**Interest in “Smart Bombs” Explodes**

Witnessing the success of 2 antibody–drug conjugates, companies accelerate research

Antibody–drug conjugates (ADC), in which a chemical linker connects a cytotoxic agent to an antibody, are not new. However, with the approval of one cancer ADC last year by the U.S. Food and Drug Administration (FDA) and the approval of a second ADC pending, companies are ratcheting up development of many more.

In the 1980s, ADC researchers tested murine monoclonal antibodies linked to anticancer drugs in humans. “The thought was that antibodies themselves wouldn’t be that helpful because the tumor had already evaded the immune system, so the idea was to send in these toxic agents with them,” explains John Lambert, PhD, chief scientific officer of ImmunoGen (Waltham, MA), founded in 1981 to develop ADCs.

When initial results were disappointing, researchers replaced the murine antibodies with humanized ones, switched to drugs that were significantly more cytotoxic, and intensified their efforts to find antigens highly expressed on cancer cells but nearly nonexistent on normal ones.

The work seemed to pay off in 2000, when the FDA gave a nod to the first ADC, gemtuzumab ozogamicin (Mylotarg; Pfizer). Targeted to the CD33 receptor, the agent was prescribed for the treatment of acute myeloid leukemia. However, a decade later, after required phase III follow-up trials failed to show a survival benefit, Mylotarg was pulled from the market. Its antibody-drug linker proved unstable, often releasing the payload before the antibody latched on to cells. Complicating matters, both normal and cancer cells expressed the receptor.

Companies learned from the early missteps and are now unveiling the next generation of ADCs, or “smart bombs.”

**WINNING TRIALS**

In August 2011, Seattle Genetics’ brentuximab vedotin (Adcetris), which targets CD30, received FDA approval for the treatment of relapsed Hodgkin lymphoma and anaplastic large-cell lymphoma. Its stable linker binds tightly to the payload—the antimicrotubule agent monomethyl auristatin E—until the tumor cell internalizes the ADC-receptor complex.

In June 2012, researchers announced that trastuzumab emtansine (T-DM1; Roche/Genentech) extended progression-free survival by more than 3 months compared with the combination of lapatinib (Tykerb; GlaxoSmithKline) and capecitabine (Xeloda; Roche/Genentech) in women with metastatic HER2-positive breast cancer previously treated with trastuzumab (Herceptin; Roche/Genentech) and a taxane. Two months later, researchers announced that the women also experienced significant improvement in overall survival. Roche/Genentech has submitted an application to the FDA for approval of T-DM1 for treatment of such patients.

“There’s a fair amount of work that goes into choosing the right linker, the right antibody, and the right drug,” says Stuart Lutzker, MD, PhD, vice president of BioOncology Exploratory Clinical Development at Genentech in San Francisco. “If T-DM1 didn’t work, the whole field could’ve stopped.”

Instead, ADC research is expanding at dozens of firms, both big and small.

At Genentech, studies of T-DM1 in combination with pertuzumab (Perjeta; Roche/Genentech) as a first-line treatment for patients with HER2-positive breast cancer are under way. In addition, Lutzker says that Genentech has about 25 more ADCs in various stages of development.

In March, ImmunoGen initiated a phase II trial to evaluate the impact of adding its IMGN901 (ivorotuzumab mertansine), designed to target and kill CD56-expressing cells, to standard therapy for patients with small cell lung cancer. Additionally, the agent has demonstrated promising activity in ovarian cancer and other malignancies that can express CD56.

The company also has launched trials of ADCs targeting CD37 in non-Hodgkin lymphoma and folate receptor 1 in ovarian and other solid tumors.

T-DM1, IMGN901, and some additional ImmunoGen ADCs in development contain DM1, one of the company’s maytansinoid derivatives; others use the maytansinoid derivative DM4. Although T-DM1 and IMGN901 both contain DM1, they use different linkers, as can agents with DM4. “We find that the linker that works best for one target may not be the best linker for another,” says Lambert.

ADCs under development at Mersana Therapeutics (Cambridge, MA) feature a flexible polymer backbone that attaches to either a full-length antibody or an antibody fragment, with linkers along the polymer connecting to drug molecules, explains Nicholas Bacopoulos, PhD, the company’s president and CEO. Multiple drugs can be attached to the polymer simultaneously.

The length of the polymer can vary, allowing significant increases in the normal cytotoxic payload of 1 to 4 small molecules. However, if the entire structure is too large, it may not make its way into the cell. Bacopoulos says Mersana carefully evaluates compounds to prevent this problem.

“If Mersana can deliver, say, 20 molecules to a tumor cell with their technology, that tumor cell is going to die; its time will be over,” says Beverly Teicher, PhD, chief of the Molecular Pharmacology Branch, Developmental Therapeutics Program at the National Cancer Institute. “If it works, it will be a beautiful thing.”—Suzanne Rose
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