Resurrecting a magic bullet

By Stephen Parmley, Senior Writer

The number of antibody–drug conjugates in development for cancer is still growing, but most have tubulin inhibitor payloads that will limit treatment options if resistance emerges. Heidelberg Pharma GmbH has resurrected a decades-old antibody–drug conjugate payload that uses a different mode of action, and the company hopes its extended deal with Roche can lead to clinical validation. The outcome will likely rest on whether the new technology can solve the toxicity profile that sank the agent the first time around.

In October, Heidelberg Pharma—a subsidiary of Wilex AG—and Roche extended their 2013 deal to apply the biotech’s ADC technology to the pharma’s antibodies. The new deal brings fees and upfront and milestone payments from Roche that, for the time being, will cover Heidelberg Pharma’s operating costs for the research collaboration.

Under the terms of the updated collaboration, Roche will add more of its antibody targets to the mix and Heidelberg Pharma will grant Roche access to a target that had been tagged for development in-house. For the latter target, Heidelberg Pharma’s total take could be up to €52 million ($64.7 million) in upfront, milestone and royalty payments if it leads to a marketed drug.

Although several companies are pursuing alternative payloads to tubulin, most of the focus is on DNA-alkylating toxins such as duocarmycin and pyrrolobenzodiazepine.

Heidelberg Pharma chose to reopen the book on an old toxin, α-amanitin, because it thought its conjugation technology could solve the main problem of insufficient linker stability that had sidelined the agent years ago. The toxin is a bicyclic peptide from the green death cap mushroom (Amanita phalloides) that kills cells by inhibiting RNA polymerase II (Pol II) and shutting down gene transcription.

Because conjugates used in the early days of ADC technology were unstable, they released too much amanitin—even in vitro—to warrant testing the compounds in vivo. The toxin never went beyond preclinical development.

But in 2003 Heinz Faulstich’s team at the Max Planck Institute for Medical Research, in collaboration with the German Cancer Research Center, began exploring new amanitin conjugation techniques for ADCs. Faulstich is an emeritus professor at Heidelberg University and was head of the biochemistry research group at the Max Planck Institute for Medical Research.

His team collaborated with Heidelberg Pharma, and in 2012 the group created safer amanitin-based ADCs by using modern linker technologies that conjugate toxins directly to specific amino acids on the antibody and are far more stable than their predecessors.

They generated proof-of-principle data showing that amanitin ADC payloads were stable in serum, could be released inside tumor cells by intracellular enzymes and killed tumors in mice at doses that showed no obvious toxicity.

Jan Anderl, director of biochemistry and cell biology at Heidelberg Pharma, told SciBX that the company optimized the platform against a variety of anticancer antibodies. “We have coupled more than 40 different antibodies for different cancer indications such as solid tumors and also for leukemia and lymphoma,” he said.

In a mouse model of prostate cancer, amanitin conjugated to an antibody against prostate-specific membrane antigen (PSMA; FOLH1; GCPII) caused complete remission at single i.v. doses of 150 μg/kg of toxin, with no more than marginal weight loss in treated animals.

According to Anderl, the data showed that the linkers were highly stable in serum and released only minor amounts of amanitin that were well tolerated in mice. The group is evaluating the compounds in cynomolgus monkeys.

Data were presented in April at the annual meeting of the American Association for Cancer Research.

À la mode

Faulstich told SciBX that amanitin’s mode of action has never been tested in patients with cancer and would have no overlap with the mechanisms used by other disclosed ADCs.

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“There are certain cancer indications where the tumor tissues and the cancer cells are completely resistant to current ADC payloads, and the amanitin toxin could be a solution for such indications,” he said.

He added that amanitin has the benefit of being hydrophilic, which makes it a weak substrate for multidrug-resistance pumps used by tumor cells to reject toxic drugs.

The challenge in the clinic will be to demonstrate an acceptable therapeutic window because the highly toxic nature of amanitin increases the risk of side effects.

Anderl told SciBX that the company is working on site-selective conjugation to enhance the activity and improve tolerability of the ADCs. But because the specificity of the anticancer antibody is also critical to the success of an ADC, the company will need to find highly specific antibodies that will optimize its chances of creating a compound with an acceptable therapeutic window.

Heidelberg Pharma managing director Jan Schmidt-Brand—who also serves as CEO and CFO of Wilex—told SciBX that there is room for additional partners. He said that Roche has selected a limited number
of targets to evaluate the technology and—if Heidelberg Pharma does exclusive development deals with Roche or other partners—it will be for specific targets only.

“Our business model is built on a licensing process which is organized and realized target by target,” he said. “So each tumor target could result in a new amanitin ADC compound.”

He added, “There are a lot of targets and a lot of antibodies that lack efficacy even though they have demonstrated specificity. This is a rich landscape for us to develop new ADCs and has a good amount of opportunities.”

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