conjugated to a specific chemical functional group, form the basis of a system for the stepwise organic synthesis of small-molecule libraries. As an initial test, Gartner *et al.* use this technique to generate and screen an array of macrocycle compounds.

Gartner, Z.J. *et al. Science*, published online 19 August 2004.

PROTEOMICS

Exploring the *O*-GlcNAc proteome: direct identification of *O*-GlcNAc-modified proteins from the brain

Khidekel *et al.* expand on a technique previously developed by their group as a strategy for the global identification and analysis of targets of *O*-GlcNAc-glycosylation. *O*-GlcNAc-modified proteins from whole-cell lysates were labeled with a ketone-biotin tag by means of an engineered galactosyltransferase enzyme, enabling affinity purification and identification by mass spectrometry.

Khidekel, N. *et al. Proc. Natl. Acad. Sci. USA* **101**, 13132–13137 (2004).