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Homogeneity a key feature of Innate Pharma's ADC platform

Ready for licensing, Innate Pharma's next-generation antibody-drug conjugate (ADC) technology platform provides the flexibility to link to a variety of toxins through site-specific conjugation in a rapid and robust process.

Essentially, an ADC is comprised of a monoclonal antibody linked to a small molecule cytotoxic drug—a potent biotherapy that is both targeted and effective. While the rationale for synergistically combining a toxin with a targeted antibody is straightforward, engineering safe and effective ADCs is not.

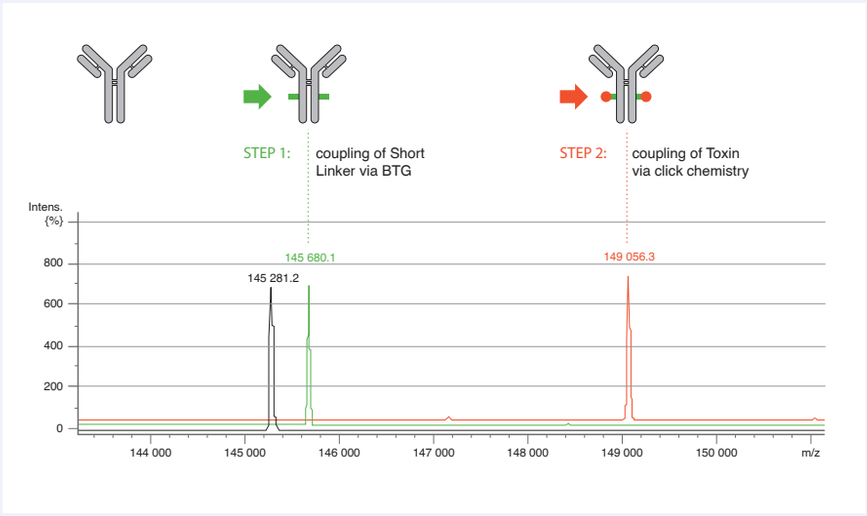
Director of Innate Pharma's pharmaceutical operations, Florence Lhospice, explained, "Obtaining an optimal drug antibody ratio, conjugating with the right linker and drug on the right place are all-time-consuming endeavors that do not always yield a safe or effective therapeutic candidate. Innate Pharma technology platform provides an unique opportunity to rapidly produce homogeneous ADCs and test multiple combinations for increasing the chances of clinical success."

Although there are several approaches to making ADCs, many result in heterogeneous drug products, complicating the development of an ADC therapy, specifically affecting chemistry, manufacturing and control processes (CMC) and pharmacokinetics, and potentially limiting the therapeutic window. To address these development obstacles, Innate Pharma has established a new, site-specific conjugation technology platform that enables the production of homogenous ADCs through a highly accurate and efficient process. The platform succeeds in overcoming the CMC, safety and efficacy issues that traditionally arise during the development of ADCs. The coupling technology utilizes the bacterial transglutaminase (BTG) enzyme.

The new approach, which involves site-specific coupling to a minimally modified scaffold, is a two-step process. First, BTG is used to attach a linker molecule to the antibody at specific positions. Second, a toxin is attached to the linker.

A single point mutation in the antibody's heavy chain generates either two or four enzyme-recognition sites, and linkers have been optimized to couple quantitatively at these positions. The chemical composition of the linker molecule enables quantitative, second-step coupling with a derivatized toxin incorporating the compatible reactive group. The whole process results in homogeneous ADCs with a drug-to-antibody ratio of exactly 2:1 or 4:1 and no detectable intermediates. The chemistry is highly versatile and compatible with most available toxins after a simple derivatization step.

"We can accommodate the two-step process with different toxins, and the process is very robust and scalable," said Lhospice. "This technology should greatly facilitate development of ADCs and improve their therapeutic window by avoiding both low and high drug-to-antibody ratio species, known to limit efficacy or generate toxicity."



Innates Pharma's technology platform employs a two step process to produce an antibody conjugate that consistently displays a drug to antibody ratio of 2:1 . A) Mass spectrometry image displaying drug antibody ratio of an ADC produced using the Innate platform.

The resulting ADCs exhibit good stability in buffer and comparable pharmacokinetic properties in animal models for both the total antibody and the conjugated antibody compared to naked antibody alone. The experiments demonstrate that antibody half-life is not affected by BTG coupling and the drug-to-antibody ratio remains stable. In addition, BTG coupling yields better biodistribution than chemical coupling. When *in vivo* efficacy is compared, Innate Pharma's technology is at least equivalent to an approved ADC in xenogenic models.

A versatile process

The BTG-coupling technique has several additional advantages over current technologies for ADC production. Other site-specific technologies involving, for example, unnatural amino acids require a new manufacturing process to produce the antibody scaffold. In contrast, Innate's process is suitable for scale-up and industrialization using well-validated antibody production processes. "Our single point mutation is simply an additional step in an already well-established manufacturing procedure that is widely accepted by regulators," said Lhospice. In addition, BTG is already used in the manufacture of a large number of food products and medical devices.

"The technology is available now," said Yannis Morel, Innate Pharma's chief business officer. "We are looking to license this technology on a nonexclusive basis to companies that are interested in antibody conjugates in order to help them produce and develop their own ADCs."

Innate Pharma is not new to collaborating with the pharmaceutical industry, and this next-generation ADC platform is the company's latest offering. Innate Pharma also has a pipeline of first-in-class immunotherapy drugs for cancer and inflammatory diseases that attracted partnerships with Bristol-Myers Squibb and Novo Nordisk. Innate Pharma's drug candidates are immune-modulatory antibodies with an original focus on innate immunity. Two candidates from the pipeline are undergoing clinical development: IPH2201 (NN8765), in phase 1 for the treatment of rheumatoid arthritis, and lirilumab, in phase 2 for the treatment of acute myeloid leukemia.

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