

Making music with MIT tech

Flu fighters: \$46.7M rocks Visterra, pieces of APRIL key in nephropathy bid

By Randy Osborne, Staff Writer

“Nobody has done this before,” Visterra Inc. CEO Brian Pereira told *BioWorld*, talking about the company’s approach in immunoglobulin A (IgA) nephropathy, an effort that is part of what fueled his company’s just-finished \$46.7 million series C financing. Using computational tools and methods from the Massachusetts Institute of Technology, Visterra is “not an antibody discovery company,” he said. “We design and engineer novel antibody-based solutions” that include monoclonal antibodies (MAbs), bispecific antibodies and antibody-drug conjugates (ADCs).

In IgA nephropathy, Cambridge, Mass.-based Visterra has the MAb VIS-649 bound for the clinic next year. “There has been very little innovation in the kidney space” lately, Pereira said, with most patients put on steroids and immunosuppressive drugs. N treatment is available for IgA nephropathy, the most common glomerular disease worldwide, and between 20 percent and 40 percent “get to kidney failure in about two decades,” he said. Building on recent discoveries, Visterra has identified the fundamental immunological mechanism involved in the disease. In healthy people, a proliferation-inducing ligand, or APRIL, turns on IgA production against an infection, which then “deals with the infection and does away with it,” he said. “But in those who have a predisposition for IgA nephropathy, the IgA they produce is poorly glycosylated, and that serves as an autoantigen,” he said. “It gets deposited in the kidney, and causes kidney damage and progression to kidney failure. Our intent has been to go right to the top and block the confluence of events at the APRIL level.”

Although APRIL is “a fairly complicated epitope” requiring exquisite computational biology to allow blocking at two receptors, he said, data in nonhuman primates have been encouraging. “Our plan is to take [VIS-649] into phase I trials next year, and then a phase Ib/IIa proof-of-concept study in 2019,” he said. “An effective therapy will reduce the amount of protein excreted in the urine, so you have a biomarker you can collect every day of the week.”

But the company’s farthest-along product is VIS-410, and among the milestones expected during the next year and a half are top-line results from VIS-410’s phase IIa trial in ambulatory patients with influenza A, due early next year, and the start of the same MAb’s phase IIb study in hospitalized patients with influenza A around the same time, as well as the entry into the clinic of VIS-513, yet another MAb for the treatment of dengue that’s being

developed by Visterra’s partner, the Serum Institute of India. There’s also VIS-705, an ADC engineered in the early stage works to kill all strains of *Pseudomonas aeruginosa* bacteria, including potentially multidrug-resistant ones. Ram Sasisekharan, scientific founder of Visterra (also a founder of Cambridge, Mass.-based Momenta Pharmaceuticals Inc.) led an investigative team in flu.

“Their interest in the evolution of influenza A virus led them



CEO Brian Pereira

to pursue a set of computational approaches that allowed them to identify what is the commonality across all influenza A viruses and is resistant to mutation – in short, the Achilles heel,” Pereira said. “This has since been taken to a new level by our chief scientific officer, Zach Shriver. We look at the interconnectedness of amino acids with each other on a given protein, and the most

interconnected amino acids are those that are constant across all strains and resistant to mutation.”

VIS-410 “covers all known influenza A viruses, but we also predicted that it will cover all influenza A viruses that emerge in the future. That’s a bold claim. The reality is, in the four years since we’ve embarked, there have been somewhere between half a dozen and a dozen new strains of influenza A that have emerged, and we effectively neutralize all of them.”

‘Coming together nicely’

VIS-410 also seems to work against a strain that’s turned up in the poultry markets of China: H7N9, which “thus far has only been seen in those who are in close contact with poultry,” Pereira said. “Human to human transmission has not quite been shown, but each year in China the number of cases seems to be growing and the mortality is about 40 percent. The biggest fear among health care authorities worldwide is that if this virus gets human-adapted, we have a big problem on our hands.”

That’s why the Biomedical Advanced Research and Development Authority, or BARDA, entered a potential

\$214 million contract for Visterra to develop VIS-410 all the way to the BLA. “The phase IIa was a safety study which we have completed, wherein the FDA wanted to be sure that VIS-410 was safe in an uncomplicated cohort of ambulatory patients – the average flu patient who doesn’t require hospitalization,” he said.

With VIS-705 in *Pseudomonas*, “we used our technology, just as we did for viruses, to identify the commonality across all *Pseudomonas* bacteria,” Pereira said. “We have linked this antibody to a drug, a peptide which directly kills the *Pseudomonas*. This is a one-two punch. The bactericidal peptide directly punches holes in the bacteria and destroys it, and the antibody causes opsonophagocytosis. We’ve taken a leaf out of the ADCs [playbook] in cancer, but the difference here is that the drug in the ADC is a peptide as opposed to a toxin.”

Development of the product was “easier said than done, because we have to make sure that this ADC does not undergo proteolysis, or breakdown, from the time we inject it and the time it gets to the infection sites,” he said. “We use novel mechanisms of stapling peptides to protect them during their journeys. It’s been a fun product.”

The firm has a contract with the Combating Antibiotic Resistant Bacteria Accelerator (CARB-X), at which Visterra was one of 168 applications, with 12 awarded money after three cycles of review. “We were the top two recipients,” he said.

Visterra also has applied its Hierotope platform to develop novel modifications to the Fc region of an antibody, to enhance half-life by as much as 10-fold while maintaining and often improving effector function. The capabilities, called Vistar antibody Fc

engineering, support the development of long-acting MAb for the extended protection in infectious diseases and less frequent dosing in chronic diseases. “This is not yet incorporated into our existing products,” Pereira said. With MAbs and bispecifics, the half-life is 15 days. “You don’t have to worry about another dose. By that time, the infection is done.” But with non-infectious candidates, the company wanted to devise MAbs with half-life of 60 days or longer. An immunoprophylactic in flu might be possible, for one thing. “The second [thing] is life-cycle planning for products such as VIS-649,” he said. “Initially, this will be a monthly dose, but with time, when we incorporate this, it could be a six-month dose.”

Visterra, “with our series C and the additional dollars that we have gotten from other, non-announced partnerships, can get to key inflection points for our lead product candidates,” Pereira said. “We’ve been fortunate that we’ve got three big partnerships that largely fund the development programs, and our plan is to try and do the same for our non-infectious disease candidates to move things rapidly through partnerships.”

The company raised the first \$23.1 million of the now-closed series C round in June 2016. Existing investors were included – the Bill & Melinda Gates Foundation, MRL Ventures Fund, Vertex Venture Holdings Ltd., Polaris Partners, Flagship Pioneering, Omega Funds, Cycad Group, Alexandria Venture Investments – as well as new investors, Serum Institute of India Pvt. Ltd., CTI Life Sciences and Allegheny Financial Group.

“New technologies take a while to mature,” Pereira said of the work at Visterra. “It’s coming together nicely.”