The next generation of antibody-drug conjugates

With its second-generation antibody-drug conjugate platform, called NanomAb®, IMMUNE Pharmaceuticals hopes to grow through partnerships to co-develop new therapies. IMMUNE is also developing the clinical stage antibody, bertilimumab with a biomarker.

IMMUNE Pharmaceuticals is a global company, and although it is only three years old, it is publicly listed (IMNP). The company is developing a significant pipeline of antibody-based therapeutics, including bertilimumab, an anti-inflammatory with blockbuster potential that is presently in phase 2 trials. IMMUNE has a head office in the US, with research facilities in Israel. Its own R&D facilities are complemented by the academic team of Shimon Benita, director of the Institute for Drug Research at the Hebrew University of Jerusalem.

At the center of IMMUNE’s R&D program is the antibody-nanoparticle conjugate platform NanomAb®. By combining the targeting properties of monoclonal antibodies (mAbs) with a nanoparticle drug-delivery vehicle, the platform provides a new strategy for cancer therapeutics. IMMUNE is looking to partner the co-development of NanomAb products.

IMMUNE considers its NanomAb platform an engine for building its future pipeline. The technology is exclusively licensed from the Hebrew University’s technology transfer company, Yissum. IMMUNE CEO Daniel Teper described the conjugates as being “like guided missiles—active only at the desired site.”

NanomAbs are comprised of a PEGylated, polymeric nanoparticle capsule, measuring about 100 nm, which can contain up to 20,000 drug molecules inside. This is connected to a therapeutic mAb via a proprietary linker molecule. The antibody functions mainly as a targeting ligand by binding to a specific antigen. The system allows for high concentration drug payloads and versatility in the deliverable drug, including small molecules, peptides, drug combinations and tailored pharmacokinetics, through the formulation of the polymeric nanoparticles.

The technology has advantages over first-generation antibody-drug conjugates. The greatest advantage is the three targeting levels that are possible with these ligand-conjugated nanoparticles, which is not available with other systems. “You have tissue targeting, cellular targeting and molecular targeting, and that differentiates us from the classical, first-generation antibody-drug conjugates where you only have cellular targeting,” said Oshrat Frenkel, vice president Nanotherapeutics R&D.

NanomAbs show an enhanced ability to get out of the vasculature and reach the tumor tissue, and they are able to actively target cell receptors through their antibodies and deliver the targeted, drug-loaded nanoparticles into the cell. In addition, patients can be pre-selected by imaging the tumor with a radioabeled antibody.

The NanomAb structure includes 5 modules: the mAb (green), conjugated by a thioether covalent bonding through a proprietary linker (orange arrow like structures) to a polymeric nanoparticle (purple sphere) incorporating high payload of drug of choice or prodrugs combination (yellow and blue dots). The PEG moiety (purple) shielding from premature elimination by the mononuclear phagocytic system.

IMMUNE is also developing other NanomAbs. One targets HER2 and contains paclitaxel and the other one contains the cancer drug crolibulin. By incorporating a chemotherapy into a NanomAb, the company believes they can improve the specificity of delivery.

In addition to its own pipeline, IMMUNE intends to pursue a business strategy of co-development and is looking for partners who would benefit from its NanomAb platform. It hopes that such partnerships will rescue previously rejected drug candidates that cannot be delivered effectively or whose toxic effects were too great. “By formulating [these drug candidates] into NanomAbs, we can give them a second life, get the most of their efficacy and minimize any off-target effects,” said Frenkel.

IMMUNE is also interested in talking to companies developing antibodies that have good binding properties but are not effective drugs on their own. Such antibodies could be combined with other drugs in a NanomAb.

A personal approach

Part of the company’s diverse portfolio, and its lead product candidate, is the drug bertilimumab, a targeted biologic with anti-inflammatory properties. In 2011, IMMUNE acquired an exclusive license from iCo Therapeutics to develop the Cambridge Antibody Technology drug, and IMMUNE is now conducting phase 2 clinical trials for use against ulcerative colitis. The drug is also about to begin a phase 2 trial for the orphan autoimmune skin condition bullous pemphigoid. This rare condition, presently treated with corticosteroids, affects elderly patients and causes blistering. Completion of the trials is expected within the next two years. Pilot studies are also planned for use in patients with Crohn’s disease or severe asthma.

Bertilimumab is a fully human mAb that targets the human protein eotaxin-1, which is found in tissue and serum and is a key mediator of inflammation in many diseases. The drug inhibits eotaxin-1-mediated inflammation. The drug is first in class against this target and represents “a typical case of a drug where the target was poorly understood ten years ago and now it’s been rediscovered,” said Teper.

What makes bertilimumab potentially game changing and unique in treating severe inflammatory disease is that researchers can select patients suitable for treatment using eotaxin-1 as a biomarker. High eotaxin-1 levels correlate with disease severity; therefore, the target provides a quantitative biomarker for the use of bertilimumab in patients.

A move toward personalized medicine and the ability to use biomarkers for patient selection and monitoring is a strategy that IMMUNE is pursuing further with a number of its antibody therapeutics. The company plans to expand its R&D operations and is confident that through partnering, its highly targeted antibody therapeutics can improve the lives of patients with inflammatory diseases and cancer.

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