A Challenging Conjugation

Bioactivity: Linking to antibody fragment enhances immune-system-regulating agent

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A conjugate of antibody (ribbon structure) and CGS-21680 (oval) demonstrated improvements over the small molecule alone in treating autoimmune disease in mice. Conjugate adopts dimers structure shown. Credit: Adapted from J. Am. Chem. Soc.

By accomplishing a particularly difficult antibody conjugation, researchers have enhanced the therapeutic properties of a small-molecule immune-system-regulating agent. The technique could be applicable to other small molecules as well.

The small molecule CGS-21680 targets adenosine 2A receptors on immune system cells and is thus a potential treatment for immune system malfunction. But it breaks down quickly and can cause side effects by entering non-immune-system cells.

To address those problems, pharmacologists Jonathan D. Powell and Philip A. Cole of Johns Hopkins University School of Medicine and coworkers used a technique called expressed protein ligation (EPL) to conjugate the agent to an antibody fragment called an Fc domain (J. Am. Chem. Soc., 2014, DOI: 10.1021/ja5006674).

The antibody fragment resists degradation and localizes only to surfaces of immune system cells. When the conjugate was used to treat an autoimmune lung disease in mice, it was more potent, stable, and target-selective than CGS-21680, and it improved mouse survival.

Protein conjugation has been used before, but Cole notes that this is the first use of EPL for Fc-domain conjugation. The domain’s glycosylation and disulfides make site-specific conjugation difficult.

EPL, developed in 1998 by Cole and others, uses a protein fragment called an intein to form a thioester, in this case on the Fc domain. The intein reacts with a thiol on CGS-21680 in this example, to effect conjugation. EPL offers better site specificity, higher yields, and greater simplicity than other protein conjugation methods, the researchers note.

Pharmacologist David A. Scheinberg of Sloan Kettering Institute comments that the approach “has the potential to dramatically
change the pharmacokinetics—the absorption, distribution, metabolism, and excretion properties—of a variety of small-molecule drugs.