Gilead Buys into Tizona’s Anti–HLA-G Strategy

Gilead announced plans in July to pay $300 million for a 49.9% stake in Tizona Therapeutics, with the option to pay another $1.25 billion for the remainder of the company. Whether Gilead follows through with the acquisition will hinge on results of a first-in-human trial involving Tizona’s investigational checkpoint inhibitor, TTX-080.

The antibody therapy is the first clinical-stage candidate designed to block the interaction of HLA-G, a histocompatibility antigen displayed on the surface of tumor cells, with corresponding receptors found on immune cells.

Because HLA-G and PD-L1 have distinct but overlapping expression patterns, Tizona’s HLA-G antagonist may help patients who do not respond to current anti–PD-1/PD-L1 treatments and deepen responses among those sensitive to existing immunotherapy agents. Receptors for HLA-G are also found on many different cell types—including T cells, B cells, natural killer cells, monocytes, and dendritic cells—so TTX-080 could promote antitumor immunity through several pathways at once.

Although the company has not publicly presented any preclinical TTX-080 data, onlookers are enthusiastic about the HLA-G-targeting approach. “It’s definitely something worth trying,” says Kerry Campbell, PhD, of Fox Chase Cancer Center in Philadelphia, PA. “Clearly HLA-G is expressed on a lot of tumors, and I think it’s worth a test.”

Yet, given the structural similarity between HLA-G, a nonclassic MHC class I molecule, and its classic counterparts involved in antigen presentation, some experts worry about the potential for cross-reactivity. “Going for an HLA molecule? Boy, you want to make sure that specificity is good,” says Mary Carrington, PhD, of the NCI.

First described for its role in protecting fetuses from their mothers’ immune systems, HLA-G was later shown to provide an immune escape mechanism for tumors. Yet, despite evidence going back more than 20 years that cancer cells seem to hijack HLA-G for their own defenses, only a handful of companies seem to have pursued the target. According to patent filings, Roche and Inversex both have HLA-G–targeted antibodies in their portfolios, and Amgen and Blond Biologies have described experimental antibodies directed against an HLA-G receptor known variously as LILRB1 or ILT2.

Inversex and another startup, Cell Biotherapy, are also working on chimeric antigen receptor T cells directed against HLA-G. This strategy takes advantage of the molecule’s tumor-biased expression pattern—the antigen is not found in normal tissues outside of immune-privileged sites such as the placenta and cornea—rather than its immune tolerance function. “It’s a very, very good target based upon that specificity and its activity on about half of all human solid tumors,” says Alan Epstein, MD, PhD, of the University of Southern California Keck School of Medicine in Los Angeles, who leads research efforts at Cell Biotherapy.

Tizona is recruiting for a phase I, dose-escalation trial evaluating TTX-080 in advanced solid tumors. The company also has two wholly owned first-in-class preclinical programs involving undisclosed targets that are covered by the Gilead deal. Not included, however, is Tizona’s other phase I candidate, the antibody therapy TTX-030, for which AbbVie has the exclusive licensing option.

That anti-CD39 therapy targets a cell-surface enzyme used by immune cells and tumors to convert immune-stimulating ATP into immune-suppressive adenosine. As Tizona scientists and their academic collaborators reported last year, CD39 blockade promotes inflammasome-driven antitumor immunity and can rescue anti–PD-1 resistance in mouse models (Cancer Discov 2019;9:1754–73). Clinicians are now evaluating TTX-030 in combination with multiple agents in patients with advanced cancers. –Elie Dolgin

A Discovery 76 Million Years in the Making

A deformed leg bone discovered in Alberta, Canada, offers the first histologically confirmed example of a malignant tumor diagnosed in a dinosaur (Lancet Oncol 2020;21:1021–2). The osteosarcoma, identified in the fossilized fibula of a plant-eating horned dinosaur called Centrosaurus apertus, shows that unregulated neoplastic growth is not a modern physiologic problem, but a vulnerability rooted deep in the genomic history of cellular development.

Those evolutionary insights could help narrow the search for genomic drivers of osteosarcoma, says hematologist Mark Crowther, MD, of McMaster University in Hamilton, ON, Canada, who co-led the study. Because all birds alive today descended from dinosaurs, and because osteosarcoma has been documented in birds, “it suggests to us strongly that the best place to look is in the genetic material that is shared between humans and birds.”

Paleontologists who found the 76-million-year-old fibula in the late 1980s chalked up the bone’s strange bulbous shape to a fracture that had not healed properly. The specimen then sat in a museum drawer for close to 30 years until Crowther—working with paleobiologist David Evans, PhD, of the Royal Ontario Museum in Toronto, Canada, and a multidisciplinary team of pathologists, radiologists, and orthopedic surgeons—decided to take another look.

The specialists formed a kind of paleo-oncologic tumor board and, using modern diagnostic techniques, offered a second opinion on their dinosaur “patient.” They compared its bone to one from a 19-year-old male, now deceased, who had confirmed osteosarcoma and had undergone lower-leg amputation. Although the dinosaur sample, unlike the human one, lacked preserved soft tissue, morphologic, radiographic, and histologic examinations of the two fibulae revealed similar patterns of abnormal bone formation, with blood vessels
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