Scientists invent a better way to make antibody-guided therapies

October 7 2013

Chemists at The Scripps Research Institute (TSRI) have devised a new technique for connecting drug molecules to antibodies to make advanced therapies.

Antibody-drug conjugates, as they're called, are the basis of new therapies on the market that use the target-recognizing ability of antibodies to deliver drug payloads to specific cell types—for example, to deliver toxic chemotherapy drugs to cancer cells while sparing most healthy cells. The new technique allows drug developers to forge more stable conjugates than are possible with current methods.

"A more stable linkage between the drug molecule and the antibody means a better therapy—the toxic drug is less likely to fall off the antibody before it's delivered to the target," said Carlos F. Barbas III, the Janet and Keith Kellogg II Chair at TSRI.

Barbas and two members of his laboratory, Research Associates Narihiro Toda and Shigehiro Asano, report the finding in the chemistry journal *Angewandte Chemie*, where their paper was published recently online ahead of print and selected as a "hot" contribution.

A Popular Approach with Limitations

The new method for making more stable antibody-drug conjugates comes as the first generation of these powerful therapies are entering the

market. Two such conjugates are now in clinical use. Brentuximab vedotin (Adcetris®), approved by the FDA in 2011, has shown powerful effects in clinical trials against otherwise treatment-resistant lymphomas. It uses an antibody to deliver the cell-killing compound monomethyl auristatin E to cells that bear the CD30 receptor, a major marker of lymphoma. The other conjugate, ado-trastuzumab emtansine (Kadcyla®), approved just this year for metastatic breast cancer, delivers the toxic compound mertansine to breast cancer cells that express the receptor HER2.

The success of these antibody-drug conjugates and the broad potential of the technology have made them popular with drug companies, particularly those trying to develop new anticancer medicines. "The current development pipeline is full of antibody-drug conjugates," says Barbas.

Yet the chemical method that has been used to make these conjugates has significant limitations. The method involves the use of compounds derived from maleimide, which can be easily added to small drug molecules. The maleimide molecule acts as a linker or bridge, making strong bonds with cysteine amino acids that can be engineered into an antibody protein. In this way, a single antibody protein can be tagged with one or more maleimide-containing drug molecules. The main problem is that these maleimide-to-cysteine linkages are susceptible to several forms of degradation in the bloodstream. When such a cut occurs, the disconnected "payload" drug-molecule—typically a highly toxic compound—is liable to cause unwanted collateral damage to the body, like a "smart bomb" gone astray. This instability of current maleimide-based conjugates probably accounts for at least some of their considerable toxicity.

A more stable linkage would mean less toxicity and higher efficacy for antibody-drug conjugates, and for the past several years research

chemistry laboratories around the world have been looking for a way to achieve this.

Improved Linkages

Now Barbas and his colleagues appear to have found one in the form of a novel Thiol-Click reaction. In their new paper, they have described a way to make improved linkages using compounds based on methylsulfonyl-substituted heterocycles instead of maleimides. "This method turns out to enable more stable linkages to an antibody protein, as well as more specific linkages, so the drug attaches to the right place on the right protein," said Barbas.

Coincident with the report of the new linking compounds in *Angewandte Chemie*, the chemical supplier Sigma-Aldrich Corporation will begin selling the compounds, so that pharmaceutical companies can start working with them to make more stable antibody-drug conjugates. Under a recent agreement, Sigma-Aldrich markets new chemical reagents from Barbas's and several other TSRI laboratories as soon as the papers describing them are released.

"Improved antibody–drug conjugate technologies are a top-priority research area in the pharmaceutical industry and exactly the type of fundamental research issue that our partnership with Scripps will continue to address," said Amanda Halford, vice president of academic research at Sigma-Aldrich.

Although linking drug molecules to target-homing antibodies is the best-known therapeutic application of the new method, Barbas emphasized its broad relevance. "It should be useful for many types of protein conjugation," he said. These include the conjugation of proteins to fluorescent beacon molecules for laboratory experiments, as well as the linkage of drug compounds to polyethylene glycol

molecules—"pegylation"—to slow their clearance from the body and thus keep them working longer.

More information: "Rapid, Stable, Chemoselective Labeling of Thiols with Julia- Kocie?ski-Like Reagents: A Serum-Stable Alternative to Maleimide-Based Protein Conjugation," onlinelibrary.wiley.com/doi/10 … e.201306241/abstract

Provided by The Scripps Research Institute